Migraine Management Toolkit: Diagnosis and Treatment Considerations

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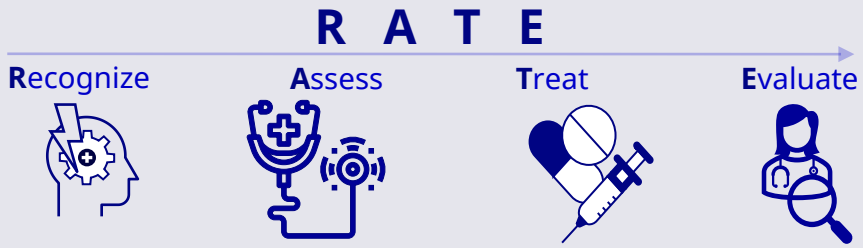


Disclaimer

- The audience for this toolkit are US healthcare professionals.

- Slides which describe Consensus Treatment Guidelines or Clinical Practice Guidelines developed by medical societies may recommend therapies within their guidelines which do not have FDA approval for the indicated use. Slides containing these off-label recommendations are distinguishable by a red overlay in the upper right-hand corner, and off-label recommendations are listed in the slide footnote.

Agree and proceed

FDA, US Food and Drug Administration; MRC, Medical Review Committee; US, United States.

Table of Contents

Table of Contents

Toolkit objectives

- To describe the unmet medical need in the diagnosis and treatment of migraine in non-headache specialties
- To review ICHD-3 diagnostic criteria and differential diagnoses of migraine
- To provide an overview of current acute and preventive treatments, and guidance on the clinical management of patients with migraine

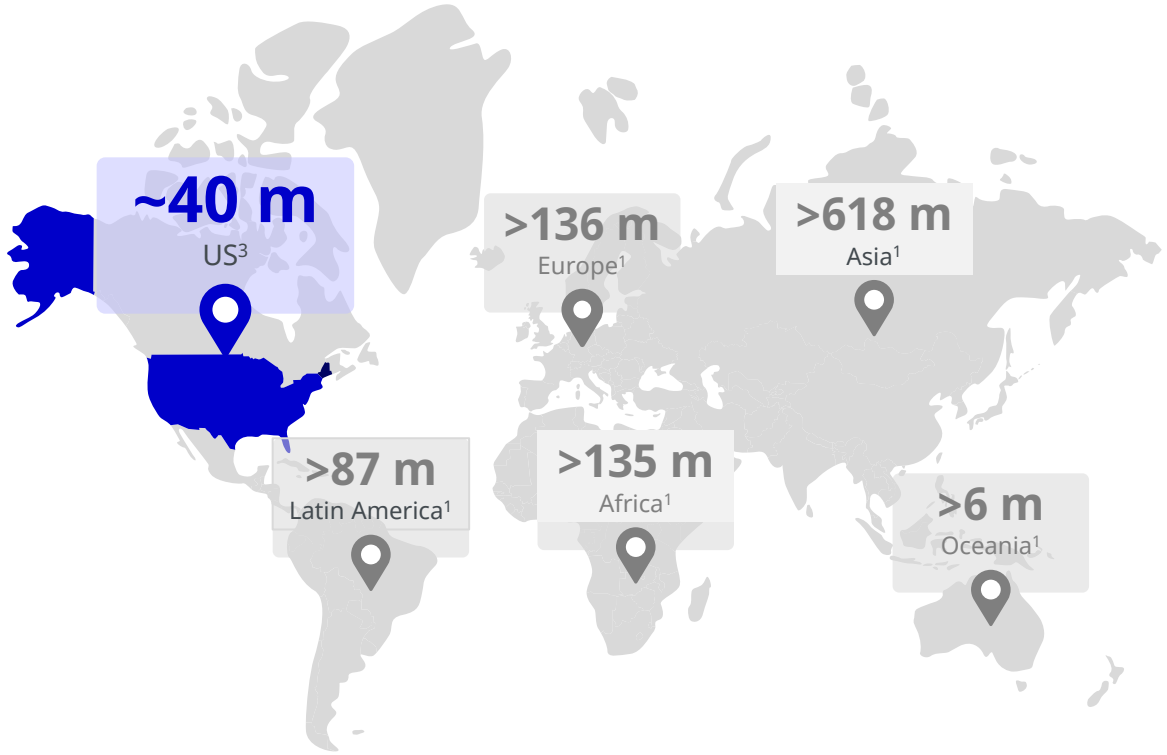
Migraine is a common neurological disease worldwide

Migraine prevalence: more than 1 billion people live with migraine globally, with approximately ~40 million in the US[1–3]

2nd
most prevalent **neurological disease** in the US[a,4]

~3×
more common in females than males[5,6]

25–55 years
Most common in the **productive years**[6]



[a]Tension-type headache is the most prevalent neurological disease.

1. GBD 2016 Headache Collaborators. Lancet Neurol 2018;17:954–76; 2. Stovner LJ, et al. J Headache Pain 2022;23:34; 3. Law HZ, et al. Plast Reconstr Surg Glob Open 2020;8:e2790; 4. GBD 2017 US Neurological Disorders Collaborators. JAMA Neurol 2021;78:165–76; 5. Lipton RB, et al. Headache 2022;62:122–40; 6. Lipton RB, et al. Headache 2018;58:1408–26.

Migraine is highly disabling and impacts patients' quality of life

Among the **top 3 most debilitating neurological diseases in the US**[1,a]

Migraine impacts multiple aspects of individuals' lives

report being very or extremely limited in completing daily activities during headache phase[2]

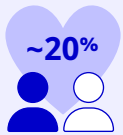
report impaired sleep[2]

feel fatigued often or always[3]

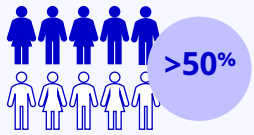
need help with daily tasks[2]

worry about long-term financial security[4]

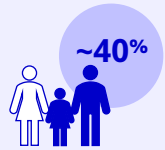
report that they would get more enjoyment from their free time without headaches[4]



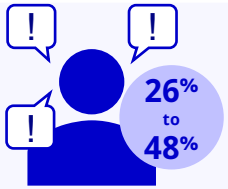
indicate that migraine has contributed to relationship problems[4]



report feeling helpless at least some of the time[5]



believe that they would be a better parent if they did not have headaches[4]



experience migraine-related stigma often or very often[6]

[a]Based on systematic analysis of the Global Burden of Disease 2017 study. Data on incidence, prevalence, mortality, and DALY in the US of 14 major neurological disorders were analyzed; migraine (2.40 million absolute DALYs) ranked third behind stroke (3.58 million) and Alzheimer disease and other dementias (2.55 million).[1]

DALY, disability-adjusted life years; US, United States.

1. GBD 2017 US Neurological Disorders Collaborators. JAMA Neurol 2021;78:165–76; 2. Gibbs SN, et al. Headache 2020;60:1351–643. Martelletti P, et al. J Headache Pain 2018;19:115. 4. Buse DC, et al. Headache 2019;59:1286-99; 5. Hubig LT, et al. J Headache Pain 2022;23:9; 6. Shapiro RE, et al. Neurology 2024;102:e208074.

Migraine is associated with substantial economic burden

High economic burden due to direct and indirect costs[1,2]

Episodic migraine costs

>$2600

per person per year in the US[1]

Chronic migraine costs

>$8200

per person per year in the US[1]

Estimated cost of productivity losses due to migraine in the US[2]

60,000–686,000
annual workdays affected by absenteeism and presenteeism across different industries

Costs of lost productive time ranging between **$18 million** and **$155 million**

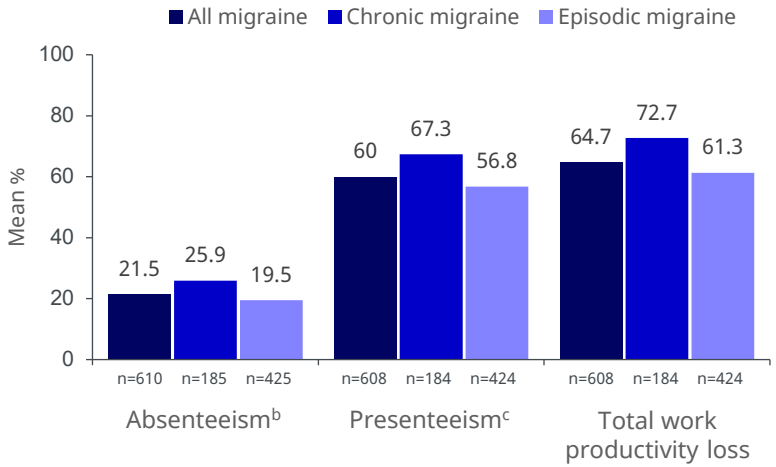
Annual indirect costs estimated to be **~6–9× higher** than direct costs

1. Messali A, et al. Headache 2016;56:306–22; 2. Yucel A, et al. Am J Manag Care 2020;26:e403–8.

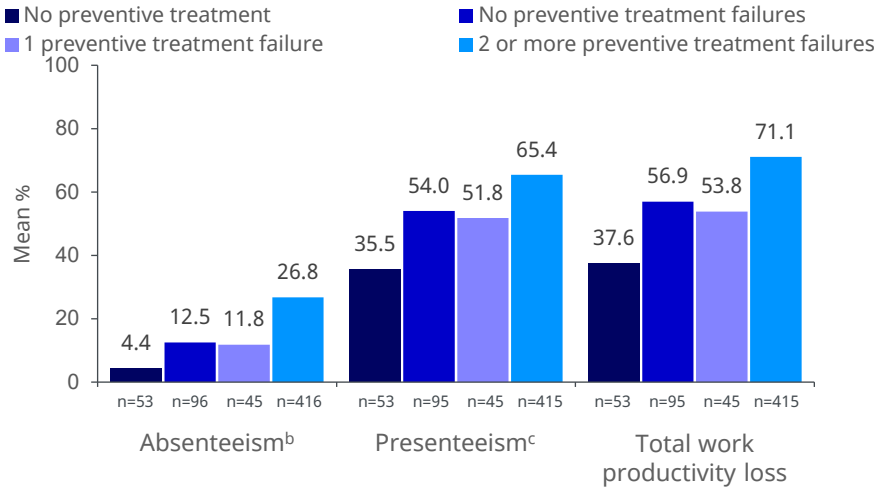
Migraine is associated with reduced work productivity

Productivity losses are greater among those with chronic migraine and those who have had two or more preventive treatment failures[1a]

Work productivity impairment by migraine frequency



Work productivity impairment by preventive treatment history



A headache education and evaluation program[2] in Japan at Fujitsu Co. Ltd. (81,159 employees)[d] consisting of an e-learning program, video seminars, and online consultation with a staff physician led to:

- Annual productivity gains of ~15.2 days per employee per year after completion of program (1.17 days for absenteeism, 14.0 days for presenteeism)
- Annual productivity savings of US $4,531 per employee

[a]Web-based survey of 1101 people with self-diagnosed migraine in the United States (My Migraine Voice); [b]Work time missed. [c]Reduced on-the-job effectiveness. [d]Employee e-learning participation rate was 90.5%; ~3 in 5 participants had a headache disorder (16.7% migraine; 40.7% tension-type headache, 0.5% cluster headache).

1. Gibbs SN, et al. Headache 2020;60:1351–64; 2. Sakai F, et al. Cephalalgia 2023;43:1–14.

Migraine is underdiagnosed

Despite advances in our understanding of the pathophysiology and management of migraine, it remains widely underdiagnosed[1]

Average time between onset and diagnosis is **~3.3 years**[1]

~20–70%
of patients with migraine do not consult an HCP[1,2]

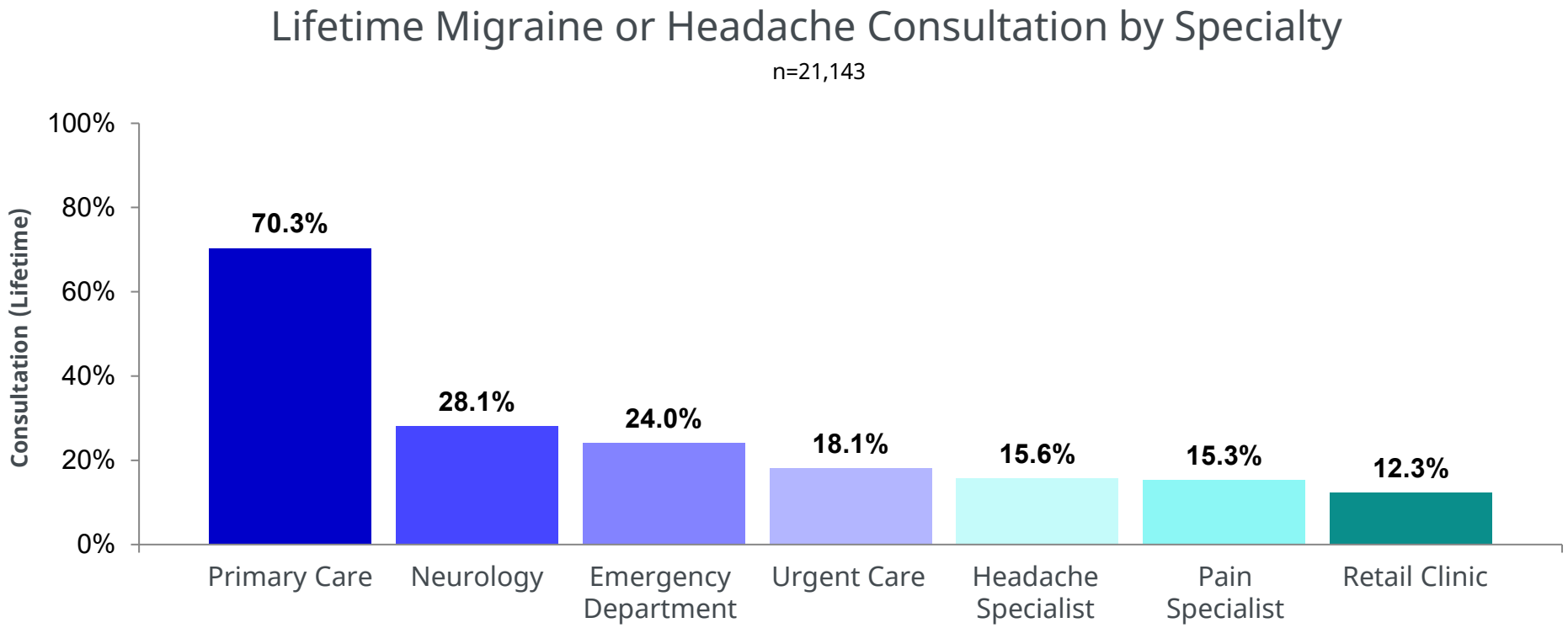
~30%
do not receive an accurate diagnosis[2,a,b]

Patients with chronic migraine are **57% less likely** to receive an accurate diagnosis than those with episodic migraine[2,a,c]

7% of patients consult with HCPs who may not be well suited for ongoing headache care; the most frequently reported HCPs providing headache care who are not customary providers of headache care were ENTs, allergists, psychiatrists, ER/urgent care physicians, and dentists.[2]

[a]Based on findings from the longitudinal internet-based survey from the CaMEO study (N=16,789; among the 9,184 patients with MIDAS scores ≥6 and valid health insurance data, 86.3% of patients met criteria for episodic migraine and 13.7% met criteria for chronic migraine
[b]Common misdiagnoses for migraine include sinus headache, stress headache and tension-type headache; [c]Among patients under care (management or treatment) of a healthcare practitioner well suited for ongoing headache care (n=2,699)
CaMEO, Chronic Migraine Epidemiology and Outcomes; ENT, ear nose and throat specialist; ER, emergency room; MIDAS, Migraine Disability Assessment
1. Lipton RB, et al. Headache 2022;62:122–40; 2. Buse DC, et al. Headache 2021;61:628–41

Patients seek treatment across many providers: Highest in primary care



Lipton RB, et al. Headache 2022;62:122–40

Variable and non-specific symptoms may lead to delayed diagnosis

Patients with migraine can experience variable and non-specific symptoms

A **range of symptoms** are associated with migraine, and these can **differ among patients** and **between headache attacks** within the same patient

Migraine diagnostic criteria (ICHD-3) require a combination of common symptoms for migraine diagnosis, but some characteristics may not be present such as **aura, throbbing,** and **severe pain**

Overlapping symptoms with other conditions such as **sinus, tension-type, and cluster headaches** can lead to misdiagnosis

Patients' **failure to describe** all of the **relevant symptoms** they experience during attacks may also lead to underdiagnosis of migraine

ICHD-3, International Classification of Headache Disorders (3rd edition).
Martin VT et al. Ann Med 2021;53:1969-90.

Recognizing, Assessing, Treating, and Evaluating patients with migraine

Introducing the mnemonic **RATE** (**R**ecognize, **A**ssess, **T**reat, **E**valuate) as a potential approach that HCPs can utilize to help guide the diagnosis and management of patients presenting with migraine[a]

Recognize

When to suspect migraine in patients[1]:

- Recurrent headache of moderate to severe intensity
- Visual aura, nausea, and vomiting
- Family history of migraine

Assess

Use a combination of[1]:

- Detailed history taking
- Physical examination
- Screening for secondary headache and considering differential diagnoses
- Validated diagnostic and screening tools

Treat

Acute treatment[1,2]

- For patients with a confirmed diagnosis of migraine

Preventive treatment[1,2]

- For patients whose attacks significantly interfere with daily routines despite optimized acute treatment
- For those who have frequent attacks, intolerance or contraindication(s) to acute treatments, or failure or overuse of acute treatments
- Based on patient preference[2]

Special populations[3,4]

- Pregnancy
- Breastfeeding

Evaluate

- Primary care practitioners should play a role in the long-term management of migraine[1]
- It is important to evaluate the impact of the treatment plan on migraine[1]
- Treatment plans should be revised and optimized for each patient, as appropriate[1]

HCPs, healthcare professionals; RATE, Recognize, Assess, Treat, and Evaluate.

[a]The RATE program described here for patients with migraine follows a similar theme to the proposed RATE strategy for the diagnosis and treatment of patients with chronic pain.[5]

1. Eigenbrodt AK, et al. Nat Rev Neurol 2021;17:501–14; 2. Ailani J, et al. Headache 2021;61:1021–39; 3. Lucas S. Obstet Gynecol 2019;134:211; 4. ACOG Committee on Clinical Practice Guidelines–Obstetrics. Obstet Gynecol 2022;139:944–72; 5. Gebke KB, et al. Postgrad Med 2023;135:244-253.

Recognize: primary versus secondary headache

Most patients presenting with headache in clinical practice have a primary headache disorder[1]

Primary Headache[2]

- No known underlying cause
- The most common primary headache disorders include:
  - **Migraine**
  - **Tension-type headache**
  - **Cluster headache**
- Most patients with a chief complaint of headache who present to their HCP for an evaluation will have primary headache

Secondary Headache[2]

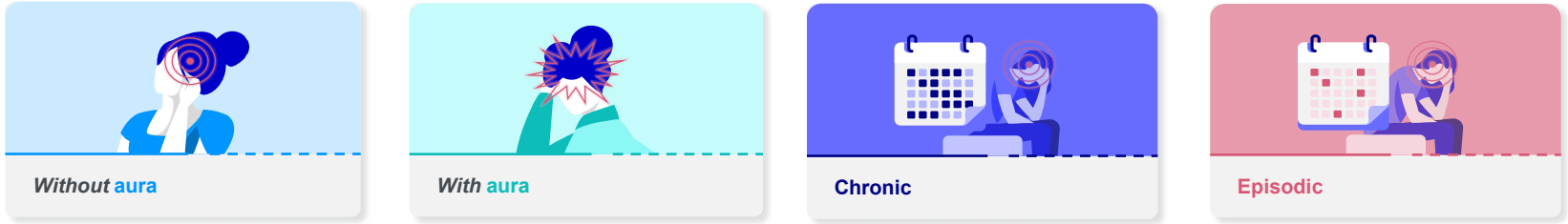
- The result of another condition causing activation of pain-sensitive structures
- Common secondary headaches include those related to:
  - Infection
  - Vascular disease
  - Trauma
- Certain "red flags" or warning signs indicate a need for evaluation

HCP, healthcare practitioner.

1. Dodick DW. Continuum (Minneapolis, MN) 2021;27(3):572-85. 2. Rizzoli P, Mullally WJ. Am J Med. 2018;131:17-24.

Recognize: migraine subtypes and association with a range of symptoms

Migraine is a primary headache disorder that can be categorized into subtypes based on symptoms and headache frequency[1]



Migraine is associated with a range of symptoms and pain can be unilateral or bilateral[2,3]

Migraine is characterized by recurrent headache attacks of moderate to severe pain often accompanied by other symptoms[2]:

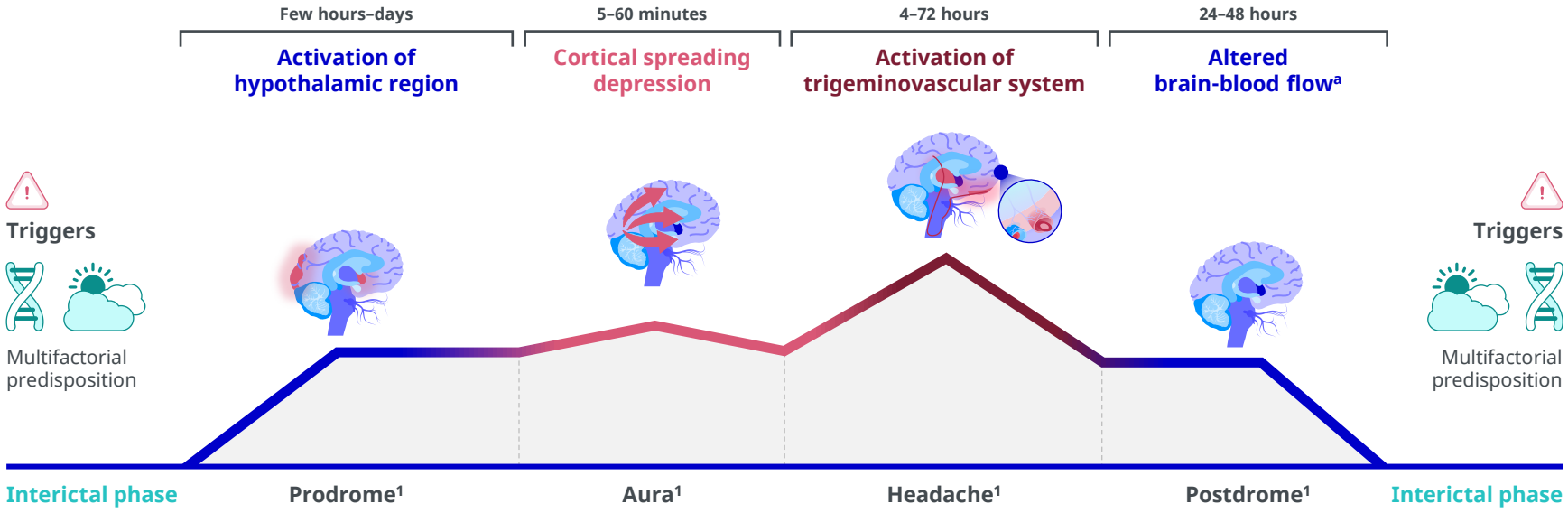
- Photophobia
- Nausea
- Phonophobia

While pain is typically unilateral, **~4 in 10 patients** report bilateral pain during migraine attacks[3]

1. Headache Classification Committee of the International Headache Society. Cephalalgia 2018;38:1–211; 2. Gupta J, and Gaurkar SS. Cureus 2022;14(8):e28347; 3. Eigenbrodt AK, et al. Nat Rev Neurol 2021;17:501–14.

Recognize: stages of a migraine attack

Functional changes in different areas of the brain produce an array of symptoms at different stages of an attack[1-3]



Stages can occur sequentially or overlap, and some may not occur at all for some patients[1]

Only ~1 in 3 people with migraine experience aura with some or every attack[4]

[a]Postdrome is the least studied and understood phase.

1. Ferrari MD, et al. Nat Rev Dis Primers 2022;8:2; 2. Dodick DW. Lancet 2018;391:1315–30; 3. Andreou AP, Edvinsson L. J Headache Pain 2019;20:117; 4. Lipton RB, et al. Neurol 2002;58:885-94.

Recognize: knowing when to suspect migraine is important

When to suspect migraine in patients presenting with headache[1,2]

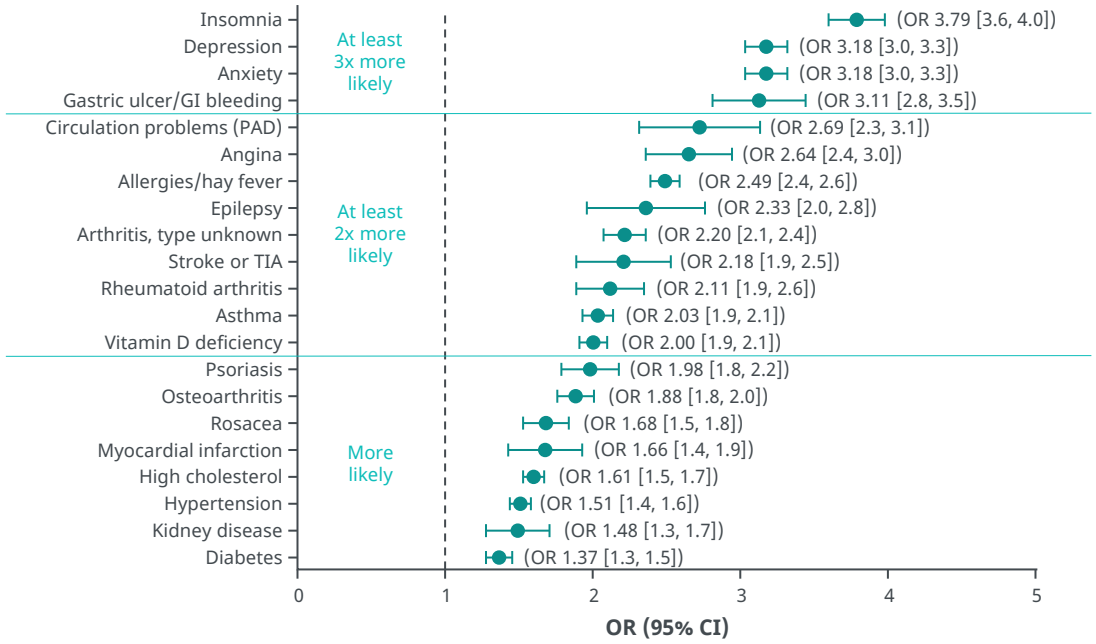
- **Recurrent headache of moderate to severe intensity**
- **Visual aura**
- **Nausea**
- **Vomiting**
- **Family history of migraine**

1. Eigenbrodt AK, et al. Nat Rev Neurol 2021;17:501–14; 2. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.

Recognize: common comorbidities associated with migraine

People with migraine experience a wide range of comorbid health conditions

Relative odds for migraine among comorbid conditions (vs migraine-free controls)[1]



Comorbidities and chronification

~3% of individuals with episodic migraine progress to chronic migraine each year[2]

Risk factors for chronification include female sex, lifestyle factors (e.g. high caffeine consumption), ineffective treatment, medication overuse and untreated comorbidities[3]

Conversely, risk of nearly all comorbidities increases with headache frequency[1,4]

Risk of sleep and psychiatric comorbidities also increases with pain intensity[1]

CI, confidence interval; GI, gastrointestinal; OR, odds ratio; PAD, peripheral artery disease; TIA, transient ischemic attack.
Data from prospective web-based survey of US population samples with migraine (N=15,133). Data adjusted for sociodemographic characteristics.
1. Buse DC, et al. J Headache Pain 2020;21:23; 2. Dodick DW. Lancet 2018;391:1315–30; 3. Torres-Ferrús M, et al. J Headache Pain 2020;21:42; 4. Lipton RB, et al. Neurology 2019;93:e2224–36

Recognize: migraine in pregnancy

Some patients experience migraine for the first time during pregnancy[1]

Migraine in pregnancy

Prevalence:

Frequency of migraine attacks tends to decrease during pregnancy; however, **~3–7%** of women experience **new-onset** migraine in pregnancy during the first trimester[1]

Migraine attacks tend to **recur**, often within the first 6 months after delivery[1]

Screen[2]

ACOG recommends careful screening of migraine during pregnancy[2]

Patients should be screened **pre-pregnancy** and at their **initial pregnancy visit** for:

- History of migraine
- Frequency of attacks
- Associated symptoms
- Intervention and/or medication history

The **appearance** or **worsening** of migraine during pregnancy warrants attention[3]

Migraine symptoms, when accompanied by **high blood pressure**, may increase the risk of developing vascular complications such as **preeclampsia**[3]

1. Lucas S. Obstet Gynecol 2019;134:211; 2. ACOG Committee on Clinical Practice Guidelines–Obstetrics. Obstet Gynecol 2022;139:944–72; 3. American Migraine Foundation. Managing and pregnancy: what moms-to-be need to know, 2017: https://americanmigrainefoundation.org/resource-library/migraine-pregnancy/.

Recognize: patient understanding of migraine attack progression may help them anticipate and identify symptoms

Recognize

Identifying symptoms associated with the earliest stages of migraine can serve as warning signs and indicate a need to consult a HCP[1,2]

Patients may report **prodromal symptoms** up to **48 hours before** the onset of headache[1]

These may include:

- hyperactivity
- hypoactivity
- depression
- specific food cravings
- yawning
- fatigue
- difficulty concentrating
- neck stiffness / pain
- blurred vision
- sensitivity to light and sound

- Patients with migraine should consider maintaining a **headache diary** to **recognize their symptoms** and phases they experience before and after each headache[2]

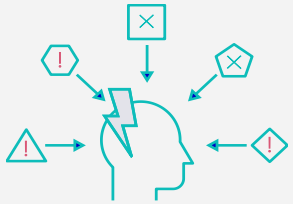
Identifying these symptoms **early** can impact treatment initiation and is key to **reducing the severity** of or **prevention of headache**[2]

HCP, healthcare practitioner.

1. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211; 2. American Migraine Foundation. The timeline of a migraine attack, 2018: https://americanmigrainefoundation.org/resource-library/timeline-migraine-attack/.

Recognize: perceived migraine triggers are unique and specific to each patient[1-3]

Patients report a variety of factors or triggers for migraine[4]



Multiple factors can culminate in a migraine episode[1,5]

Exposure to a known trigger **does not reliably produce migraine attacks**[3]

- Different triggers may be responsible through distinct mechanisms[5]
- Not all patients respond to the same triggers[5]

Commonly reported triggers include[4a]:

- **Stress** 80%
- **Hormones in women** 65%
- **Weather** 53%
- **Not eating** 57%
- **Sleep disturbance** 50%

Patient management strategies for identification and mitigation of triggers[1]

- While prodromal symptoms can make it difficult to identify triggers, patients should consider the following:

RECORD: Keeping a diary or calendar may help patients to identify triggers

ACT: Trigger avoidance is often unsuccessful and may disrupt participation in social and leisure activities. Patients should consider healthy lifestyle choices, improvement in diet and sleep

FIND OUT ABOUT FEAR: Worrying about the next attack may lead to patients avoiding or reducing their activities. This is an important predictor of migraine chronification and medication overuse, meaning identification and treatment are crucial

Identification of specific triggers may not always be possible; HCPs should encourage positive health behaviors and shared decision-making for a preventive approach[6]

[a]Based on a retrospective study of 1750 patients with migraine.
HCPs, healthcare providers

1. Marmura MJ. Curr Pain Headache Rep 2018;22:81; 2. Lipton RB, et al. Headache 2014;54:1661–9; 3. Martin VT and Behbehani MM. Med Clin North Am 2001;85:911–41; 4. Kelman L. Cephalalgia 2007;27:394–402; 5. Hoffmann J, et al. Ann Clin Transl Neurol 2015;2:22–8; 6. Sauro KM, Becker WJ. Headache 2009;49:1378–86.

Recognize: knowing when to suspect migraine is important

Summary

Suspect migraine when there is the following:[1,2]

- Recurrent headache of moderate to severe intensity
- Visual aura
- Family history of migraine

- Psychiatric, pain, sleep, cardiovascular, neurologic, and respiratory disorders are the most common comorbidities associated with migraine[3]

- Patients should be screened pre-pregnancy and at their initial pregnancy visit for history and frequency of attacks, associated symptoms, intervention and/or medication history[4]

- Patient identification of triggers and early symptoms may help to reduce the severity of, or in some cases, prevent migraine attack[5,6]

1. Eigenbrodt AK, et al. Nat Rev Neurol 2021;17:501–14; 2. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211; 3. Buse DC, et al. J Headache Pain 2020;21:23; 4. ACOG Committee on Clinical Practice Guidelines–Obstetrics. Obstet Gynecol 2022;139:944–72; 5. American Migraine Foundation. The timeline of a migraine attack, 2018: https://americanmigrainefoundation.org/resource-library/timeline-migraine-attack/; 6. Graf M, et al. Headache 2023;63:506–16.

Assess: patient history taking and physical examination as key first steps for diagnosis

Patient history

A thorough **headache history** is the **most** important tool in diagnosing **migraine**[1]

To aid **accurate diagnosis**, it is necessary to ask patients a series of **questions** on **symptoms** experienced and **severity** of migraine attacks[2]

Physical examination

A physical examination can determine other factors that may exacerbate migraine and include **fundoscopy, palpation of head and neck, cardiovascular screening**, and **neurologic examination**[2]

Example questions when conducting a patient history of suspected migraine[2,3]

Pain pattern

- **When** and **how** do headaches **begin**?
- Are they **episodic** or **chronic**?
- **How long** do headaches last?
- How **frequent** is headache pain?
- Are there factors that **trigger** an attack?

Associated symptoms

- Do other **symptoms precede the attack**?
- Are there any **symptoms that accompany the attack** (e.g., nausea, photophobia, phonophobia)?

Nature of pain

- What is the **location** of the pain?
- How **severe is** the pain?

Medical history

- Has there been any experience of **depression, anxiety and/or sleep disorders**?
- Are there any **comorbidities** such as asthma, hypothyroidism, or hypertension?

Treatment history

- What **previous and current treatments** have been taken and when?
- To exclude **medication overuse headache,**[a] what acute headache medications have been taken?
- What **non-headache specific treatments** have been taken?
- If treatment was **discontinued**, why?

Family and social history

- Is there a **family history** of migraine?
- How have the headaches **impacted your lifestyle?**
- Have there been any **sleep disturbances**?

[a]Medication overuse: ≥15 days/month use of simple (non-opioid) analgesics for >3 months; ≥10 days/month use of opioids, triptans, ergotamines, or their combination analgesics for >3 months.[4]

1. Martin VT, et al. Ann Med;2021:53:1979–1990; 2. Weatherall MW. Ther Adv Chronic Dis;2015:6:115–123; 3. Ravishhankar K. Ann Indian Acad Neurol 2012;15:7–14; 4. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.

Assess: primary headache disorders

Differential diagnoses: characteristics of primary headache disorders

Migraine[1]

Headache characteristics:

Usually unilateral in location

4–72 hours

Moderate or severe intensity

Usually pulsating pain

Accompanying symptoms:

Photophobia, phonophobia, nausea, vomiting

Often aggravated by routine physical activity

Tension-type headache[1]

Headache characteristics:

Typically bilateral or circumferential

Hours to days[a]

Mild or moderate intensity

Usually pressing or tightening pain

Accompanying symptoms:

Often none; sometimes photophobia or phonophobia (but not both); sometimes mild nausea in chronic tension-type headache

Not aggravated by routine physical activity

Cluster headache[1]

Headache characteristics:

Strictly unilateral and orbital, supraorbital, and/or temporal

15–180 minutes

Severe or very severe

Overwhelming pain

Accompanying symptoms:

Ipsilateral to the headache: cranial autonomic symptoms, e.g., conjunctival injection,[b] lacrimation (tearing) and nasal congestion

Associated with restlessness or agitation

[a]Or unremitting; [b]Increased redness of the eye due to enlargement of conjunctival vessels.[2]

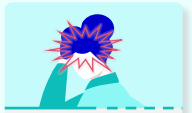
1. Eigenbrodt AK, et al. Nat Rev Neurol 2021;17:501–14; 2. Park IK, et al. Invest Ophthalmol Vis Sci 2013;54:5249–57.

Assess: apply ICHD-3 diagnostic criteria to determine migraine category

Assess

A patient's clinical history should be evaluated against diagnostic criteria to aid migraine diagnosis

The ICHD-3 provides diagnostic criteria for three main categories of migraine[1]

Migraine categories				
 **Migraine *without* aura** History of ≥5 attacks	Headache attacks lasting **4–72 hours** *(when untreated or unsuccessfully treated*	**With ≥2 of the following characteristics:** • Unilateral location • Pulsating quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity[a]	**Accompanied by ≥1 of the following symptoms:** • Nausea and/or vomiting • Photophobia AND phonophobia	Symptoms not better accounted for by another ICHD-3 diagnosis
 **Migraine *with* aura[b]** History of ≥2 attacks	Recurrent migraine aura symptoms lasting **5–60 minutes** that accompany or are followed **within 60 minutes**, by headache which may not fulfil criteria for migraine with aura	**With ≥3 of the following characteristics:** • ≥1 aura symptom that spreads gradually over ≥5 minutes • ≥2 aura symptoms that occur in succession • Individual aura symptoms of 5–60 minutes • ≥1 unilateral[c] aura symptom • ≥1 positive aura symptom e.g., scintillations/pins and needles • Aura with/followed by headache within 60 min	**≥1 of the following fully reversible aura symptoms:** • Visual • Sensory • Speech and/or language • Motor • Brainstem • Retinal	Symptoms not better accounted for by another ICHD-3 diagnosis Transient ischemic attack excluded
 **Chronic migraine** Attacks on ≥15 days/month for >3 months	**≥5 headache attacks** meeting criteria for migraine with or without aura	**With ≥1 of the following characteristics on ≥8 days/month for >3 months:** • Features of migraine without aura • Features of migraine with aura • Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative		Symptoms not better accounted for by another ICHD-3 diagnosis

ICHD-3, International Classification of Headache Disorders (3rd edition).
;[a]E.g., walking or climbing stairs; [b]Migraine with aura can be subcategorized as typical aura, brainstem aura (≥2 brainstem symptoms, e.g., dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, decreased consciousness), hemiplegic migraine (motor weakness) or retinal migraine (monocular visual disturbances); [c]Aphasia is always unilateral while dysarthria may or may not be.

Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.

Assess: assessing secondary headaches

Secondary headaches are those in which the headache is a symptom of another disorder recognized as a potential underlying cause[1]; patients with suspected secondary headache require a diagnostic workup that depends on the red flag identified and suspected underlying disease[2]

SNOOP4 and **SNNOOP10+** are red flag detection tools used to identify potentially life-threatening secondary headaches[2-4]

SNOOP4				
Red flag sign or symptom	**History and examination findings**	**Secondary headache causes**		**Diagnostic workup**
Systemic	• Signs of infection (e.g., fever, chills, weight loss) • Secondary risk factors include HIV or systemic cancer[5]	• Infection • Malignancy	• Rheumatic disease • Giant cell arteritis	• Neuroimaging • Lumbar puncture
Neurologic	• Abnormal neurologic examination[a] • Change in behavior or personality	• Malignancy • Inflammatory disorder	• Infection	
Onset (sudden)	• Headache reaching peak intensity in <1 minute (thunderclap, often triggered by subarachnoid hemorrhage or RCVS[6,b])	• Subarachnoid hemorrhage • Stroke	• RCVS	• Head CT • Lumbar puncture (if CT negative)
Older age at onset	• New onset headache at age >50 years	• Malignancy • Infection	• Giant cell arteritis	• MRI
Pattern change	• Change in headache pattern or characteristics • Progressive headache[c]	• Malignancy • Inflammatory or vascular disorder		
Precipitated by Valsalva maneuver	• Headache precipitated by Valsalva maneuver, sneezing, coughing, or exercise	• Chiari malformation type 1 • Posterior fossa lesions • Intracranial hypertension or hypotension	• Malignancy • Arachnoid cysts • Subdural hematoma	• Neuroimaging
Postural	• Headache precipitated or aggravated by postural change	• Intracranial hypertension • Intracranial hypotension		• Neuroimaging • Lumbar puncture • MRI with gadolinium[d]
Papilledema	• Papilledema, visual obscurations, diplopia, or field defects	• Intracranial hypertension • Inflammatory disorder	• Malignancy	• Thorough funduscopic examination

[a]E.g. confusion, impaired consciousness.[2,7] [b]Factors associated with RCVS include: sexual activity, postpartum state, vasoactive drugs, autoimmune disorders, temperature differences, air travel, and COVID-19 infection.[8] [c]Loss of headache-free periods. [d]To rule out dural enhancement with suspected CSF leak.[2]

CT, computed tomography; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; RCVS, reversible cerebral vasoconstriction syndrome; SNOOP, systemic symptoms, neurological signs, onset, older age at onset, and prior medical history.

1. Ravishhankar K. Headache 2016;56:1685-1697; 2. Martin VT, et al. Ann Med;2021:53:1979–1990; 3. Do TP, et al. Neurology 2019;92:134–144; 4. Dodick DW. Semin Neurol 2010;30:74–81; 5. Smith JH. Practical Neurology, March/April 2018: 40–49; 6. Schwedt TJ. Continuum (Minneap Minn) 2015;21:1058–71; 7. Micieli A and Kingston W. Front Public Health 2019;7:52; 8. Ribas MZ, et al. Egypt J Neurol Psychiatric Neurosurg 2023;59:5.

Assess: assessing secondary headaches

SNNOOP10 retains the red flags of SNOOP4 and adds additional signs or symptoms of related secondary headaches[1,2]

SNOOP4
Red flag sign or symptom
Systemic
Neurologic
Onset (sudden)
Older age at onset
Pattern change
Precipitated by Valsalva maneuver
Postural
Papilledema

SNNOOP10	
Additional red flag sign or symptom	**Notes**
Neoplasm in history	Relevant accompanying symptoms include emesis, headache duration ≤10 weeks, atypical headache pattern, pulsating quality and moderate to severe intensity, gait instability, and extensor plantar response
Progressive headache and atypical presentations	Not commonly described and defined in the literature; may be the only signs of serious underlying pathology
Pregnancy or puerperium	Headaches during this period have a higher risk of severe pathology due to physiologic changes and interventions
Painful eye with autonomic features	Can be due to a structural lesion; neuroimaging is recommended
Posttraumatic onset of headache	Headache occurring directly in relation to a trauma is a red flag
Pathology of the immune system (such as HIV)	The risk of severe pathology is dependent on the degree of immunosuppression
Painkiller overuse or new drug at onset of headache	Medication overuse is the most common cause of a secondary headache; onset of headache due to a new drug can be a sign of incompatibility with the given drug

1. Dodick DW. Semin Neurol 2010;30:74–81; 2. Do TP, et al. Neurology 2019;92:134–144.

Assess: when to consider referring for neuroimaging

Neuroimaging is occasionally required to confirm or reject suspected secondary headache[1]

AHS guidelines recommend *against* neuroimaging in patients with headaches consistent with migraine who have a normal neurologic examination and there are no atypical features or **red flags** present[2]

Strong recommendation, high quality evidence

AHS guidelines note that **neuroimaging may be considered** for presumed migraine for the following reasons[2a]:

Strong recommendation, low quality evidence

- Unusual, prolonged, or persistent aura
- Increasing frequency, severity, or change in migraine clinical features
- First or worst migraine
- Migraine with brainstem aura
- Confusional migraine
- Hemiplegic migraine
- Late-life migrainous accompaniments
- Migraine aura without headache
- Side-locked migraine
- Post-traumatic migraine

MRI is preferred to CT as it provides a higher resolution and avoids harmful exposure to ionizing radiation[1]

- **MRI has its limitations** as it can also **detect clinically insignificant** findings (such as white matter lesions, arachnoid cysts, and meningiomas) which can alarm patients and lead to further unnecessary evaluations

[a]Most of these are consensus based with little or no literature support.[2]

AHS, American headache society; CT, computed tomography; MRI, magnetic resonance imaging.

1. Eigenbrodt AK, et al. Nat Rev Neurol 2021;17:501–14; 2. Evans RW, et al. Headache 2020;60:318-336.

Assess: assessing migraine in pregnancy

Pregnancy can increase the risk of some secondary headache disorders[1]

ACOG recommends careful screening and assessments of headache during pregnancy[2]

Secondary headaches should be carefully evaluated[2]:

- History
- Physical examination
- Other tests (e.g., imaging or spinal fluid examination), as appropriate

Strong recommendation; low-quality evidence

Features of secondary headache that warrant prompt attention[2]:

- "Thunderclap" headache
- Rapid onset
- Visual changes
- High blood pressure
- Vomiting
- Fever
- Neurologic deficits or altered consciousness

Good practice point

Primary headache disorders typically improve during pregnancy; therefore, HCPs should have[1]:

Lower threshold for further investigation

Higher clinical suspicion for secondary headache (particularly in the third trimester when vascular risk increases)

ACOG, American College of Obstetricians and Gynecologists; AHS, American Headache Society; HCP, healthcare practitioners.
[a]For additional information, please refer to the full guideline.
1. Negro A, et al. J Headache Pain 2017; 18:106; 2. Adapted from: ACOG Committee on Clinical Practice Guidelines–Obstetrics. Obstet Gynecol 2022;139:944–72;

Assess: diagnostic screening tools aid migraine diagnosis

Various screening tools are available to aid in the diagnosis of migraine

Screening tools

Headache diary
Can assist with re-evaluation of diagnosis at follow-up

Headache calendar
Records temporal occurrence of headaches and related events at follow-up

ID Migraine™ screener
Identifies individuals who are likely to have migraine based on their answers to three questions regarding headache-associated nausea, photophobia, and disability

Migraine Disability Assessment (MIDAS)
A brief, self-administered questionnaire designed to quantify headache-related disability over a 3-month period; the MIDAS score has moderately high test-retest reliability in headache sufferers and is correlated with clinical judgment regarding the need for medical care

Eigenbrodt AK. Nat Rev Neurol. 2021;17(8):501-514.

Assess: diagnostic screening tools aid migraine diagnosis

Headache diary can assist with re-evaluation of diagnosis at follow-ups[1–3]

Name (first name(s)): _____ (family name) _____

Record in this diary for 1 week. Start date: _____ / _____ / _____ Finish date: _____ / _____ / _____

Please read **the instructions** carefully. Then complete the following **every** evening at bedtime (where indicated, tick the most appropriate box or circle the most appropriate answer.

Please remember to bring this diary to your next appointment

1. Date (day/month)	/	/	/	/	/	/	/
2. Did you have a headache today? (circle one) (If no, the diary is completed today)	yes / no	yes / no	yes / no	yes / no	yes / no	yes / no	yes / no
3. At what time today did your headache start? (hours and minutes) (if It began yesterday and was still there today, draw a left arrow ←———)							
4. When did it go away? (hours and minutes) (if it is still there when you go to bed for the night, draw a right arrow ———→)							
5. On which side is/was the headache (circle one)	right left both	right left both	right left both	right left both	right left both	right left both	right left both

1. Eigenbrodt AK. Nat Rev Neurol. 2021;17(8):501-514. 2. Stewart WF et al. Pain. 2000;88(1):41-52. 3. European Headache Federation. Accessed June 20, 2024. https://static-content.springer.com/esm/art%3A10.1186%2Fs10194-018-0899-2/MediaObjects/10194_2018_899_MOESM16_ESM.pdf.

Assess: diagnostic screening tools aid migraine diagnosis

Headache calendar records temporal occurrence of headaches and related events at follow-ups[1,2]

YEAR: **NAME:** **DOB:**

Symptomatic drugs:

Daily prophylactic drugs:

Hormones:

Other regular medication:

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
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1. Eigenbrodt AK. Nat Rev Neurol. 2021;17(8):501-514. 2. European Headache Federation. Accessed June 20, 2024. https://static-content.springer.com/esm/art%3A10.1186%2Fs10194-018-0899-2/MediaObjects/10194_2018_899_MOESM17_ESM.pdf.

Assess: diagnostic screening tools aid migraine diagnosis

The ID Migraine™ screener can help increase the recognition of migraine in previously undiagnosed individuals[1,2]

The 3-item **ID Migraine screener** is a validated and reliable tool that may help rapidly diagnose migraine in the primary care setting:

	1.	Has a headache limited your activities for a day or more in the last 3 months?
	2.	Are you nauseated or sick to your stomach when you have a headache?
	3.	Does light bother you when you have a headache?
		Total (Questions 3)

If the patient responds affirmatively to 2 or all 3 items, a migraine diagnosis is likely[a]

[a]Testing positive ≥2 time yields a sensitivity of 0.81 (95% CI, 0.77–0.85).

1. Lipton RB et al. Neurology. 2003;61(3):375-382. 2. de Mattos ACM, et al. Arq Neuro-Psiquiatr. 2017;75 (7):446-450.

Assess: diagnostic screening tools aid migraine diagnosis

The Migraine Disability Assessment (MIDAS)[1,2]

The **MIDAS** (Migraine Disability Assessment) questionnaire was put together to help you measure the impact your headaches have on your life.

INSTRUCTIONS: Please answer the following questions about ALL of the headaches you have had in the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months.
Please take the completed form to your healthcare professional.

1.	On how many days in the last 3 months did you miss work or school because of your headaches?
2.	How many days in the last 3 months was you productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school
3.	On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?
4.	How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)
5.	On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?
	Total (Questions 1-5)

What your Physician will need to know about your headache:

A.	On how many days in the last 3 months did have a headache? (If a headache lasted more than 1 day, count each day.)
B.	On a scale of 0-10, on average how painful were these headaches? (where 0=no pain at all, and 10=pain as bad as it can be.)

MIDAS Grade	Definition	MIDAS Score
I	Little or No Disability	0-5
II	Mild Disability	6-10
III	Moderate Disability	11-20
IV	Severe Disability	21+

1. Stewart WF et al. *Pain*. 2000;88(1):41-52. 2. Lipton RB,et al. *Handb Clin Neurol*. 2010;97:23-32

Assess: referring to a specialist

Reasons for specialist referral for patients with migraine, TTH, or MOH:
A migraine diagnosis cannot be confirmed
Diagnosis of any of the following, which are best managed by specialists: • migraine with aura including motor weakness • chronic migraine • cluster headache • trigeminal neuralgia • persistent idiopathic facial pain
Serious secondary headache or serious etiology are suspected
Unusual migraine aura, especially: • prolonged aura (duration >1 hour) • aura featuring brainstem symptoms and/or motor weakness • new aura without headache in a patient >50 years and in the absence of a prior history of migraine
• Persistent management failure
• Comorbid disorders requiring specialist management

MOH; medication overuse headache; TTH, tension-type headache.
Steiner TJ, et al. J Headache Pain 2019;20;57.

Assess: patient centricity and education have key roles in the diagnosis of migraine

- Appropriate explanation and reassurance needed
- Identify predisposing and/or trigger factors
- Identify migraine severity and level of disability
- Shared decision-making on realistic goals

Tailor treatment strategy to individual needs and symptoms

Eigenbrodt AK. Nat Rev Neurol. 2021;17(8):501-514.

Assess: diagnosis and assessment of migraine

Summary

Key recommendations for diagnosing migraine

History and physical exam

Exclude secondary headache
Screen for presence of red flags (SNOOP4 or SNNOOP10)
(−) → *Identify primary headache disorder*
(+) → Secondary headache

Identify primary headache disorder
ID Migraine™ screen
If necessary, refer to headache specialist
(−) → **Diagnose primary headache disorder** such as tension-type or cluster headaches using **ICHD-3 criteria**
(+) → **Diagnose migraine**

ICHD-3, International Classification of Headache Disorders (3rd edition); SNOOP4, Systemic symptoms, Neurological signs, Onset (sudden), Older age at onset, Pattern change, Precipitated by Valsalva maneuver, Postural, and Papilledema; SNNOOP10, SNOOP4 plus Neoplasm in history, Progressive headache and atypical presentations, Pregnancy or puerperium, Painful eye with autonomic features, Posttraumatic onset of headache, Pathology of the immune system (such as HIV), and Painkiller overuse or new drug at onset of headache.
Martin VT et al. Ann Med 2021;53:1979-1990.

Treat: an individualized treatment management plan should be implemented following diagnosis

American Headache Society 2021 Consensus Statement

Acute migraine treatment[1,2]

- For patients with a confirmed diagnosis of migraine

Preventive migraine treatment[1]

- For patients whose attacks significantly interfere with daily routines despite acute treatment
- For those who have frequent attacks, intolerance or contraindication(s) to acute treatments, or failure or overuse of acute treatments
- Based on patient preference

Migraine treatment in special populations[3,4]

- Pregnancy
- Breastfeeding

1. Ailani J, et al. Headache 2021;61:1021–39; 2. Headache Classification Committee of the International Headache Society. Cephalalgia 2018;38:1–211; 3. Lucas S. Obstet Gynecol 2019;134:211; 4. ACOG Committee on Clinical Practice Guidelines–Obstetrics. Obstet Gynecol 2022;139:944–72.

Treat: **acute** migraine treatment aims to stop attacks, or reduce headache severity and other associated symptoms

2021 AHS Consensus Statement:

Goals of **acute** migraine treatment

1. **Provide rapid symptomatic relief without recurrence**
2. **Restore function**
3. **Minimize the need for rescue medications or repeat dosing**
4. **Optimize self-care and reduce healthcare utilization**
5. **Minimize adverse events**
6. **Reduce overall treatment costs**

Acute treatments

AHS, American Headache Society.
The AHS Consensus Statement provides timely recommendations for clinicians and is not intended to be, and should not be understood or applied as, a Clinical Practice Guideline.
Adapted from: Ailani J, et al. Headache 2021;61:1021–39.

Treat: **acute** migraine treatment aims to stop attacks, or reduce headache severity and other associated symptoms

Treat

Migraine-Specific Treatments[1]

- Triptans
- Ergotamine derivatives
- Ditans
- CGRP receptor antagonists (gepants)
- Neuromodulation devices

Nonspecific Treatments[1]

- NSAIDs[a]
- Acetaminophen
- Others (combination analgesics)

FDA Approved Acute Migraine Treatments:

Year of approval of initial product within class

AHS Consensus >

[a]Celecoxib oral solution is approved as a migraine-specific treatment[1]

CGRP, calcitonin gene-related peptide; FDA, Food and Drug administration; NSAIDs, non-steroidal anti-inflammatory drugs.

1. Ailani J et al. *Headache*. 2021;61:1021-1039. 2. Sumatriptan. Package insert. GlaxoSmithKline. 3. FDA. https://www.accessdata.fda.gov/drugsatfda_docs/NDA/97/020148_migranal_toc.cfm. Accessed April 6, 2022. 4. FDA https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211280Orig1s000TOC.cfm. Accessed April 6, 2022. 5. FDA https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=211765. Accessed April 6, 2022.

Treat: **acute** migraine treatment aims to stop attacks, or reduce headache severity and other associated symptoms

Acute treatment of migraine

The AHS 2021 Consensus Statement recommends that all patients with a confirmed diagnosis of migraine should be offered acute pharmacological and/or nonpharmacological treatment[1]

The AHS 2021 Consensus Statement[1]

Nonpharmacologic interventions include counseling patients on the benefits of:

- Proper nutrition
- Regular exercise
- Adequate hydration
- Proper sleep
- Stress management
- Maintaining a migraine diary

Mild-to-moderate attacks → **NSAIDs, nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations**

Moderate-to-severe attacks OR **Mild-to-moderate attacks that respond poorly to nonspecific medications** → **Migraine-specific agents (triptans, ergotamine derivatives, gepants[a], ditans)**

Criteria for initiating gepants, ditans or neuromodulatory devices for acute treatment[1]:

- Contraindication or inability to tolerate triptans **or**
- Inadequate response to ≥ 2 oral triptans

< Approval Timeline

[a]Among the available gepants: rimegepant, ubrogepant, and zavegepant are indicated for treatment of acute migraine.
NSAID, nonsteroidal anti-inflammatory drug.
1. Ailani J, et al. Headache 2021;61:1021–39.

Treat: **preventive** migraine treatment aims to reduce the frequency, severity, and duration of attacks

2021 AHS Consensus Statement on Preventive Treatments for Migraine

Patients with migraine should be considered for preventive treatment if:

Attacks significantly interfere with patient daily routines despite acute treatment

Patient has contraindications to and/or failures with acute treatments

Patient experiences ≥2 headache days per month based on the degree of disability[a]

Patient overuses acute treatments

Patient experiences tolerability issues with acute treatments

Patient preference for prevention

Prevention should be	Headache days/month	Degree of disability
Offered	6 or more 4 or more 3 or more	None Some Severe
Considered	4 or 5 3 2	None Some Severe

Overuse defined as follows:

Ten or more days per month for ergotamine derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused

Fifteen or more days per month for nonopioid analgesics, acetaminophen, and NSAIDs

[a]As measured by the MIDAS, Migraine Physical Function Impact Diary, or Headache Impact Test.
AE, adverse event; AHS, American Headache Society; HRQOL, health-related quality of life.
Ailani J et al. *Headache*. 2021;61:1021-1039.

Treat: **preventive** migraine treatment aims to reduce the frequency, severity, and duration of attacks

2021 AHS Consensus Statement:

Goals of **preventive** migraine treatment

1. Reduce attack frequency, severity, duration, and disability
2. Improve function and reduce disability
3. Improve responsiveness to and avoid escalation in use of acute treatment
4. Improve health-related quality of life
5. Reduce reliance on unwanted, poorly tolerated, or ineffective acute treatments
6. Optimize self-care and enhance sense of personal control
7. Reduce psychological symptoms and headache-related distress
8. Reduce overall treatment costs

Preventive treatments

AHS, American Headache Society.
The AHS Consensus Statement provides timely recommendations for clinicians and is not intended to be, and should not be understood or applied as, a Clinical Practice Guideline.
Adapted from: Ailani J, et al. Headache 2021;61:1021–39.

Treat: **preventive** migraine treatment aims to reduce the frequency, severity, and duration of attacks

Interventions with evidence of efficacy in migraine prevention[1]

- Anti-CGRP monoclonal antibodies
- Anticonvulsants
- Beta-Blockers
- CGRP receptor antagonists (gepants)
- Neurotoxin
- SSRIs
- Tricyclic antidepressants

Non-pharmacological interventions[1]

- Non-invasive neuromodulation
- Nutraceuticals
- Biobehavioral therapies
- Lifestyle modifications

FDA Approved Preventive Migraine Treatments:

Year of approval of initial product within class

AHS Consensus >

CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody; SSRI, selective serotonin reuptake inhibitor.
1. Ailani J et al. Headache. 2021;61:1021-1039. 2. FDA. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016762. Accessed May 6, 2022. 3. FDA. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018723. Accessed May 6, 2022. 4. FDA. https://www.accessdata.fda.gov/drugsatfda_docs/bla/2010/103000orig1s5215.pdf. Accessed May 6, 2022. 5. FDA. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-preventive-treatment-migraine. Accessed May 6, 2022. 6. FDA. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=212728. Accessed May 6, 2022.

Treat: **preventive** migraine treatment aims to reduce the frequency, severity, and duration of attacks

Treat

Includes off-label content

Preventive treatment of migraine

The AHS 2021 Consensus Statement recommends that preventive treatment should be considered for patients whose attacks significantly interfere with daily routines despite acute treatment; for those who have frequent attacks, intolerance or contraindication(s) to acute treatments, or failure or overuse of acute treatments; or based on patient preference[1a]

The AHS 2021 Consensus Statement[1] and the 2024 Updated Position Statement[2]

Use evidence-based treatments[1,2]

2024 Update: CGRP-targeting migraine therapies are a first-line option for migraine prevention. Initiation of these therapies should not require trial and failure of non-specific migraine preventive medication approaches.[2]

Classes of agents[b] with an FDA-approved indication for preventive treatment of migraine[c] include:

- **Oral treatments: anticonvulsants, beta-blockers, gepants**
- **Intramuscular injection: neurotoxin**
- **Subcutaneous injection: anti-CGRP monoclonal antibodies**
- **Intravenous infusion: anti-CGRP monoclonal antibodies**

Allow an adequate trial before switching[1]

Oral treatments:	Neurotoxin:	Anti-CGRP mAbs:
≥8 weeks at target therapeutic dose or usual effective dose	After ≥2 quarterly injections (6 months)	≥3 months (monthly administration) or ≥6 months (quarterly administration)

< Approval Timeline

CGRP, calcitonin gene-related peptide; HIT, Headache Impact Test; IV, intravenous; mAb, monoclonal antibody; MIDAS, Migraine Disability Assessment; MHD, monthly headache day; MMD, monthly migraine day.
[a]Overuse defined as use of ergotamine derivatives, triptans, opioids or combination analgesics on ≥10 days/month for >3 months, or use of nonopioid analgesics, nonsteroidal anti-inflammatory drugs or simple analgesics on ≥15 days/month for >3 months. "Frequent attacks" includes ≥3 monthly headache days with severe disability, ≥4 monthly headache days with some disability or ≥6 monthly headache days without disability; [b]Only specific medications within each class are recommended in the AHS 2021 Consensus Statement[1]; [c]The 2021 AHS Consensus Statement identifies additional agents with evidence of efficacy in migraine prevention which do not possess FDA approval for that use; see the Consensus Statement for the full list.[1]

1. Ailani J, et al. Headache 2021;61:1021–39; 2. Charles AC, et al. Headache 2024; 64:333-41.

Treat: unique considerations for special populations experiencing migraine

Migraine affects women during key stages in their lifecycle

Migraine is more common and disabling in women than in men

~3× more common in women than men[1,2]

The largest prevalence difference occurs at **30.2 years of age**[3]

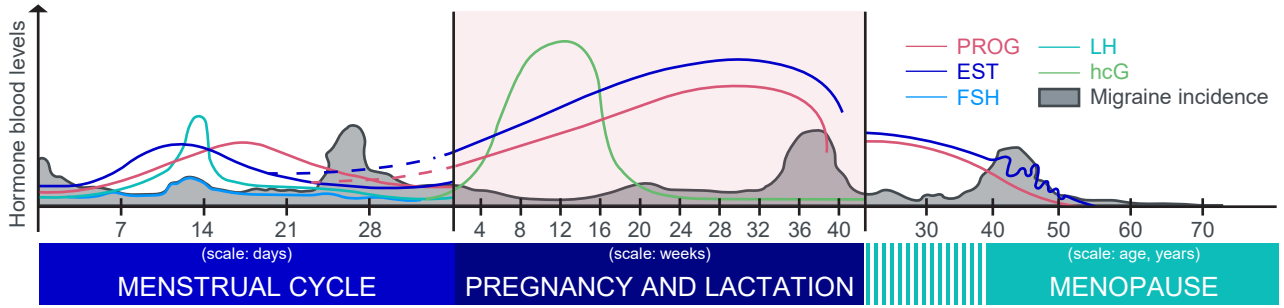
Migraine is the **leading cause of disability** among women of **reproductive age** (15–49 years) worldwide[6]

Compared with men with migraine, women with migraine experience:[4,5]

- **More frequent** headache
- **More intense** headache
- Higher risk of **chronification**
- Greater headache-related **disability**

Migraine can be triggered by fluctuations in hormones throughout a woman's lifetime[7]

Incidence of migraine rises steeply at puberty, peaks during the reproductive years and subsides after menopause[8]



Menstrually-related migraine +

Migraine treatment during pregnancy +

Migraine treatment during breastfeeding +

1. Andreou AP, et al. J Headache Pain. 2019;20:117:1–17; 2. Dodick DW. Migraine. Lancet. 2018;391:1315–30; 3. Victor TW, et al. Cephalalgia. 2010;30:1065–72; 4. Buse DC, et al. Headache. 2013; 53(8):1278–99; 5. Labastida-Ramirez A, et al. Cephalalgia. 2019;39:435-44; 6. Steiner TJ, et al. J Headache Pain. 2020; 21(1):4–7; 7. Sacco S, et al. J Headache Pain. 2012;13:177–189; 8. Krause DN, et al. Nat Rev Neurol 2021;17:621–33.

Treat: unique considerations for special populations experiencing migraine

Menstrually-related migraine

Estrogen withdrawal hypothesis: drop in estrogen during menses is thought to trigger migraine attacks

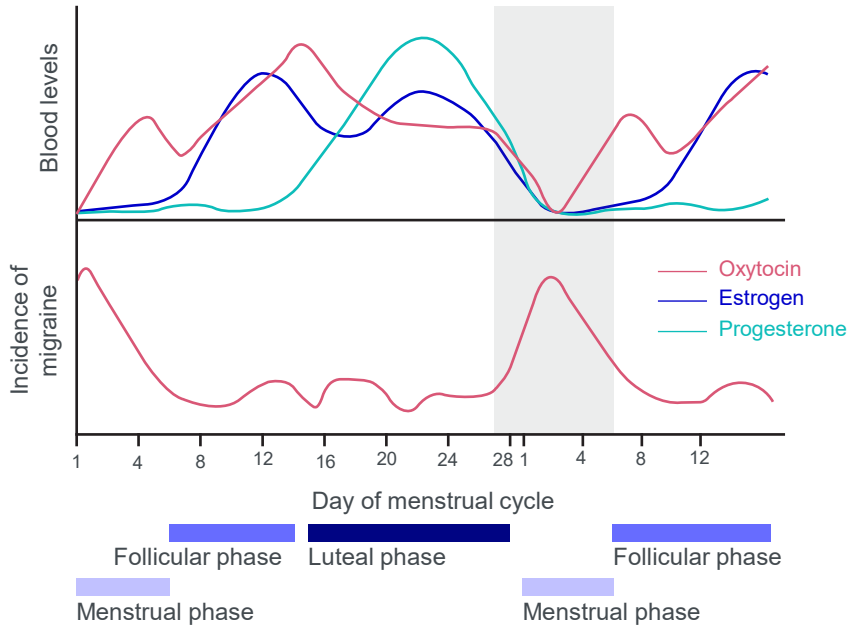
10% of women with migraine report migraine onset **at menarche**[1]

Among women who have **migraine without aura**, the greatest risk of an attack is around **menses**[2]

Estrogen withdrawal is thought to trigger the attacks, though the drop in oxytocin may also contribute[2]

Sharp decline in estrogen **shifts the balance toward a pro-migraine state** through increased CGRP signaling[2]

Fluctuations in the incidence of migraine and hormone blood levels over the menstrual cycle[2]



There is currently no specific treatment for menstrually-related migraine[3]

Figure adapted from Krause D, et al. 2021.
CGRP, calcitonin gene-related peptide.
1. Victor TW, et al. Cephalalgia 2010;30:1065–72; 2. Krause DN, et al. Nat Rev Neurol 2021;17:621–33; 3. Determan M. Pharmacy Times July 28, 2023.

Treat: ACOG recommends timely treatment of headaches during pregnancy

Treat

Includes off-label content

Introduction

Recognize

Assess

Treat

Evaluate

Acute Treatment[1a]

- ACOG strongly recommends **acetaminophen** for initial therapy for acute migraine
  Strong recommendation; very low-quality evidence
- ACOG recommends the addition of **metoclopramide[b] (alone or in combination with diphenhydramine[b])** for persistent headache in pregnancy
  Strong recommendation; moderate-quality evidence
- ACOG strongly recommends *against* the use of **combination products containing butalbital, ergot alkaloid-containing products, and opioid-containing medications** (e.g., codeine, oxycodone, hydrocodone or hydromorphone) to treat migraines in pregnancy
  Strong recommendation; moderate-quality evidence

Prevent[2a]

- AHS **generally recommends avoidance** of preventive pharmacotherapy during pregnancy, but the risks and benefits of treatment should be considered on an **individual basis**

ACOG, American College of Obstetricians and Gynecologists; AHS, American Headache Society.
[a]For additional information, please refer to the full guideline; [b]agent is not approved by the FDA for treatment of migraine.
1. ACOG Committee on Clinical Practice Guidelines–Obstetrics. Obstet Gynecol 2022;139:944–72; 2. Ailani J, et al. Headache 2021;61:1021–39.

Treat: unique considerations for special populations experiencing migraine

Treat

Includes off-label content

Migraine preventive treatments in pregnancy

ACOG recommends obstetricians review a patient's preventive migraine medications and consider therapy adjustments **due to the likely decrease in headache symptoms during pregnancy**
Strong recommendation; very low-quality evidence

For some preventive migraine therapies, there may be a lack of evidence-based data and a need for careful weighing of potential risks and benefits. Other therapies are not recommended due to a known risk of fetal toxicity[a]

May consider as first-line use for prevention[a]	Not recommended[a]	Only if potential benefit justifies the potential risk to the fetus[a]
Calcium channel blocker (amlodipine[b], nifedipine[b], verapamil[b])	Neurotoxin (onabotulinumtoxinA[c])	Neurotoxin (onabotulinumtoxinA[d])
	Anti-CGRP mAb (erenumab, galcanezumab, fremanezumab, eptinezumab)	Beta-blocker (atenolol[b], labetalol[b], metoprolol[b], propranolol)
Antihistamine (cyproheptadine[b], diphenhydramine[b])	NMDA receptor antagonist (memantine[b])	Benzodiazepine (alprazolam[b], clonazepam[b], diazepam[b], lorazepam[b])
	ACE inhibitor (lisinopril[b])	Antidepressant (amitriptyline[b], venlafaxine[b], nortriptyline[b])
	ARB (candesartan[b])	
	Anticonvulsant (topiramate, divalproex sodium, gabapentin[b], valproate sodium[b])	Anticonvulsant (carbamazepine[b], lamotrigine[b])
		Alpha-2 adrenergic agonist (clonidine[b])

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CGRP, calcitonin gene-related peptide; FDA, US Food and Drug Administration; mAb, monoclonal antibody; NMDA, N-methyl-d-aspartate receptor antagonist.
[a]For additional information, including dietary supplements and lifestyle modifications for headache prevention in pregnancy, please refer to the full guideline; [b]agent is not approved by the FDA for preventive treatment of migraine; [c]Not recommended for episodic nor tension-type headaches; [d]Balance risk and benefit for chronic migraine.

ACOG Committee on Clinical Practice Guidelines–Obstetrics. Obstet Gynecol 2022;139:944–72.

Treat: aim of treatment during breastfeeding is to achieve the highest efficacy and safety for the woman and infant[1]

Treat

Includes off-label content

Safety and recommended use of a drug during pregnancy is different from recommended use during breastfeeding[1]

Treatment options in lactating women for primary headache[3a]

- ACOG recommends the use of **acetaminophen, NSAIDs (with the exception of standard-dose aspirin), caffeine[b],** and **metoclopramide[b]** in lactating women for the treatment of migraine headache
  Strong recommendation; low-quality evidence

- ACOG recommends *against* use of combination products containing butalbital during lactation due to the absence of supplemental analgesia and the associated risks of medication overuse headache and addiction
  Strong recommendation; moderate-quality evidence
- ACOG recommends *against* the use of **medications containing opioids (codeine, hydrocodone, oxycodone, hydromorphone)** in lactating women for treatment of headaches
  Strong recommendation; moderate-quality evidence
- ACOG recommends *against* the use of ergot alkaloids in lactating women for the treatment of migraine headache
  Strong recommendation; low-quality evidence

- AHS generally recommends avoidance of **preventive pharmacotherapy** among breastfeeding women, but the risks and benefits of treatment should be considered on an individual basis[2]

ACOG, American College of Obstetricians and Gynecologists; AHS, American Headache Society; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody; NMDA, N-methyl-d-aspartate receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug.
[a]For additional information, please refer to the full guideline; [b]agent is not approved by the FDA for treatment of migraine.
1.Lucas S. Obstet Gynecol 2019;134:211; 2. Ailani J, et al. Headache 2021;61:1021–39; 3. ACOG Committee on Clinical Practice Guidelines–Obstetrics. Obstet Gynecol 2022;139:944–72.

Treat: an individualized treatment management plan should be implemented following diagnosis

Summary (1/2)

AHS Consensus Statement: Acute treatment of migraine[1]

- Mild-to-moderate attacks:
  - NSAIDs
  - Nonopioid analgesics
  - Acetaminophen
  - Caffeinated analgesic combinations
- Moderate-to-severe attacks or mild-to-moderate attacks that respond poorly to nonspecific medications:
  - Migraine-specific agents (triptans, dihydroergotamine, gepants, ditans)

AHS Consensus Statements: Preventive treatment of migraine[1,2,a]

- Oral:
  - Antihypertensives
  - Anticonvulsants
  - Beta-blockers
  - Antidepressants
  - Gepants
- Parenteral or IV:
  - Anti-CGRP mAbs
  - Neurotoxin[b]

[a] [b]Only specific medications within each class are recommended in the AHS 2021 Consensus Statement[1]; [b]for chronic migraine only.
AHS, American Headache Society; CGRP, calcitonin gene-related peptide; mAbs, monoclonal antibodies; NSAID, nonsteroidal anti-inflammatory drug.
1. Ailani J, et al. Headache 2021;61:1021–39; 2. Charles AC, et al. Headache 2024; 64:333-41.

Treat: an individualized treatment management plan should be implemented following diagnosis

Treat

Includes off-label content

Summary (2/2)

Special Populations

Menstrually-related migraine[1]

- There is currently no specific treatment for menstrually-related migraine

Treatment of migraine during pregnancy[2,3]

- **Acute**: acetaminophen; addition of metoclopramide[a] (alone or in combination with diphenhydramine[a]) for persistent headache
- **Preventive:** amlodipine[b], nifedipine[b], verapamil[b], cyproheptadine[b], diphenhydramine[b]

Treatment of migraine during breastfeeding[3]

- Acetaminophen
- NSAIDs (excluding standard-dose aspirin)
- Caffeine[a]
- Metoclopramide[a]

[a]agent is not approved by the FDA for acute treatment of migraine; [b]agent is not approved by the FDA for preventive treatment of migraine.
AHS, American Headache Society; CGRP, calcitonin gene-related peptide; mAbs, monoclonal antibodies; NSAID, nonsteroidal anti-inflammatory drug.
1. Determan M. Pharmacy Times July 28, 2023; 2. Ailani J, et al. Headache 2021;61:1021–39; 3. ACOG Committee on Clinical Practice Guidelines–Obstetrics. Obstet Gynecol 2022;139:944–72.

Evaluate: appraisal of treatment plans is important to ensure ongoing efficacy and safety

Evaluate

EHF & EAN Consensus statement for the management of migraine

Clinical management & follow-up

1 Evaluating response

- Assess effectiveness and tolerability regularly[a]
- **Suboptimal outcomes:** Review diagnosis, treatment strategy, dosing and adherence
- **Treatment failure:** Conclude only after thorough review of underlying reasons
- **Specialist referral:** Only if diagnostically challenging, difficult to treat or complicated by comorbidities

2 Managing complications

- Discourage or stop medication overuse
- **MOH:** Withdraw overused medications (ideally abruptly, except in case of opioids)
- **Chronic migraine:** Specialist referral and use of preventive treatment indicated

3 Recognizing comorbidities

- Identify comorbid conditions
- Select migraine drugs and adjust dose according to comorbidities
- Alleviate comorbidities if possible

4 Long-term follow-up

- **Primary care** should be **responsible** for the **long-term management** of **patients with migraine**, maintaining stability of effective treatment and reacting to change
- Timely transition from specialist care back to primary care with comprehensive treatment plans in place
- Patients can be referred to primary care once sustained efficacy with preventive therapy for up to 6 months is achieved with no substantial treatment-related adverse effects

CGRP, calcitonin gene-related peptide; EAN, European Academy of Neurology; EHF, European Headache Federation; MOH, medication overuse headache.
[a]Evaluate treatment responses shortly after initiation (after 2–3 months) or a change in treatment, and regularly thereafter (every 6–12 months). Note that the efficacy of CGRP antibodies and onabotulinumtoxinA should only be assessed after 3–6 months or 6–9 months, respectively.
Adapted from: Eigenbrodt AK, et al. Nat Rev Neurol 2021;17:501–14.

Evaluate: treatment plans and long-term follow-up

- **Engage** in long-term management in primary care to maintain stability of effective treatment and to react to change[1]
- **Manage** complications and discourage medication overuse[1]
- **Identify** and alleviate comorbidities if possible[1]
- **Appraise** treatment response to assess effectiveness and tolerability regularly[1]
  - Patient-oriented, validated outcome measures can help to verify that patients have experienced a meaningful response and identify the need for therapy adjustments[2]

1. Eigenbrodt AK. Nat Rev Neurol. 2021;17(8):501-14; 2. Ailani J, et al. Headache 2021;61:1021–39.

Evaluate: treatment plans and long-term follow-up

Various validated tools are available to measure response in treatment

Migraine Disability Assessment (MIDAS)[1,2]

Five scorable questions on school, social, and employment impact, frequency of headache and intensity of headache pain

Migraine Treatment Optimization Questionnaire (MTOQ-5)[3]

Five questions on functioning, rapid relief, consistency of relief, risk of occurrence, tolerability (to evaluate acute treatment response)

Migraine Assessment of Current Therapy (Migraine-ACT)[4]

Four questions on consistency of response, global assessment of relief, headache impact, emotional response (to evaluate acute treatment response)

Work Productivity and Activity Impairment Questionnaire: Migraine (WPAI:Migraine)[5]

Six questions on absenteeism, presenteeism, work productivity loss, activity impairment

1. Lipton RB, et al. Headache 2001;41:854–61; 2. Stewart WF, et al. Pain 2000;88:41–52; 3. Lipton RB, et al. Cephalalgia 2009; 29:751–9; 4. Dowson AJ, et al. Curr Med Res Opin 2004;20:1125–35; 5. Ford JH, et al. J Patient Rep Outcomes 2023;7:34;

Summary

- Migraine is a primary headache disorder that can be categorized into subtypes (migraine with or without aura, chronic migraine, episodic migraine) based on symptoms and headache frequency[1]
- It has a high socioeconomic and personal impact[2] and yet is widely underdiagosed[3]

Recognize

- Early identification of symptoms, triggers, and comorbidities may help to plan treatment plan and reduce the severity of or prevent migraine attack[4]

Assess

- Key recommendations for diagnosing migraine include:[5-7]
  - History and physical exam
  - Screen for presence of red flags
  - Identify primary headache disorder using diagnostic tools

Treat

- Acute treatments include: NSAIDs, nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations, triptans, ergotamine derivatives, gepants, ditans[8]
- Preventive treatments include: antihypertensives, anticonvulsants, beta-blockers, anti-CGRP mAbs, gepants, neurotoxin[8]

Evaluate

- Providers should engage in long-term follow-up to evaluate response to treatment, manage complications, and recognize comorbidities in patients
- Validated tools can assess disability, effectiveness of acute medications and quality of life[9-13]

NSAIDs, nonsteroidal anti-inflammatory drugs; CGRP, calcitonin gene-related peptide; mAbs, monoclonal antibodies.

1. IHS Headache Classification Committee. The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211; 2. Ashina M et al. Lancet. 2021;397:1485-98; 3. Buse DC, et al. Headache 2021;61:628–41; 4. American Migraine Foundation. The timeline of an attack, 2018: https://americanmigrainefoundation.org/resource-library/timeline-migraine-attack/; 5. Martin VT, et al. Ann Med;2021:53:1979–1990; 6. Weatherall MW. Ther Adv Chronic Dis;2015:6:115–123; 7. Eigenbrodt AK. Nat Rev Neurol. 2021;17(8):501-514; 8. Ailani J, et al. Headache 2021;61:1021–39; 9. Lipton RB, et al. Headache 2001;41:854–61; 10. Stewart WF, et al. Pain 2000;88:41–52; 11. Lipton RB, et al. Cephalalgia 2009; 29:751–9; 12. Dowson AJ, et al. Curr Med Res Opin 2004;20:1125–35; 13. Ford JH, et al. J Patient Rep Outcomes 2023;7:34