The MIGRAINE Puzzle and the PA

Insights and Strategies for Diagnosis and Management

Provided by AAPA American Academy of PAs and The France Foundation

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Disclosures

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- The planners, reviewers, editors, staff, CME committee, or other members at the AAPA and TFF who control content have no relevant financial relationships to disclose

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Learning Objectives

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

What Is Migraine?

- Not just a bad headache[1]
- Disabling neurovascular disorder[1,2]
- Characteristic symptoms[1]
- Variable presentation[1]

- **Four phases:** not experienced by all people and might not be experienced by a given person in all their attacks[1-3]
  - **Prodrome:** hours or days before an attack
  - **Aura:** symptoms shortly before an attack
  - **Headache:** duration of hours to days
  - **Postdrome:** "migraine hangover"

1. American Migraine Foundation. https://americanmigrainefoundation.org/resource-library/what-is-migraine/; 2. Karsan N et al. *Int J Mol Sci*. 2023;24:11993; 3. Kowacs P, et al. *Arq Neuropsiquiatr*. 2023;81:1084-1097.

Migraine Pathophysiology Is Complex

Some neuropeptides implicated in migraine pathophysiology:

- CGRP (calcitonin gene-related peptide)
- PACAP (pituitary adenylate cyclase activating polypeptide)
- VIP (vasoactive intestinal peptide)
- NPY (neuropeptide Y)
- AgRP/POMC/CART (agouti-related peptide/proopiomelanocortin/cocaine and amphetamine-related transcript)
- Orexins A and B
- Leptin
- Substance P and neurokinin A

Karsan N et al. *Int J Mol Sci*. 2023;24:11993.

Notable Events in CGRP-Based Therapy Development

1984
CGRP identified as potent vasodilator in the TGVS

1985
CGRP proposed to play a role in migraine

1988
CGRP release measured on trigeminal stimulation in humans

1990
CGRP release measured during migraine in humans

1993
Sumatriptan normalizes CGRP in parallel with migraine headache relief

1994
Triptans shown to inhibit trigeminal CGRP release

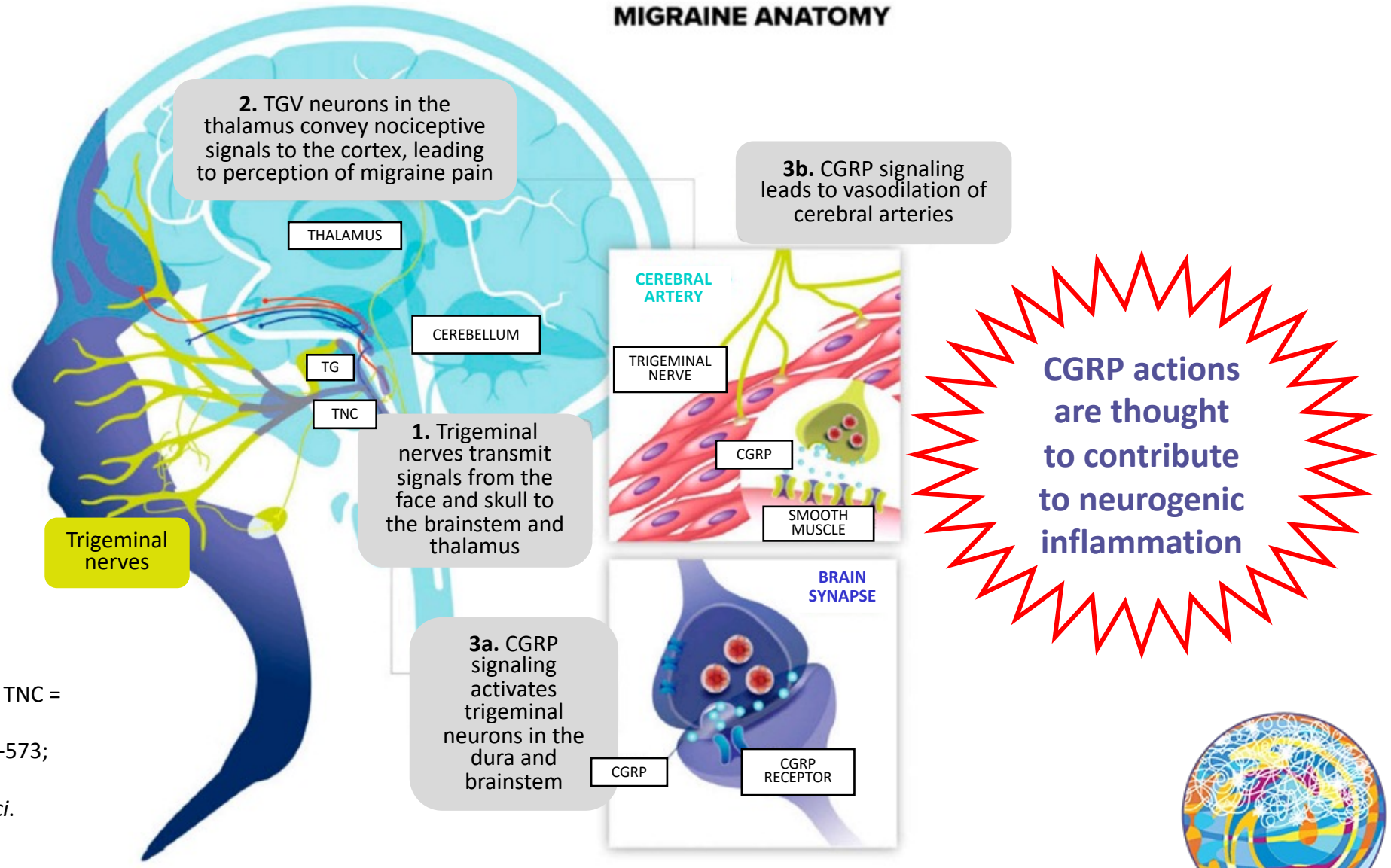
2002
CGRP infusion triggers migraine in PwM

2004
CGRP receptor blocker alleviates migraine headache

PwM = people with migraine; TGVS = trigeminovascular system.

Edvinsson L, et al. *Nat Rev Neurol*. 2018;14(6):338-350.

CGRP in Migraine Pathophysiology[1-4]



CGRP = calcitonin gene-related peptide; TG = trigeminal ganglion; TGV = trigeminovascular; TNC = trigeminal nucleus caudalis.

1. Davis L, Torphy B. *Br J Pain*. 2022;16(5):560-573; 2. Cutrer FM. In: Swanson JW, ed. UpToDate. UpToDate; 2024; 3. Karsan N et al. *Int J Mol Sci*. 2023;24:11993; 4. Lipton RB et al. *J Neurol*. 2023;270:5692-5710.

Migraine Is Common and a Leading Cause of Disability

- Approximately 15% of adults have migraine, globally and in the U.S.[1-3]
  - > 40% having ≥ 4 monthly headache days[4]
  - 2- to 3-fold more women than men have migraine[2-4]
  - Reported rates range (9%-19%) among racial groups in the U.S.[5,6]
- Globally, migraine is[7]
  - The **second leading cause of disability**
  - The **leading cause of disability among women 15-49 years of age**
  - **Responsible for most of the disability attributable to headache disorders**

MHD = monthly headache days.

1. Steiner TJ, Stovner LG. *Nat Rev Neurol.* 2023;19(2):109-117; 2. Stovner LJ, et al. *J Headache Pain*. 2022;23:34; 3. Burch R, et al. *Headache*. 2021;61:60-68; 4. Lipton RB, et al. *Headache*. 2022;62:122-140; 5. Najib U, et al. *Curr Pain Headache Rep*. 2019;23(2):9; 6. Kiarashi J, et al. *Neurology*. 2021;97:280-289; 7. Steiner TJ, et al. *J Headache Pain*. 2020;21:137.

Patient Challenges Associated With Migraine

Compared with people who do not have migraine, people with migraine have:

- More HCP and ED visits[1]
- Higher annual direct healthcare resource utilization costs[1]
- Higher annual indirect costs due to absenteeism/ presenteeism[1]
- Higher risk of many comorbid conditions, including insomnia, depression, stroke[1-3]
- Higher rates of disability[1]

ED = emergency department; HCP = health care professional.

1. Buse DC, et al. *J Manag Care Spec Pharm*. 2020;26(10):1334-1343; 2. Buse DC, et al. *J Headache Pain*. 2020;21:23; 3. Kalkman DN, et al. *Eur Heart J*. 2023;44:2815-2828.

Suboptimal Care: Challenges, Barriers, and Inequities

Suboptimal care in PwM

- 41% without diagnosis[1]
- 40% eligible for preventive medication, but only 17% using it[1]
- As few as 12% obtained consultation, accurate diagnosis, and appropriate pharmacological treatment[2]

Challenges, Barriers, and Inequities

- Limited care availability and access[3,4]
- Failure to receive accurate diagnosis[4]
- Not offered appropriate medication[4]
- Limited treatment options based on health status (e.g., pregnancy, CVD)[5,6]
- Bias/discrimination[4,6]
- Socioeconomic/insurance status[4,7]
- Geographical challenges[4,7]

CVD = cardiovascular disease; PwM = people with migraine.

1. Lipton RB, et al. *Headache*. 2022;62:122-140; 2. Buse DC, et al. *Headache*. 2021;61:628-641; 3. Najib U, et al. *Curr Pain Headache Rep*. 2019;23(2):9; 4. Buse DC, et al. *Headache*. 2021;61:628-641; 5. Raffaelli B, et al. *J Headache Pain*. 2023;24:167; 6. Ailani J, et al. *Headache*. 2021;61:1021-1039; 7. Kiarashi J, et al. *Neurology*. 2021;97:280-289.

Case #1

Increasing Headache Frequency

Markie

- 26-year-old African American female
- Chief complaint:
  - Intermittent headaches (HAs) x 5 years
  - Increasing frequency x1 year
- Social history:
  - Masters program
  - Recently on university student insurance, changed from parents (out of state, rural)
- Past medical history:
  - None
- Medications:
  - Oral contraceptive pill

Markie: Headache History

- MHD: 6
- Duration: many hours; not usually more than 1-2 days
- Location: frontal, unilateral, or bilateral
- Intensity: moderate-severe, 6-8/10
- Character: pressure
- Trigger(s): studying, stress, decreased sleep, not having morning coffee
- Additional symptom(s): nausea, no vomiting

MHD = monthly headache days.

Markie: Treatment History

- PCP: PA at rural clinic near home
  - Diagnosis: tension-type headache
  - Treatment:
    - NSAIDs, about 6 days/month
    - Stress management
    - Not entirely helpful

Markie: Treatment History

- Headache more frequent, interfering with her learning
- Couldn’t find a local provider in network
- ED visit(s)
  - 3-4 occasions
  - CT head: unrevealing
  - Treatments: IV fluids, magnesium sulfate, ketorolac, promethazine, diphenhydramine
  - Recommended a neurology consultation outpatient

ICHD-3 Diagnostic Criteria: Tension-Type Headache (TTH)

Infrequent: <1 day/month (average) Frequent: 1-14 days/month (average) Chronic: ≥15 days/month (average)

- At least 2 of the following 4 *(infrequent, frequent, or chronic)*
  - Bilateral X (sometimes)
  - Pressing or tightening (non-pulsating) X
  - Mild or moderate intensity
  - Not aggravated by routine activity
- Duration
  - *Infrequent or frequent:* 30 minutes to 7 days X
  - *Chronic:* hours to days, or unremitting
- Non-headache symptoms
  - *Infrequent or frequent:* **no** nausea or vomiting; **no more than one of** photophobia/phonophobia
  - *Chronic:* **no more than one of** mild nausea/photophobia/phonophobia; **no** moderate/severe nausea or vomiting
- Not better accounted for by another ICHD-3 diagnosis

ICHD-3 = International Classification of Headache Disorders, 3rd edition.

International Headache Society. *Cephalalgia*. 2018;38(1):1-211.

ICHD-3 Diagnostic Criteria: Migraine Without Aura

- ≥ 5 attacks
- Attacks lasting 4-72 hours* X
- At least two of the following:
  - Unilateral location X (sometimes)
  - Pulsating quality
  - Moderate or severe pain X
  - Aggravation by/causing avoidance of routine physical activity X
- At least one of the following:
  - Nausea and/or vomiting X
  - Photophobia/phonophobia
- And not better accounted for by another ICHD-3 diagnosis

ICHD-3 = International Classification of Headache Disorders, 3rd edition.
*When not successfully treated.
International Headache Society. *Cephalalgia*. 2018;38(1):1-211.

ICHD-3 Diagnostic Criteria: Migraine With Aura

≥ 2 attacks fulfilling criteria below

- ≥ 1 fully reversible aura symptom
  - Visual
  - Sensory
  - Speech and/or language
  - Motor
  - Brainstem
  - Retinal
- At least 3 of
  - Symptom spread over ≥ 5 min
  - ≥ 2 symptoms in succession
  - ≥ 1 unilateral symptom
  - ≥ 1 positive symptoms
  - Aura accompanied by or followed within 60 min by headache[a]

…and not better accounted for by another ICHD-3 diagnosis

ICHD-3 = International Classification of Headache Disorders, 3rd edition
[a]Might not meet criteria for headache in migraine without aura
International Headache Society. *Cephalalgia*. 2018;38(1):1-211.

P.I.N. the Diagnosis of Migraine: ID Migraine Screener

- At least 2 of the following are positive
  - Photophobia
  - Impaired function
  - Nausea

Lipton RB, et al. *Neurology*. 2003;61(3):375-382.

“Red Flags” Suggesting Secondary Headaches

SNOOP5[1-3]		
S	Systemic Secondary risks	Fever, weight loss, night sweats Cancer, HIV, immunocompromised state, trauma, OAC
N	Neurologic deficit, abnormal signs	Focal neurological deficit, confusion, impaired/altered LOC
O	Onset (time course)	Thunderclap (max intensity < 60 sec), wakes from sleep
O	Onset (age)	> 50 years: secondary HA until proven otherwise; consider giant cell arteritis < 5 years
P1	Previous HA history	First HA, different/change in HA
P2	Postural or positional aggravation	CSF pressure too high or low, inc/dec ICP
P3	Precipitated by Valsalva	Coughing, bending, sneeze, lift, bearing down, exertional
P4	Papilledema or pulsatile tinnitus	Vision changes/loss, inc ICP, IIH
P5	Pregnancy or peripartum	Preeclampsia, hypercoagulable, CSF leaks, treatment selection

CSF = cerebrospinal fluid; HA = headache; HIV = human immunodeficiency virus; ICP = intracranial pressure; IIH = idiopathic intracranial hypertension; LOC = level of consciousness; OAC = oral anticoagulation.

1. Dodick DW. *Adv Stud Med*. 2003;3(6C):5550-5555; 2. Dodick DW. *Semin Neurol*. 201-;30(1):74-81; 3. Do TP, et al. *Neurology*. 2019;92:134-144.

Markie: Making a Diagnosis

- Additional information
  - P.I.N. the diagnosis
    - Photophobia: prefers to rest in a dark room when she has a headache
    - Impaired function: limits daily activities, missed a few days of school
    - Nausea
  - SNOOP5 assessment: no “red flag” features
- Diagnosis: migraine without aura, episodic
- Markie will schedule an appointment for next week to discuss migraine treatment options

Race Has Been Associated With Care Disparity/Gaps in Migraine[1,2]

Examples of Disparity/ Care Gaps/Unmet Need[1]	Steps to Address Potential Care Disparity/Gaps for Markie
Compared with White patients, African American and Hispanic and/or Latino patients are significantly less likely to:[1] • ***Receive a migraine diagnosis*** • ***Receive appropriate migraine treatment*** • ***Receive effective analgesic therapy***	Systematic: Train providers to display cultural humility and deliver equitable care[1,2] Practice: • Accurate diagnosis: ICHD criteria applied to history • Documentation: headache type, impact to patient, treatments tried • Accurate diagnosis and documentation can help with prior authorization

ICHD = International Classification of Headache Disorders.

1. Kiarashi J, et al. *Neurology*. 2021;97:280-289; 2. Najib U, et al. *Curr Pain Headache Rep*. 2019;23(2):9.

Case #2

Seeking More Effective Acute Treatment

Iris

- 35-year-old Native American female
- Social History:
  - Lives in a rural town; drives several hours for medical care
  - Needs to drive for work
- Past medical history:
  - Migraine w/aura (20 years)
  - Peptic ulcer disease

Iris: Headache History

- MHD: 10 – 7 severe; often calls out of work
- Duration: about 24 hours
- Location: unilateral
- Intensity: gradual onset, gets to 8/10 on pain scale after 1-2 h
- Character: throbbing, worsens with movement
- Additional symptoms: visual aura, light and sound sensitivity

MHD = monthly headache days; NSAID – nonsteroidal anti-inflammatory drug; SQ = subcutaneous.

Iris: Treatment History

- Has had prior ED visits for pain control
- NSAIDs worked initially but no longer helpful
- Oral triptan (rizatriptan) prescribed 1 year ago at her last follow up
  - Helped about 25% of her migraines
  - Often found headaches would improve but return
- Reached out to her PCP after 6 months – prescription changed to sumatriptan SQ
  - Has found sumatriptan SQ sedating
  - Reluctant to use due to fear of injections
  - Often waits until she's in severe pain to use

MHD = monthly headache days; NSAID – nonsteroidal anti-inflammatory drug; SQ = subcutaneous.

Goals of Acute Treatment

- Optimal self-care (e.g., self-administration, reduced ED visits)[1,2]
- Rapid and consistent freedom from pain and associated symptoms[1,2]
- Restored ability to function[1,2]
- Minimal need for repeat dosing, rescue medications[1,2]
- Minimal or no adverse events
- Cost considerations[1]

Effective acute treatment can reduce:

- **Pain**
- **Symptoms**
- **Disability**

Suboptimal acute treatment is associated with higher:

- **Disability**
- **Risk of progression**

1. Ailani J, et al. *Headache*. 2021;61:1021-1039; 2. Ailani J, et al. *Continuum*. 2021;27 (3, HEADACHE);597-612.

Acute Therapies: Not Migraine Specific[1]

Category[1-3]	Agents (Oral Dosing Unless Indicated[1-3]	Common Adverse Effects and Precautions[2,3]
Non-opioid analgesics/ NSAIDs	• Acetaminophen • Aspirin • Celecoxib[a] • Diclofenac • Flurbiprofen • Ibuprofen • Ketoprofen • Ketorolac (IM, IV, nasal spray) • Naproxen	• **FDA warning (CV and GI risk) for NSAIDs** • **Discuss medication-overuse headache w/pts.** • NSAIDs (except aspirin) may increase risk of MI or stroke with increased duration of use in people with underlying CVD risk factors
Combination analgesics	Acetaminophen/aspirin/caffeine Sumatriptan/naproxen	• See NSAIDs and triptans (next slide) • **Discuss medication-overuse headache w/pts.**
Antiemetics	• Chlorpromazine • Droperidol • Metoclopramide (oral, IM) • Prochlorperazine (oral, IM, suppository) • Promethazine	• Drowsiness, dizziness, extrapyramidal symptoms • Avoid in patients with QT_c interval prolongation

[a]Oral solution approved for acute treatment of migraine with or without aura.[4]

1. Ailani J, et al. *Headache*. 2021;61:1021-1039; 2. Zhang N, Robbins MS. *Ann Intern Med*. 2023;176(1):ITC1-ITC16;3. Ailani J, et al. *Continuum*. 2021;27 (3, HEADACHE);597-612; 4. Celecoxib oral solution prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212157s002lbl.pdf.

Acute Therapies: Migraine Specific (Ergots, Triptans) All FDA Approved

Category/ Mechanism[1,3]	Agents (Oral Dosing Unless Indicated)[2,3]	Common Adverse Effects and Precautions[2,3]
Ergots 5HT1B/1D/1F agonists	Dihydroergotamine (IV/IM/SC/nasal spray)	• **FDA contraindications: use w/ potent CYP3A4 inhibitors; CVD** • **Discuss medication-overuse headache w/pts.** • Rhinitis, nausea, taste alteration, dizziness, vomiting, flushing
Triptans 5HT1B/1D agonists (some with 5HT1F affinity)	• Almotriptan • Eletriptan • Frovatriptan • Naratriptan • Sumatriptan (also SC, nasal spray) • Zolmatriptan (also ODT, nasal spray) • Rizatriptan (also ODT)	• **FDA contraindication: CVD** • **Discuss medication-overuse headache w/pts.** • Nausea, dizziness, somnolence, dry mouth, parasthesia, dyspepsia, hot/cold, chest pain/ tightness, flushing, heaviness, throat symptoms

About 30% of patients prescribed a triptan have insufficient response.[1]

5HT = serotonin; ODT = orally disintegrating tablet.

1. Ailani J, et al. *Headache*. 2021;61:1021-1039; 2. Zhang N, Robbins MS. *Ann Intern Med*. 2023;176(1):ITC1-ITC16; 3. Ailani J, et al. *Continuum*. 2021;27 (3, HEADACHE);597-612; 4. Zavegepant prescribing information. https://labeling.pfizer.com/ShowLabeling.aspx?id=19471#section-12.

Acute Therapies: Migraine Specific (Ditans, Gepants) All FDA Approved

Category/ Mechanism[1]	Agents (Oral Dosing Unless Indicated)[2-4]	Common Adverse Effects and Precautions[2-4]
Ditans 5HT1F agonist	Lasmiditan	• **Warning (driving restriction for 8h after use)** • **Discuss medication-overuse headache w/pts** • Schedule V controlled substance
Gepants CGRP receptor antagonists	• Rimegepant (ODT) • Ubrogepant (may be dosed >1x/24h) • Zavegepant (nasal spray)	• Review drug interactions before use • Dry mouth, dizziness, nausea

5HT = serotonin; CGRP = calcitonin gene-related petide; ODT = orally disintegrating tablet.

1. Ailani J, et al. *Headache*. 2021;61:1021-1039; 2. Zhang N, Robbins MS. *Ann Intern Med*. 2023;176(1):ITC1-ITC16; 3. Ailani J, et al. *Continuum*. 2021;27 (3, HEADACHE);597-612; 4. Zavegepant prescribing information. https://labeling.pfizer.com/ShowLabeling.aspx?id=19471#section-12.

Warning: Medication Overuse Headache

ICHD-3 Criteria: Medication Overuse Headache[1,2]

- **HA ≥ 15 days/month** in patient with preexisting HA disorder
- **Regular overuse of acute meds for > 3 months**
  - ≥ 10 days/month for ergot derivatives, triptans, opioids, combination analgesics, or a combination of drugs
  - ≥ 15 days/month for nonopioid analgesics, acetaminophen, NSAIDs
- **Not better accounted for by another diagnosis**

HA = headache; ICHD-3 = International Classification of Headache Disorders, 3rd edition.

1. Ailani J, et al. *Headache*. 2021;61:1021-1039; 2. Headache Classification Committee of the International Headache Society. *Cephalalgia*. 2018;38(1):1-211.

Avoiding Medication Overuse Headache

- **Limit use of acute treatments to an average of 2 days/week**
- **Offer preventive treatment** if exceeds this limit
- **Adjust therapy as needed** if overuse of acute medication continues with preventive medication
  - Escalate preventive dose or
  - Change acute or preventive therapy or
  - Add a second preventive treatment

Ailani J, et al. *Headache*. 2021;61:1021-1039.

Iris: Personalized Care

- Medication choice affected by
  - Route of delivery: prefers oral
  - Dosing: multiple administration routes possible
  - Speed of headache onset, associated symptoms
  - Avoiding adverse effects

Iris: Next Steps

- Prescribed CGRP receptor antagonist (gepant)
- Educate patient:
  - Administer medication as soon as her migraine begins
  - Keep a headache journal
  - Appointment for 3-month follow-up via telehealth

Challenges for Migraine Care in Remote Settings

Examples of Disparity, Care Gaps, and Unmet Need	What Can We Do?
• Fewer specialists • Social stigma and privacy concerns as barriers • Transportation concerns • Greater loss of income due to time taken off work for visits for headache	• Telemedicine may address geographic-based disparities in care • Connect patients to resources so they can access telemedicine technology

Kiarashi J, et al. *Neurology*. 2021;97:280-289.

Case #3

Revisiting Medication Options

Luna

- 33-year-old Latina
- Past medical history:
  - Migraine x 12 years
  - Asthma
  - Depression
  - Obesity (BMI = 30 kg/m^2)
- Chief complaint:
  - Increasing frequency of headaches
  - "I am always chasing my pain"
  - Friend takes medication daily for migraine, wondering if this is an option for her

Luna: Headache History

- MHD: 18, x 6 months, increasing over time
- Duration: 6 hours - 2 days
- Location: Left frontotemporal, typically
- Intensity: 6/10 on average, fluctuates
- Character: Pulsating
- Additional symptoms
  - Nausea, occasional vomiting
  - Light sensitivity

Ask about DAYS not ATTACKS

Migraine: Episodic or Chronic

- Episodic migraine: headache on < 15 days/month[1]
- Chronic migraine: Headache on ≥ 15 days/month for > 3 months[1]
- Preventive therapy can be used for both episodic and chronic migraine[2]
  - Some agents are only approved for one or the other
  - Examples
    - OnabotulinumtoxinA: indicated for prophylaxis of headaches in adults with chronic migraine[3]
    - Rimegepant: indicated for the preventive treatment of episodic migraine in adults[4]

ICHD-3 = International Classification of Headache Disorders, 3rd edition.

International Headache Society. *Cephalalgia*. 2018;38(1):1-211.

Luna: Treatment History

- Triptan
  - Effective in reducing HA severity 60% of the time
  - 3 times/week, 12 times/month, x 6 months
  - Well tolerated
- Combination analgesic: aspirin/acetaminophen/caffeine
  - Less severe attacks, before or with triptan
  - 2 times/week, 8 times/month
- Other medications: venlafaxine for depression

Meets criteria for medication overuse headache

Considerations When Starting Preventive Therapy

- Frequency of attacks, MHDs
- Degree of disability with attacks
  - MIDAS, HIT
  - Despite acute treatment
- Acute treatments
  - Adverse events
  - Contraindicated
  - Ineffective
  - Overused- Medication Overuse Headache (MOH)
- Patient preference

Prevention should be…	Monthly headache days	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

HIT = Headache Impact Test; MIDAS = Migraine Disability Assessment Scale.

Ailani J, et al. *Headache*. 2021;61:1021-1039.

Medication Options for Migraine Prevention[1,2]
Established/Probable Efficacy – Bolded Are FDA Approved

Category	Specific Agents (Oral Dosing Unless Indicated)	Additional Notes
Antiepileptics	**Divalproex sodium[a,b], topiramate[a]**, gabapentin, pregabalin[c]	• Divalproex sodium: thrombocytopenia, hepatotoxicity, weight gain, hair loss, *fetal teratogenicity (contraindication[b])*[3] • Topiramate: weight loss, nephrolithiasis, paresthesia, cognitive slowing, fetal teratogenicity
Beta-blockers	Metoprolol, **propranolol[a]**, atenolol, nadolol, **timolol[a]**	Fatigue, exercise intolerance, hypotension, bradycardia
Antihypertensives	Lisinopril, candesartan	• Hypotension • *Avoid if possibility of pregnancy (boxed warning)*[4,5]
Antidepressants	Amitriptyline, venlafaxine, duloxetine, nortriptyline	• Both: Dry mouth, drowsiness, weight gain • Venlafaxine: risk of withdrawal syndrome
Other	Memantine	Diarrhea, constipation, dizziness
Neurotoxin	**OnabotulinumtoxinA[a]**, IM, by trained clinician, every 12 weeks for chronic migraine[3]	Muscle weakness, neck pain; lack of systemic side effects and drug interactions makes this a high-priority option for patients with chronic migraine

Evaluate risk/benefit in patients who are or may become pregnant or are breast-feeding

[a]FDA approved for migraine prevention, except onabotulinumtoxinA, which is approved for chronic migraine; [b]Contraindicated in pregnant women or women of childbearing potential not using effective contraception; [c]Schedule V controlled substance.

1. Zhang N, Robbins MS. *Ann Int Med*. 2023;172(1)ITC1-ITC16; 2. Burch R. *Continuum*. 2021;27(3, HEADACHE):613-632; 3. Divalproex sodium prescribing information.; 4. Lisinopril prescribing information.; 5. Candesartan prescribing information.; 6. OnabotulinimtoxinA prescribing information.

CGRP-Based Therapies for Migraine Prevention

Migraine Specific Medications – All FDA Approved

Class	Medication	Administration	Notes
CGRP-based monoclonal antibodies – injected or i.v.	Galcanezumab (α-CGRP)[1]	s.c., monthly (self)	Injection site reaction, hypersensitivity
	Fremanezumab (α-CGRP) [2]	s.c., monthly/every 3 mo (self)	
	Erenumab (α-CGRP receptor)[3]	s.c., monthly (self)	Constipation, hypertension, hypersensitivity
	Eptinezumab (α-CGRP)[4]	i.v., every 3 mo (see note)	• Hypersensitivity • Administered by health care professional at infusion center, office/clinic, or home[5]
CGRP receptor antagonists (gepants) – oral[a]	Rimegepant[6,7]	Orally disintegrating tablet, every other day	• For episodic migraine (also approved as acute therapy) • Nausea
	Atogepant[7,8]	Oral, daily	• For episodic and chronic migraine • Nausea, constipation, fatigue, hypersensitivity, may cause fetal harm[b]

Evaluate risk/benefit in patients who are or may become pregnant or are breast-feeding; limited data.

[a]Zavegepant, approved as a spray for acute treatment, is also in a study (NCT04804033) as an oral preventive migraine treatment[9]; [b]Based on animal data.

1. Galcanezumab prescribing information.; 2. Fremanezumab prescribing information.; 3. Erenumab prescribing information.; 4. Eptinezumab prescribing information.; 5. Find an infusion location that's right for you. https://www.vyepti.com/vyepti-locator; 6. Rimegepant prescribing information.; 7. Zhang N, Robbins MS. *Ann Int Med*. 2023;172(1)ITC1-ITC16; 8. Atogepant prescribing information.; 9. Dhillon s. *Drugs*. 2023;83(9):825-831.

Other Options for Preventive Treatment

Herbal and nutritional supplements[2,3]

- Magnesium
- Vitamin B_2 (riboflavin)
- Feverfew
- Coenzyme Q10
- Melatonin

- Neuromodulation[1]
  - Monotherapy or adjunctive therapy
  - External trigeminal neurostimulation (eTNS)
  - Noninvasive vagus nerve stimulation (nVNS)
  - Single-pulse transcranial magnetic stimulation (sTMS)
- Biobehavioral therapies[1]

eTNS = electrical trigeminal nerve stimulation; nVNS = noninvasive vagus nerve stimulation; sTMS = single-pulse transcranial magnetic stimulation.

1. Ailani J, et al. *Headache*. 2021;61:1021-1039; 2. Zhang N, Robbins MS. *Ann Int Med*. 2023;172(1)ITC1-ITC16; 3. Burch R. *Continuum*. 2021;27(3, HEADACHE):613-632.

Luna: Personalized Care

- Comorbidities: depression, asthma, and obesity
  - Already on venlafaxine which is effective in managing her depression
  - Beta-blocker is contraindicated, given her asthma
- Not sexually active or planning to become pregnant in the next year
- Prefers a pill, fearful of injections
- Prescribed topiramate with up-titration schedule
- Plans to discuss OCP options with her gynecologist

Luna: Next Steps

- 3- month follow up
  - Decreased headache frequency, 1-2/week
  - Weight loss, 10 lbs
  - “Dopey feeling” making work challenging
- Down-titrated topiramate
- Prescribed an oral CGRP receptor antagonist

Goals of Preventive Treatment

- Reduce attack
  - Frequency
  - Severity
  - Duration
  - Disability
- Improve health-related quality of life (HRQoL)
- More effective acute treatment
  - Improve response
  - Avoid escalation
  - Reduce reliance
- Reduce overall cost
- Empower patients to manage their own disease

Ailani J, et al. *Headache*. 2021;61:1021-1039.

Establishing Preventive Treatment Effectiveness

- Establish realistic expectations
  - Fewer attacks, not abolished attacks
  - Better use of acute treatment
- Ensure an adequate trial before moving to another agent!
- Oral treatments
  - Start low dose, titrate slowly, reach target dose
  - Continue x 8 weeks minimum at target dose
  - Partial response: educate patient – benefits may accumulate over 6-12 months
  - No response: switch to another agent
- CGRP-based mAbs (injectable and IV treatments)
  - Onset of therapeutic benefits is often rapid
  - Assess monthly treatments after at least 3 months
  - Assess quarterly treatments after at least 6 months

Ailani J, et al. *Headache*. 2021;61:1021-1039.

Initiation of CGRP-Based Therapy

- Generally, **8-week trials** of **at least 2** agents from other classes[1,2]
- Authorization
  - Often can include contraindications to preventive agents/classes
  - Exact recommendations vary based on patient case and medication
  - After trial, need to demonstrate effectiveness for re-authorization

Luna

- Lack of relief on venlafaxine
- Contraindication for beta-blockers
- Trial with topiramate x 3 months
- Eligible to try CGRP-based therapy

1. Ailani J, et al. *Headache*. 2021;61:1021-1039; 2. Zhang N, Robbins MS. *Ann Int Med*. 2023;172(1)ITC1-ITC16.

Challenges for Migraine Care Considering Women's Health Needs: Family Planning/Reproductive Health

Examples of Disparity, Care Gaps, and Unmet Need	What can we do?
Hormonal contraception options are limited for women with migraine with aura due to increased risk of stroke.[1] Most women report improvement in migraine during pregnancy, but some do not – **pregnancy and breastfeeding limit use of many (acute and preventive) migraine medications**.[2]	**It is important to understand recent guidelines and evidence!** **Contraception:** No contraindications for progestin-only contraception in women with migraine[1] **Conception, pregnancy, breastfeeding and migraine meds[3]** • Generally, avoid preventive therapies • Assess individual risks/benefits (some should not be used) • Consider alternatives to (e.g., neuromodulation) **Refer to sources of current evidence**, such as: • MotherToBaby: https://mothertobaby.org/ • LactMed: https://www.ncbi.nlm.nih.gov/books/NBK501922/

1. Committee on Practice Bulletins—Gynecology. *Obstet Gynecol*. 2019;133(2):e128-e150; 2. Raffaelli B, et al. *J Headache Pain*. 2023;24:167; 3. Ailani J, et al. *Headache*. 2021;61:1021-1039.

Case #4

Recurrent Migraines and Cardiovascular Disease

Marshall

- 65-year-old African American male
- Chief complaint: persistent migraines that started immediately after stroke
- Past medical history:
  - Hypertension
  - Type 2 diabetes
  - Hyperlipidemia
  - Stroke (7 months ago)

Marshall: Headache History

- MHD: 13 days/month post stroke
- Duration: 1 day
- Location: unilateral
- Intensity: reach 6/10 on pain scale
- Character: throbbing
- Additional symptoms: nausea, vomiting, sound sensitivity

Marshall: Treatment History

- Current regimen:
  - Preventive: Topiramate 100mg BID
  - Acute: Ibuprofen as needed
- Reports 6 MHD now, Ibuprofen no longer helpful

Acute Migraine Therapies in Cardiovascular/Cerebrovascular Disease

Acetaminophen[1,2]

No dose adjustment, no specific warning

NSAIDs[1,2]

No dose adjustment

FDA warning: Increased risk of MI or stroke in people with risk factors for CVD

Triptans[1,2]

Contraindicated in patients with a history of CVD, uncontrolled hypertension, prior stroke or TIA

Ergotamines[1,2]

Avoid or use with caution in patients with a history of CVD, cerebrovascular disease, and other vascular conditions

Ditans (lasmitidan)[1-3]

No dose adjustment, no specific warning

Gepants (rimegepant, ubrogepant, zavegepant)[1,2,4,5,6]

No dose adjustment, no specific warning

1. Ailani J, et al. *Continuum*. 2021;27 (3, HEADACHE);597-612; 2. Zhang N, Robbins MS. *Ann Intern Med*. 2023;176(1):ITC1-ITC16; 3. Lasmiditan prescribing information. https://uspl.lilly.com/reyvow/reyvow.html#pi; 4. Rimegepant prescribing information. https://labeling.pfizer.com/ShowLabeling.aspx?id=19036#section-8.5; 5. Ubrogepant prescribing information. https://www.rxabbvie.com/pdf/ubrelvy_pi.pdf; 6. Zavegepant prescribing information. https://labeling.pfizer.com/ShowLabeling.aspx?id=19471#section-8.5

Marshall: Next Steps

- Continue topiramate (50% reduction in MHD)
- Trial gepant or ditan for acute treatment of headache
- Provide headache journal instructions to identify possible triggers
- Follow up in 3-6 months to assess efficacy

Challenges for Migraine Care in Older Adults

Examples of Disparity, Care Gaps, and Unmet Need	What can we do?
• Lower prevalence with age (10%), but continues to be a significant issue[1] • Second most common headache disorder in older adults[1] • Likely to become a more significant issue with population aging[1] • Typical agents may be more problematic for older patients[1]	**Identify potential problems before prescribing** **Assess for secondary headache!** **Consider comorbidities and medication interactions[2]** • Cardiovascular disease • Renal impairment (RI): many agents can still be used even in severe RI, but be aware of dose adjustments • Hepatic disease: many agents can be used in mild or moderate disease, but be aware of dose adjustments

1. Riggins N, Ehrlich A. *Curr Pain Headache Rep*. 2022;26:331-335; 2. Stern JI, et al. *Headache*. 2023;63:9-24.

Summary

- Migraine is one of the leading causes of disability worldwide and has health, social, and socioeconomic impacts
- Accurate diagnosis is the first step to appropriately managing migraine
- Treatment options for migraine are rapidly evolving/expanding – there are many acute and preventive therapies available
- Migraine management is highly individualized
- There are barriers to migraine care and abundant health disparities
- Clinicians need to be aware of ways to address barriers and disparities (e.g., appropriate diagnosis, preparation for prior authorization) to help patients get therapies they need, including newer therapies

What Can We Do?

- Educate yourself (and others)
  - Support migraine awareness and advocacy, including the need for better representation in headache research
  - Know diagnostic criteria and be familiar with treatment options (acute and preventive)
  - Train providers in cultural sensitivity and competence and in implicit bias
- Be creative with resources to overcome barriers and connect with patients (e.g., leverage telemedicine)

Kiarashi J, et al. *Neurology*. 2021;97:280-289.

Thank You!