The MIGRAINE Puzzle and the PA

Insights and Strategies for Diagnosis and Management

RAPID RECAP

Learning Objectives

After participating in this activity, learners should be better able to:

1. Explain the prevalence, burden, and impact of migraine in different patient populations
2. Review the diagnostic criteria for migraine and its differential diagnosis from other headache disorders
3. Describe the role of CGRP in migraine pathophysiology
4. Compare and contrast clinical profiles of acute and preventative migraine treatments

Migraine is common, disabling, and associated with significant treatment-related burdens.[1]

- Approximately 15% of adults, globally and in the US, have migraine[2-4]
- Prevalence is 2- to 3-fold higher in women than men and ranges from 9%-19% across ethnic/racial groups in the US[3-6]
- Worldwide, headache is the second-leading cause of disability and the leading cause of disability among women 15-49 years of age[7]
- People in certain groups (e.g., African Americans, Latinx, remote communities) are less likely to receive appropriate diagnosis and care due to challenges such as discrimination/bias, socioeconomic status, insurance coverage, and transportation obstacles[6]
- Health status limits treatment options for people in some groups, including patients who are pregnant, breastfeeding, or may become pregnant; older patients; and patients with comorbidities[8-11]

Migraine is a complex neurovascular disorder involving multiple brain regions and signaling pathways, and calcitonin gene-related peptide (CGRP) plays a prominent role.[12]

- CGRP is a neuropeptide thought to contribute to migraine pathophysiology via pain signaling and roles in neurogenic inflammation (e.g., vasodilation, inflammatory cytokine release)[13-15]
- Newer acute and preventive therapies developed to inhibit CGRP activity are effective in migraine treatment[13,16]

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Migraine can be diagnosed by applying available criteria.[8]

Diagnostic Criteria for Primary Headache Disorders: Migraine[17]

Migraine Without Aura	Migraine With Aura	Chronic Migraine
≥5 attacks	≥2 attacks with:	Headache ≥15 days/month for >3 months, and:
Attacks lasting 4-72h when not successfully treated	≥1 fully reversible aura symptom: visual, sensory, speech and/or language, motor, brainstem, retinal	≥5 attacks fulfilling duration and/or symptom criteria of migraine without or with aura
At least 2 of: • Unilateral location • Pulsating quality • Moderate or severe pain • Aggravation by/causing avoidance of routine physical activity	At least 3 of: • Symptom spread over ≥5 min • ≥2 symptoms in succession • ≥1 unilateral symptom • ≥1 positive symptom • Aura accompanied by or followed within 60 min by a headache (might not meet criteria for headache in migraine without aura)	On ≥8 days/month for >3 months, fulfilling any of: • Symptom criteria for migraine without aura • Symptom criteria for migraine with aura • Believed by patient to be migraine and relieved by triptan or ergot derivative
At least one of: • Nausea and/or vomiting • Photophobia/ phonophobia		
Not better accounted for by another International Classification of Headache Disorders, edition 3 (ICHD-3) diagnosis		

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All people with migraine should be offered acute treatment.[8]

Pharmacotherapies for Acute Treatment of Migraine[8,16,18-22]

Category/Class	Agents (oral dosing unless indicated)
Therapies used to treat migraine, but not specific for migraine management	
Non-opioid analgesics/NSAIDs	Acetaminophen, aspirin, celecoxib[a], diclofenac, flurbiprofen, ibuprofen, ketoprofen, ketorolac (IM, IV, nasal spray), naproxen
Combination analgesics	Acetaminophen/aspirin/caffeine
Antiemetics	Chlorpromazine, droperidol, metoclopramide (oral, IM), prochlorperazine (oral, IM, suppository, promethazine)
Migraine-specific therapies[a]	
Ergotamine derivatives (5HT1B/1D/1F agonists)	Dihydroergotamine (IV, IM, SC, nasal spray)
Triptans (5HT1B/1D agonists)	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan (also ODT), sumatriptan (also SC, nasal spray), zolmitriptan (also ODT)
Ditans (5HT1F agonists)	Lasmiditan
Gepants (CGRP receptor antagonists)	Rimegepant (ODT), ubrogepant, zavegepant (nasal spray)

[a]US FDA approved for acute treatment of migraine.
5HT1B, 5HT1D, 5HT1F = serotonin receptors 1B, 1D, and 1F; CGRP = calcitonin gene-related peptide; NSAID = nonsteroidal anti-inflammatory drug; ODT = orally disintegrating tablet.

- Ergotamine derivatives and triptans are contraindicated for people with certain cardiovascular conditions, including ischemic heart disease[8,16,18]
- NSAIDs carry boxed warnings for risk of cardiovascular events and gastrointestinal bleeding[8,16,18]
- Lasmiditan has a warning to restrict driving for 8h after administration[23]
- Clinicians should discuss steps for avoiding medication overuse headache with patients taking agents from any categories/classes other than antiemetics or gepants[8]
- Use of gepants, ditans, or neuromodulatory devices is appropriate when there is a contraindication to, inability to tolerate, or inadequate response to triptans[8]

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Consider preventive migraine treatment in any of these situations[8]:

- Attacks interfere with daily living despite acute treatment
- Attacks are frequent
- Acute treatments are contraindicated, have failed, or are overused
- Acute treatments cause adverse events
- A patient would prefer preventive treatment

Pharmacotherapies for Preventive Treatment of Migraine[8,16,24-33]

Category/Class	Agents (oral dosing unless indicated)
Established/Probable Efficacy	
Antiepileptics	Divalproex sodium[a], topiramate[a], gabapentin, pregabalin
Beta-blockers	Metoprolol, propranolol[a], atenolol, nadolol, timolol[a]
Antihypertensives	Lisinopril, candesartan
Antidepressants	Amitriptyline, venlafaxine, duloxetine, nortriptyline
Other	Memantine
Neurotoxin	OnabotulinumtoxinA[a] (IM by trained clinician every 12 weeks) for chronic migraine
CGRP-based Therapies[a]	
Monoclonal antibodies	Galcanezumab (SC, monthly), fremanezumab (SC, every 3 months), erenumab (SC, monthly), eptinezumab (IV, every 3 months)
Receptor antagonists (gepants)	Rimegepant (ODT) for episodic migraine, atogepant

[a]US FDA approved for preventive treatment of migraine.
CGRP = calcitonin gene-related peptide; ODT = orally disintegrating tablet

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Pharmacotherapies for Preventive Treatment of Migraine[8,16,24-33]

- Divalproex sodium is contraindicated in pregnant women and women of childbearing potential not using effective contraception[25]
- Lisinopril and candesartan have boxed warnings against use in pregnancy[26,27]
- Current guidelines generally recommend avoiding preventive therapies for patients who are pregnant, breastfeeding, or trying to conceive[8]
- Guidelines recommend initiating CGRP-based therapies for migraine prevention after trials of agents from other classes[8,16]

Key Takeaways

- Migraine is common and a leading cause of disability worldwide
- Clinicians need to be aware of challenges and disparities so they can help patients get treatments they need, including newer therapies
- Accurate diagnosis is the first step to appropriately managing migraine
- Many acute and preventive migraine therapies are available to help individualize care

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