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Strategies to Improve the Diagnosis and Management of Migraine in Primary Care: A Focus on CGRP-Targeted Agents for the Acute Treatment and Prevention of Episodic Migraine

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Disclosures

- **James North, MD**
  - Advisory Board – Eli Lilly and Company
  - Speakers' Bureau – Eli Lilly and Company, AbbVie

- **Anne Damian Yacoub, MD**
  - Advisory Board - AbbVie

Learning Objectives

- Describe current unmet needs related to the diagnosis and management of migraine in primary care practice
- Evaluate the role of CGRP in the pathophysiology of migraine
- Assess the safety/efficacy data of CGRP receptor antagonists in the acute treatment of migraine and the preventive treatment of episodic migraine
- Implement personalized care plans that consider healthcare disparities and comorbidities for the optimal management of patients with migraine

CGRP = calcitonin gene-related peptide.

Program Agenda

This is an educational migraine program focused on the following topics:

Part One

- Migraine history, epidemiology, and burden
- Prevalence and under-recognition in primary care
- Diagnosing migraine in primary care
- Episodic and chronic migraine
- Neurology referral

Part Two

- Current understanding of migraine pathophysiology
- The role of CGRP in migraine
- Migraine treatment guidelines
- Targeting CGRP in acute and preventive migraine therapy

Part Three

- We can make a difference if we ask

Part One: Dr. North

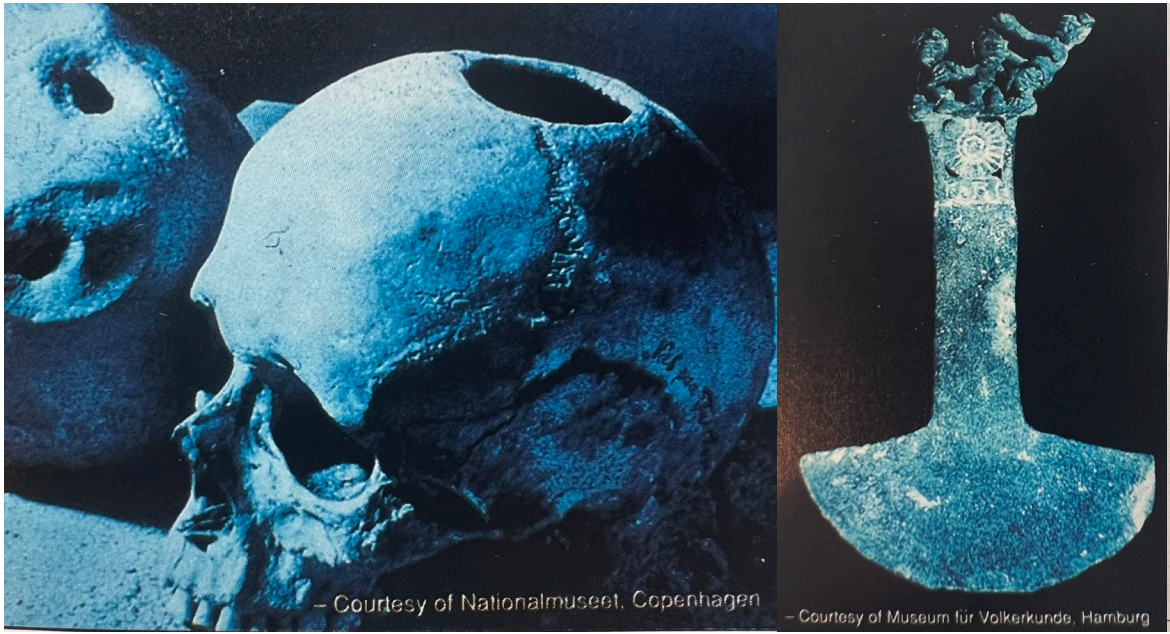
Migraine:

More common than you think

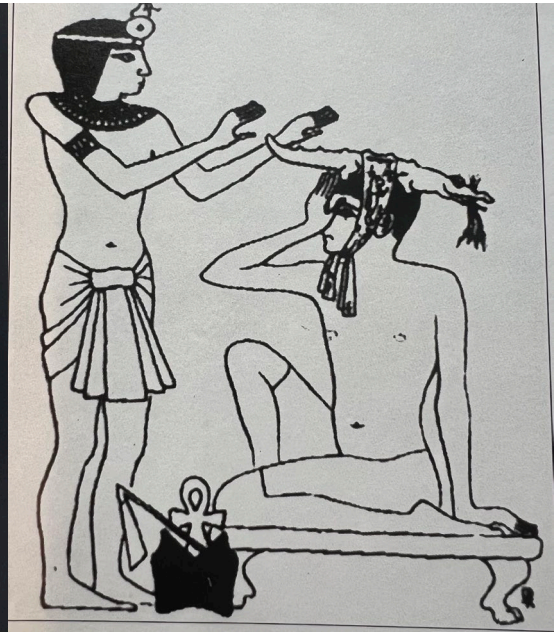
Less complicated than we were taught

Migraine and Mankind: Torment for Millennia

Treponation Skull and Tool c.7000BC



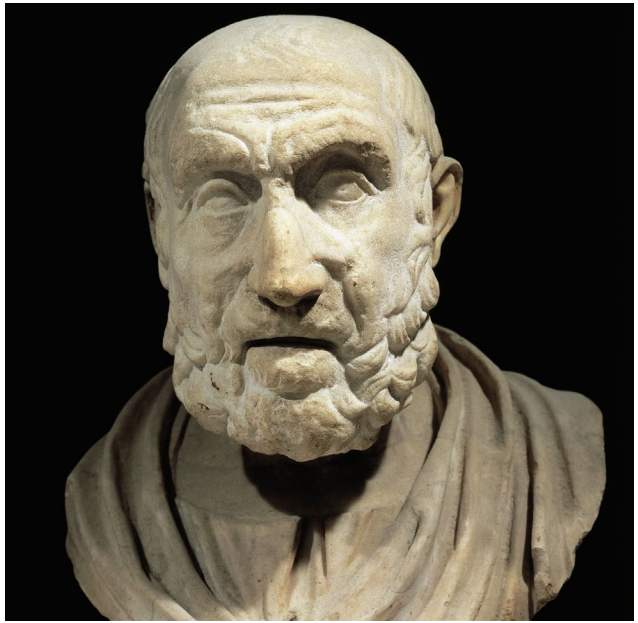
Egypt c.1200BC



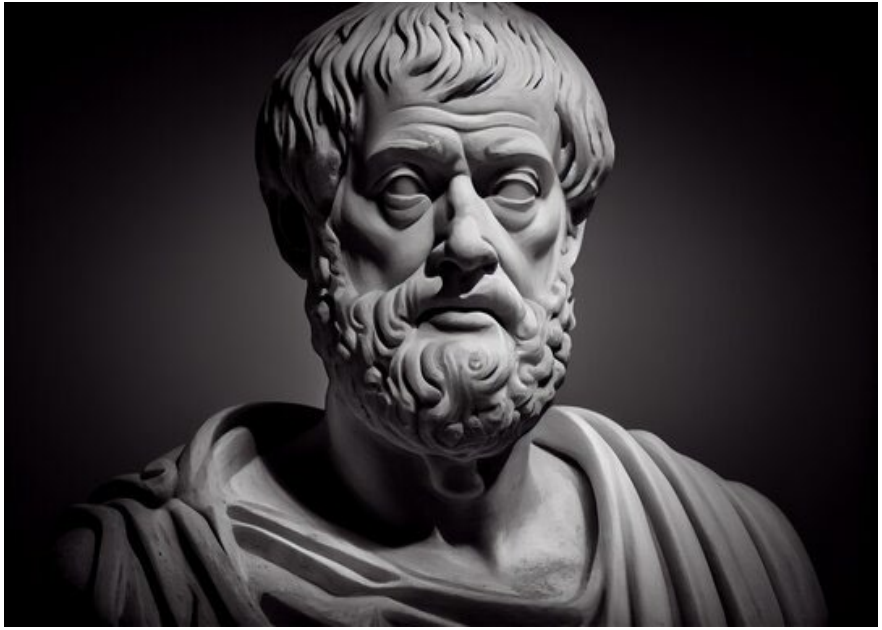
Venzmer G. *5000 Years of Medicine*. Taplinger; 1972. Smith R (ed). *Background to Migraine*. Heinemann; 1967.

Migraine and Ancient Greece c. 400 BC

Hippocrates:
Triggered by exercise or intercourse… vapors rising from the stomach and relieved by vomiting



Plato:
Triggered by preoccupation with the body… forever imagining headaches



Lance JW. *Mechanisms and Management of Headache*. 4th ed. Butterworth; 1982.
Hamilton E, Cairns H (eds). *Plato: The Collected Dialogues*. Pantheon; 1961.

19th Century Migraine Misperceptions

Joseph Jules François Félix Babinski (1857-1932)

extensively studied hysteria (Greek *hystera* or uterus);

he was immortalized for his 1896 description of:

Phénomène des orteils (*Babinski* response)

He used his test to distinguish *hysterical paralysis* from *spinal cord injury*

Babinski termed migraine with visual aura as:

Migraine ophtalmique hystérique

19th century interventions for hysteria:

Marriage
Hysterectomy

Clarac M, et al. *History of Neuroscience: Joseph Babinski (1857-1932)*. International Brain Research Organization; 2008. Babinski J. *Arch Neurol* (Paris). 1890;20:305-335.

20th Century Migraine: Pervasive Skepticism

Joan Didion (1934-2021), iconic author/writer/journalist (*A Star Is Born*), wrote in 1979:

For I had no brain tumor, no eye-strain, no high blood pressure, nothing wrong with me at all.

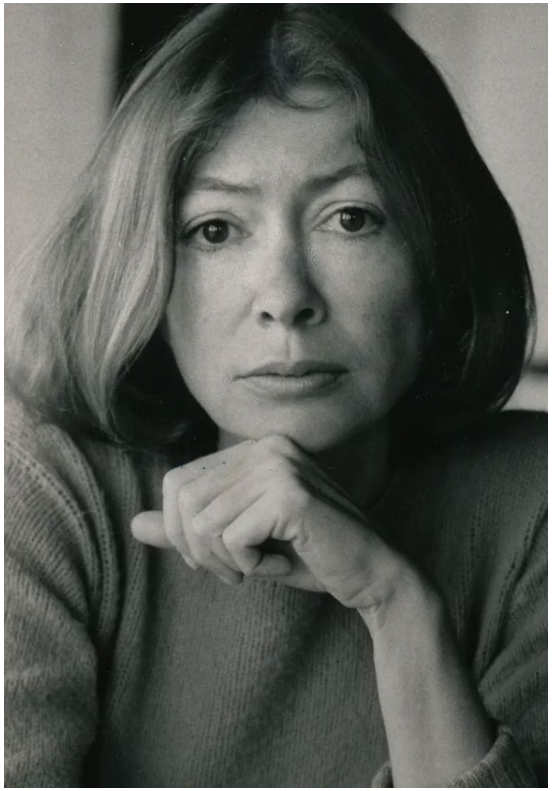
I simply had migraine headaches, and migraine headaches,

as everybody who did not have them knew, were imaginary.

Her physician revealed ongoing migraine misperceptions, making the observation:

You don't look like a migraine personality…Your hair's messy.

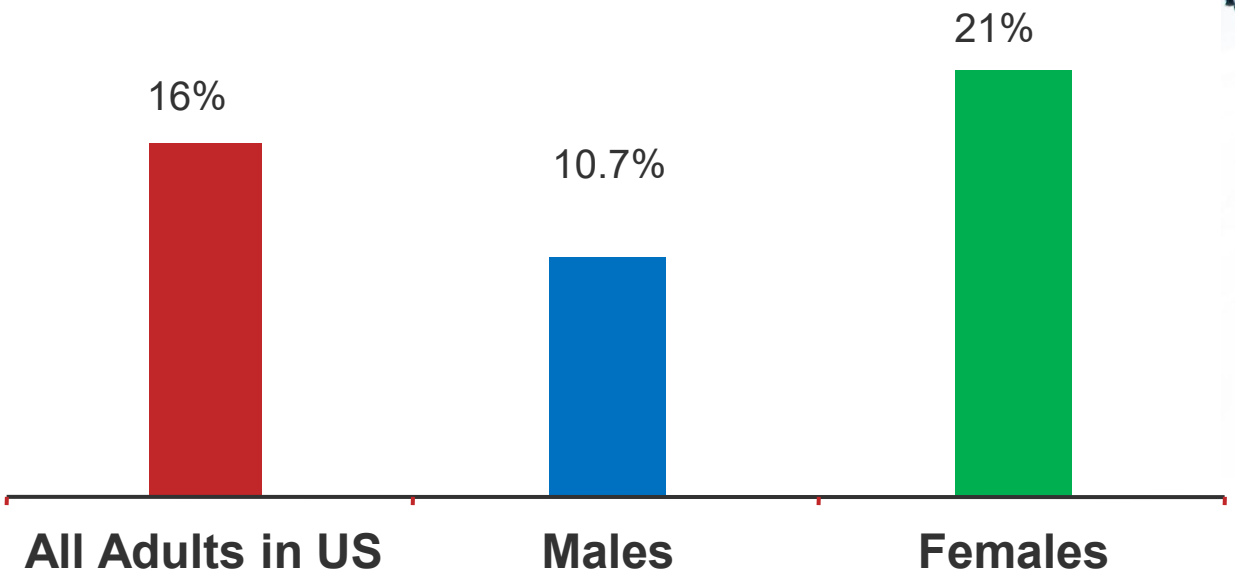
But I suppose you're a compulsive housekeeper.



Didion J. *The White Album*. Farrar, Straus, and Giroux; 1979.

Migraine: Impacts 1 in 6 US Households

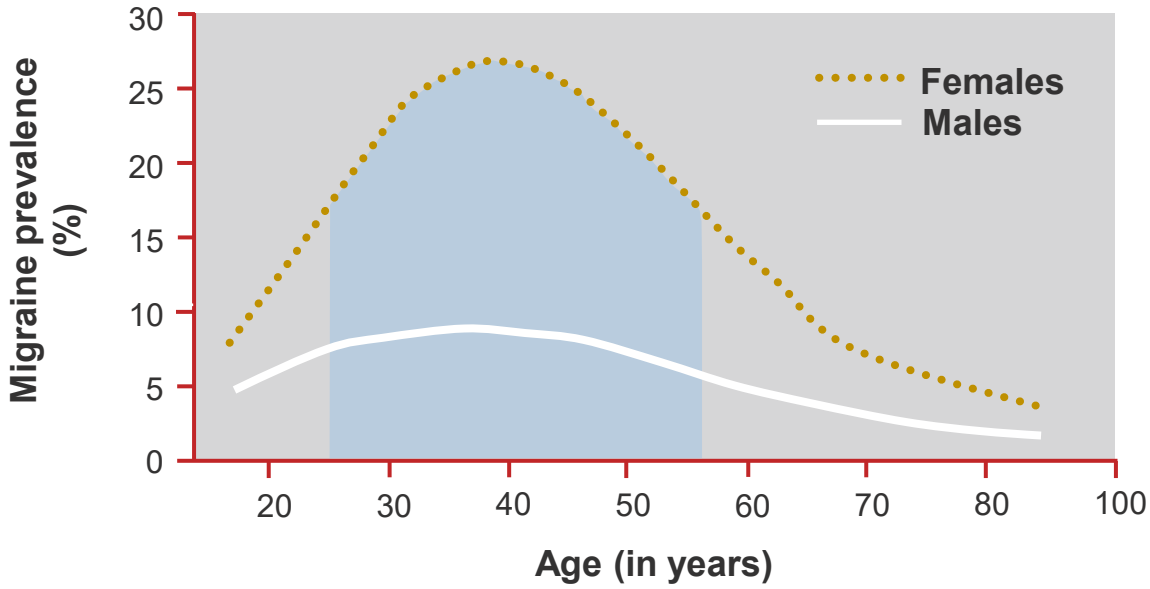
42 million Americans have migraine



Burch R, et al. *Headache*. 2021;61(1):60-68.

Migraine: Just When We Should Be Doing Our Best Work

Highest prevalence between 25-55 years of age



Global Burden of Disease (GBD) 2016 Headache Collaborators. *Lancet Neurol*. 2018;17(11):954-976.

Migraine: Major Impact on Quality of Life

In the US and globally, **migraine** is…

#2

cause of years lived with disability

#1

cause of disability in women aged 15-49

Steiner TJ, et al. *J Headache Pain*. 2020;21(1):137.

Migraine: Waiting to Be Seen in Primary Care

29% of people
and
37% of women

in a PC waiting room
(for any reason)
have
migraine

Couch J, et al. *Headache*. 2003;43(5):570-571.

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Migraine: Hiding in Plain Sight

Of ≈21,000 patients determined to meet criteria for migraine with at least 2 migraine headache days/month

One-half did not have a diagnosis of migraine

Nicholson RA, et al. *Headache*. 2020;Suppl 1:132-133.

Migraine: More Than *Just a Headache*…

Burch RC, et al. *Headache*. 2015;55(1):21-34. Lipton RB, et al. *Neurology*. 2007;68(5):343-349.

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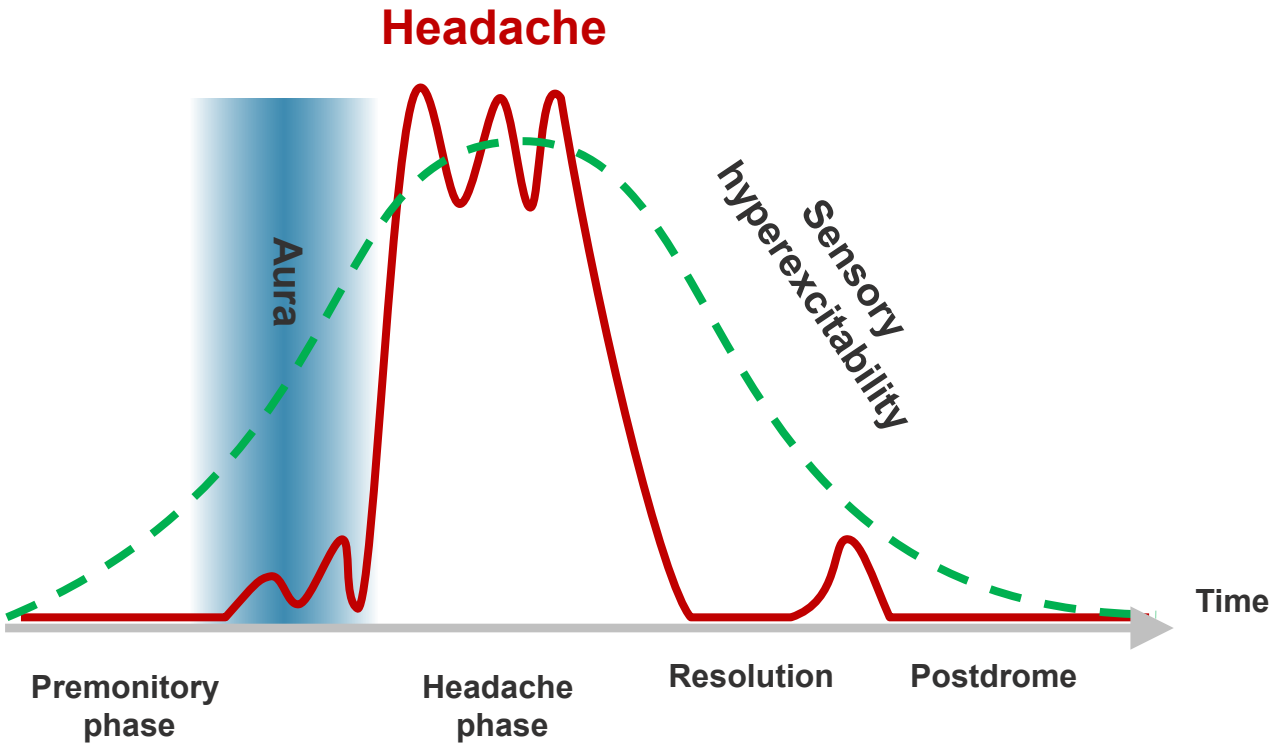
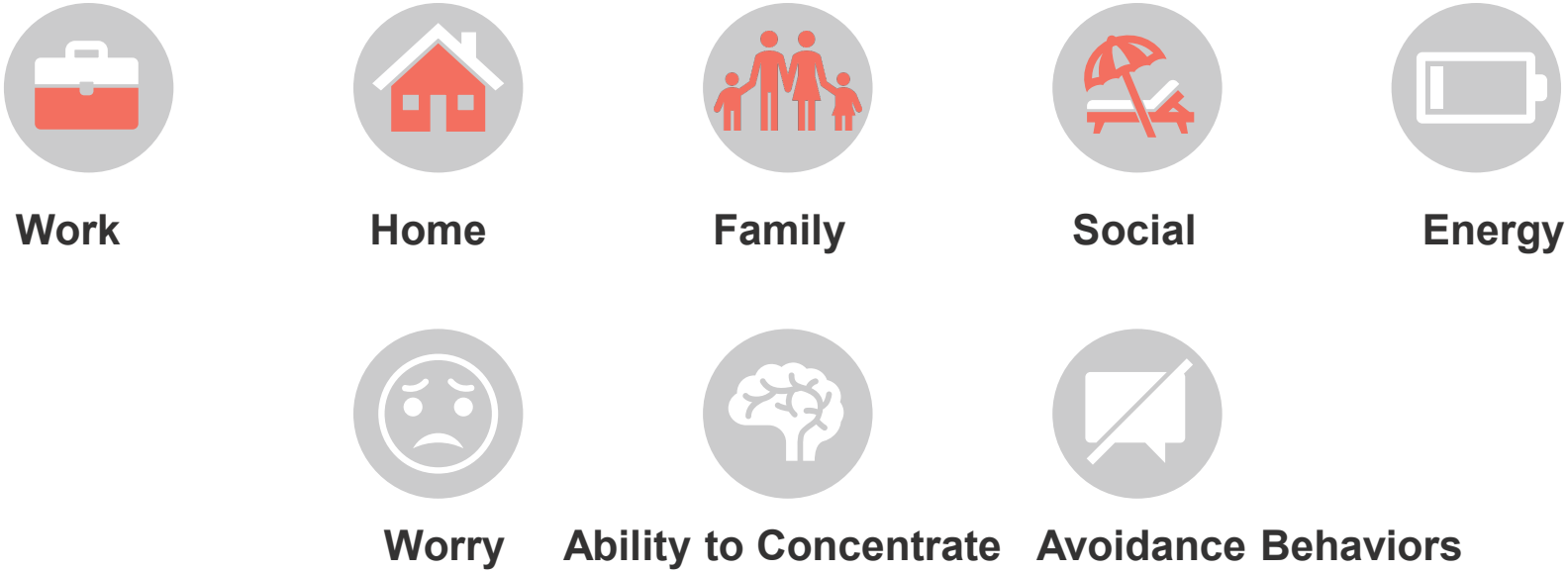
Migraine: Before, During, and After…
…*More Than Just a Headache*



Adapted with permission from Linde M. *Acta Neurol Scand*. 2006;114(2):71-83.

Migraine: Impact on Everything Both During *and* Between Migraines (*Interictal*)

50-90% of patients with migraine report *substantial* impairments with…



Lipton RB, et al. *Neurology*. 2007;68(5):343-349. Lipton RB, et al. *Cephalalgia*. 2003;23(6):429-440. Brandes JL. *Headache*. 2008;48(3):430-441.

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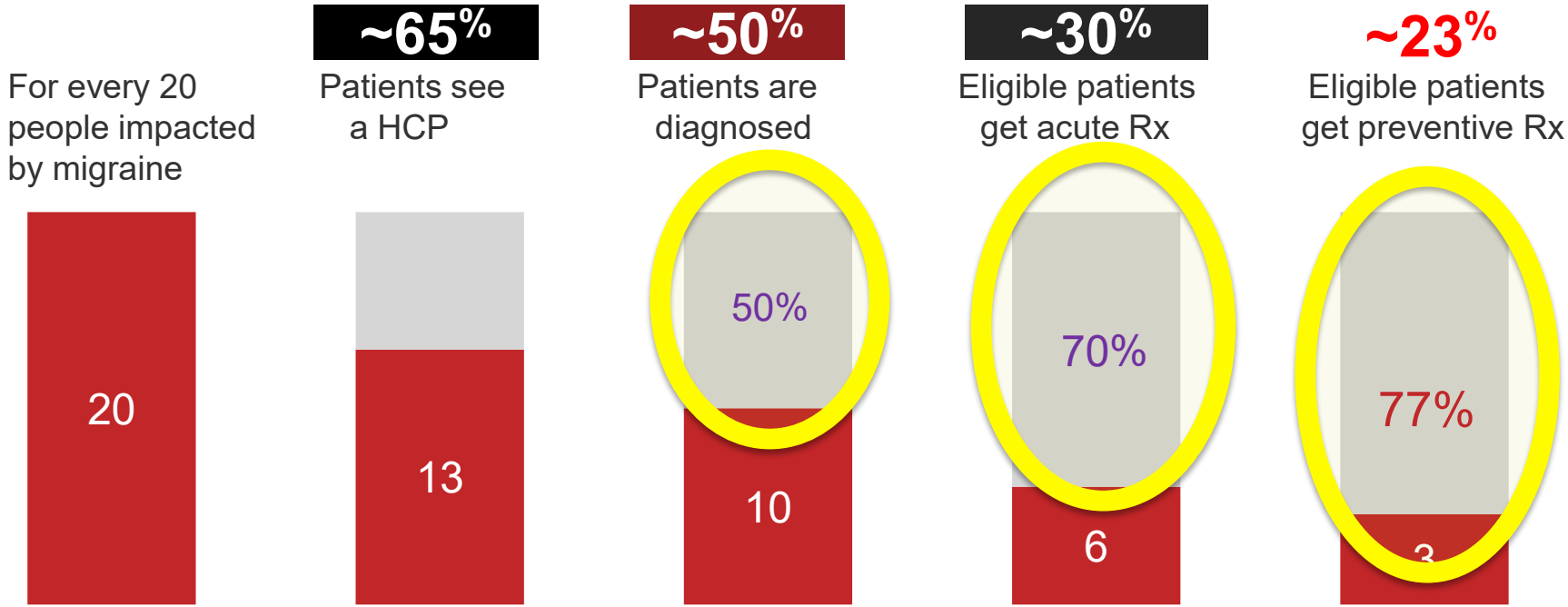
Migraine: Beware the Opportunity Cliff

Survey of people who are ***impacted by migraine*** at least **2 days per month**



HCP = healthcare provider; Rx = prescription.

Nicholson RA, et al. *Headache*. 2020;Suppl 1:132-133. Ashina S, et al. *Headache*. 2020;Suppl1:127-128.

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Migraine: Barriers to Diagnosis in Primary Care

- Too *little time*
- Too *much else* to do during an office visit
- *Comorbidities* can conceal
- Patients may be *confident* they have something other than migraine
- *Overcomplicating* migraine diagnostic criteria
- *We didn't ask*

Martin VT, et al. *Ann Med*. 2021;53(1):1979-1990.

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Migraine: Patients Don't Make it Easy…

Of 39,494 patients with migraine
who didn't have migraine addressed
at their most recent medical visit

45% wanted to take care of their migraine on their own

29% did not consider it serious enough to warrant talking about it

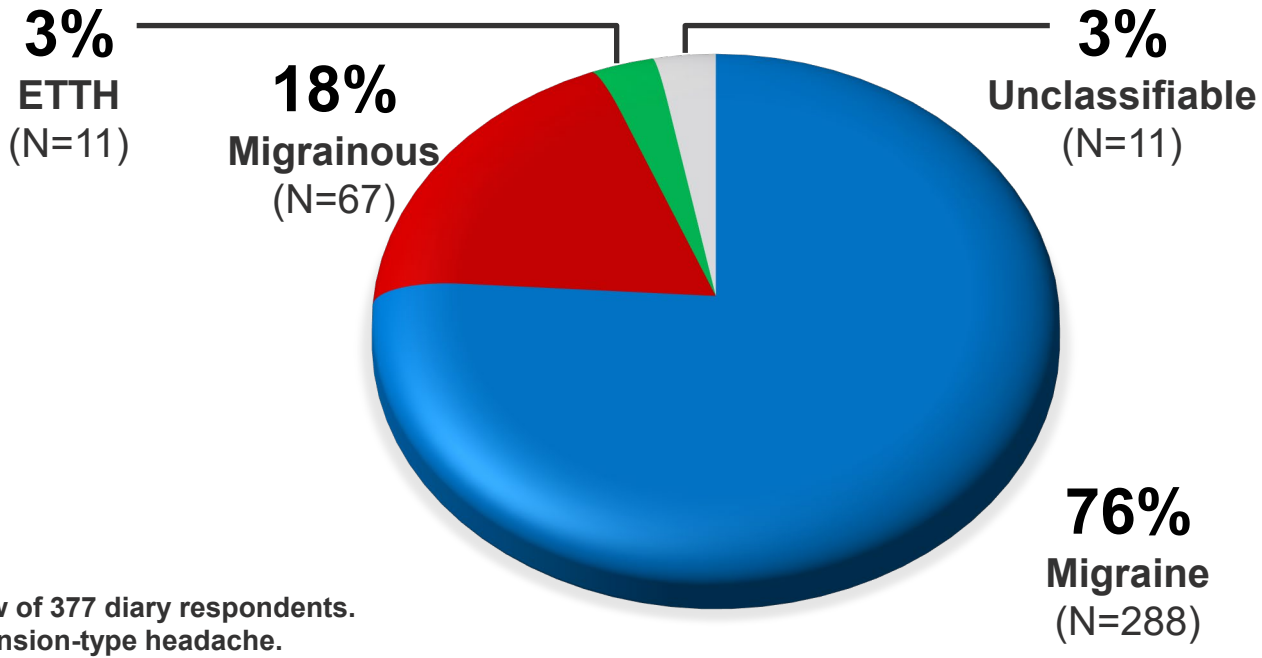
35% were concerned that their provider would not take their migraine seriously

The majority of these patients reported being disabled by migraine on average ***at least 1 day per week***

Shapiro RE, et al. *Headache*. 2021;61:10.

Migraine: The *Most Likely Diagnosis* in Patients Who Present with Headache

94% *migraine* or ***probable migraine***



Expert panel review of 377 diary respondents.
ETTH = episodic tension-type headache.
Tepper SJ, et al. *Headache*. 2004;44(9):856-864.

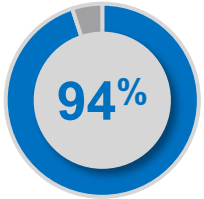
Migraine in Primary Care: Our Opportunity to Make an Impact

Patients in primary care *for any reason* with migraine

Women 37%

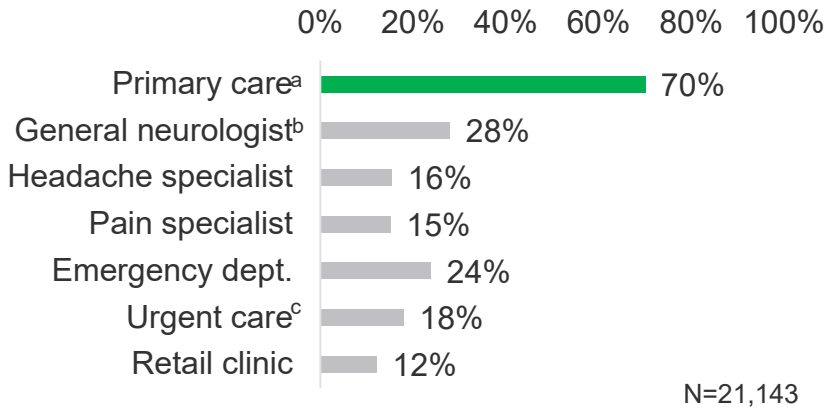
Men 18%

US data show that when outpatients present with headache,



have migraine

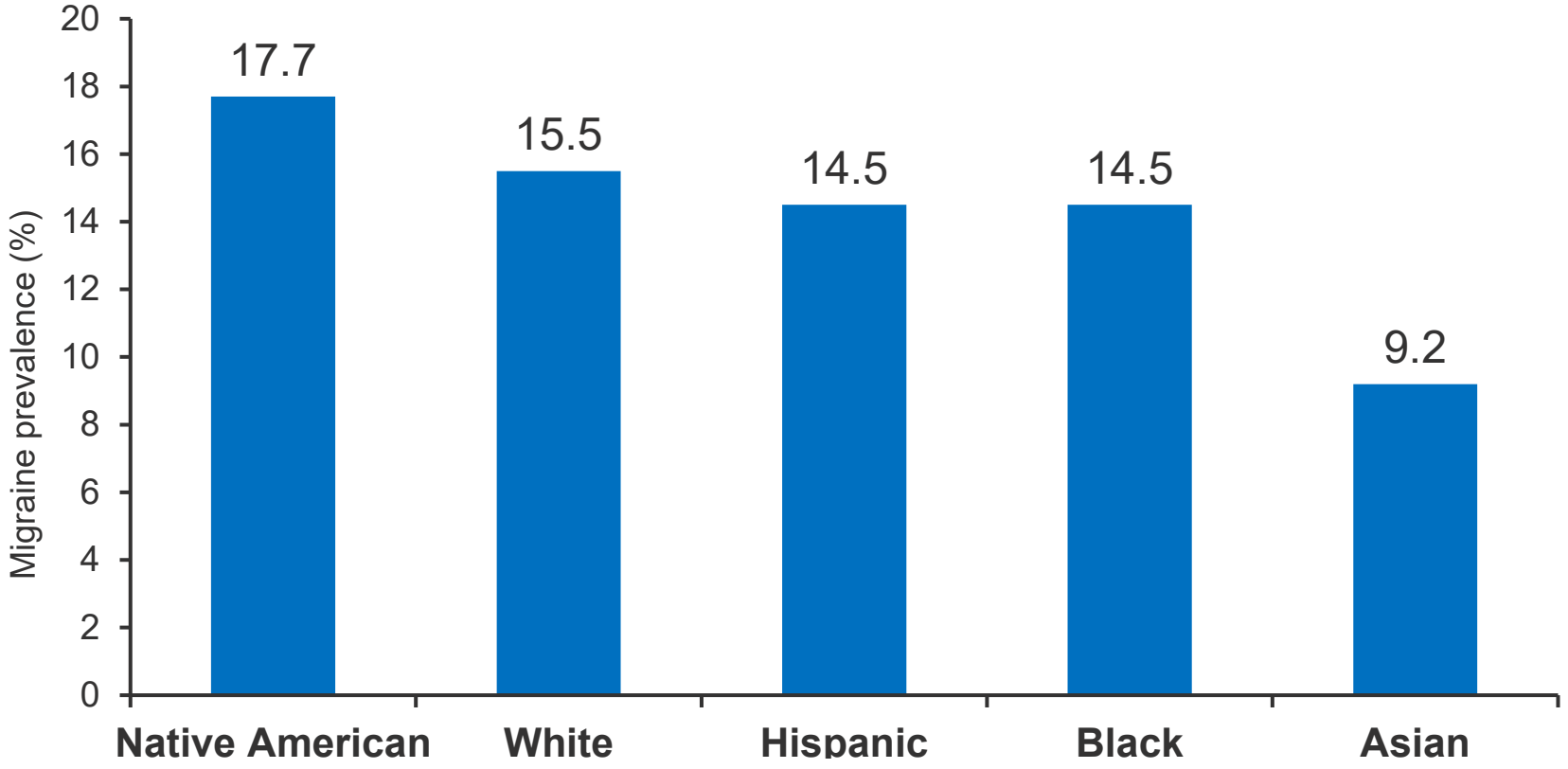
Type of providers patients reported having ever seen for *migraine* or *severe headache*



N=21,143

[a]Includes primary care, family medicine, internal medicine; [b]Non-headache specialists; [c]Clinics providing non-urgent care such as those termed "walk-in", "convenient care" located in a retail or a standalone establishment. Couch JC, et al. *Headache*. 2003;43(5):570-571. Tepper SJ, et al. *Headache*. 2004;44(9):856-864. Lipton RB, et al. *Headache*. 2022;62(2):122-140.

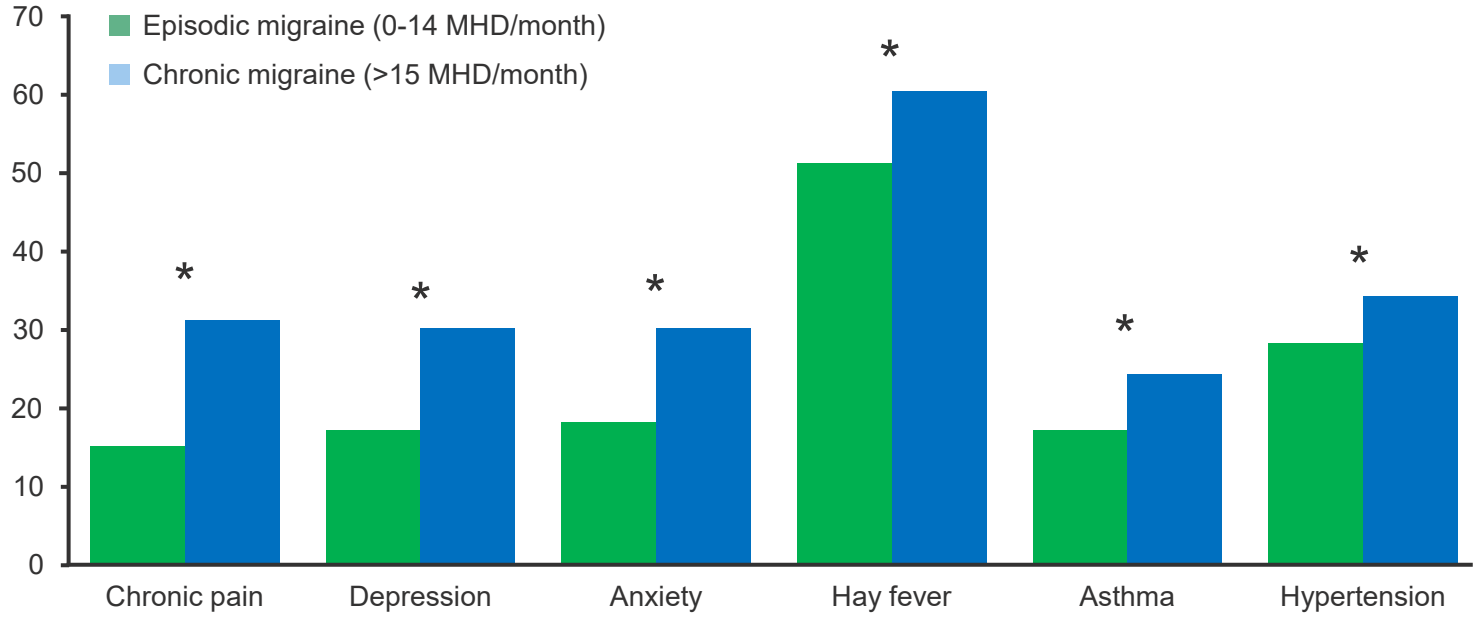
Migraine Demographics: Similar Prevalence / Dissimilar Diagnosis



White patients 2x more likely to be diagnosed with migraine vs Hispanics, 1.3x vs Black patients

Loder S. *Headache*. 2015;55(2):214-228.

Migraine: Common, Comorbid (and Concealed?)



****P*<.05.**
MHD = migraine headache days.
Buse DC, et al. *J Neurol Neurosurg Psychiatry*. 2010;81(4):428-432.

Migraine: The Diagnosis – ID Migraine™ Validated Screener

2/3 "yes" is a *positive* screen

93%
of positive screens in PC will have migraine

During the last 3 months, did you have the following with your headaches?

1. You felt nauseated or sick to your stomach

Yes ___ **No ___**

2. Light bothered you (a lot more than when you don't have headaches)

Yes ___ **No ___**

3. Your headaches limited your ability to work, study, or do what you needed to do?

Yes ___ **No ___**

ID Migraine™ is a screening tool for migraine.
Lipton RB, et al. *Neurology*. 2003;61(3):375-382.

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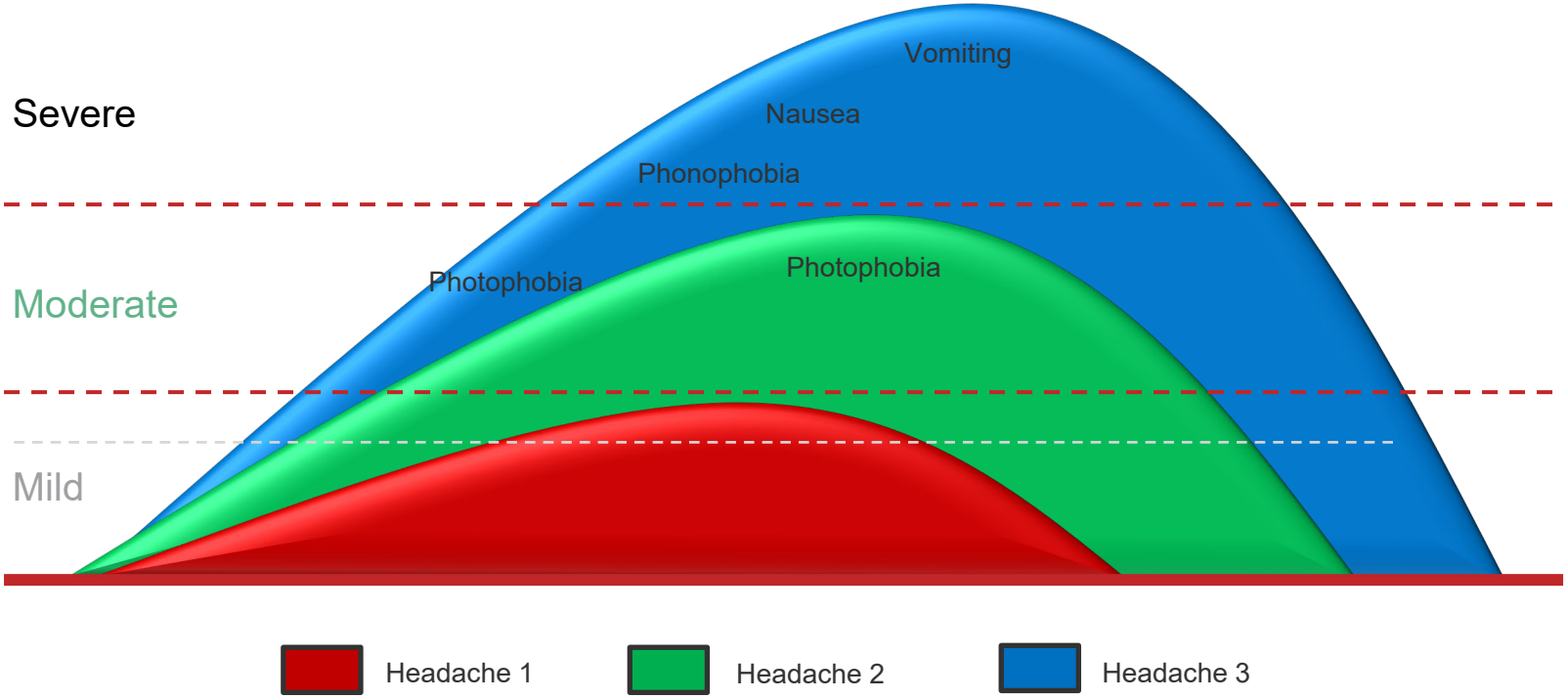
Migraine: A Headache with…

- ***Nausea***
- ***Photophobia***
- ***Impact on daily activities***

If headache is accompanied by
2 or more of the key signs or symptoms,
there is a ***93% positive predictive*** **value for** ***migraine***

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

More Than One Type of Headache?
Ask about the Patients' *Most Severe Headaches*…



Migraine and Aura: The Neurological Event before the Headache

70-85% of migraines *DO NOT* have aura

Visual aura
Visual disturbance

Sensory aura
Numbness of the face
Tingling down arm

Hemiplegic aura
One side of the body

Charles A, et al. *Curr Opin Neurol*. 2015;28(3):255-260. Digre KB. *J Neuroophthalmol*. 2018;38(2):237-243.
Lipton RB, et al. *Neurology*. 2007;68(5):343-349.

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Migraine History: Confirm the Details

- Onset, aggravation, duration, amelioration
- Location and laterality
- Severity and quality
- Frequency and impact (days of *impact*/month)
- Associated symptoms
- Neurological symptoms
- Age of onset and family history

Migraine Diagnosis: Examine the Patient…

- Vital signs
- Fundoscopic exam
- Cranial nerve assessment
- Muscular strength testing
- Reflexes (*including Babinski*)
- Cerebellar testing

Headaches: Flags That Deserve Additional Testing…

SNOOP4

Sign or symptom	
S	Systemic symptoms
N	Neurological signs or symptoms
O	Onset
O	Older
P4	Progression, papilledema, position, precipitated by Valsalva

Dodick DW. *Semin Neurol*. 2010;30(1):74-81.

Migraine (and Other PHDs): How Often Is PC Wrong?
Risk of Secondary Headache in Primary Care

	New PCP diagnosis Primary headache disorder (n=21,758 [25%])	New PCP diagnosis Undifferentiated headache disorder (n=63,921 [74%])
Brain tumor	0.045%	0.15%
SAH	0.02%	0.14%
Temporal arteritis	0.18%	0.66%
Stroke	0.45%	1.06%
TIA	0.25%	0.43%
Benign space-occupying lesions	0.009%	0.05%
Total	0.95%	2.49%

PHDs = primary headache disorders; PCP = primary care provider; SAH = subarachnoid hemorrhage; TIA = transient ischemic attack.

Kernick D, et al. *Cephalalgia*. 2008;28(11):1188-1195.

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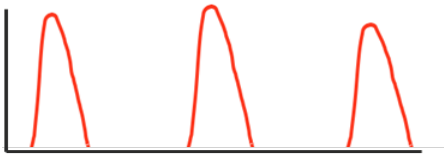
Migraine Frequency: A Continuum for Patients, a Threshold for Care

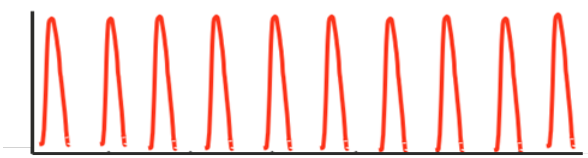
1-6 days/month
Episodic
Low frequency



Intermittent headaches, lots of headache-free days

Low frequency
80%

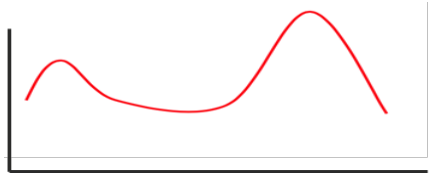
7-14 days/month
Episodic
High frequency



Frequent headaches, still headache-free days

High frequency
14.5%

15-30 days/month
Chronic migraine
High disability



Rare headache-free days, may be daily with exacerbations

Chronic
5.5%

Every patient with migraine deserves to be offered acute migraine treatment; any patient with *4 or more MHD/month* ***should also be offered prevention***

Blumenfeld AM, et al. *Cephalalgia*. 2011;31(3):301-315.

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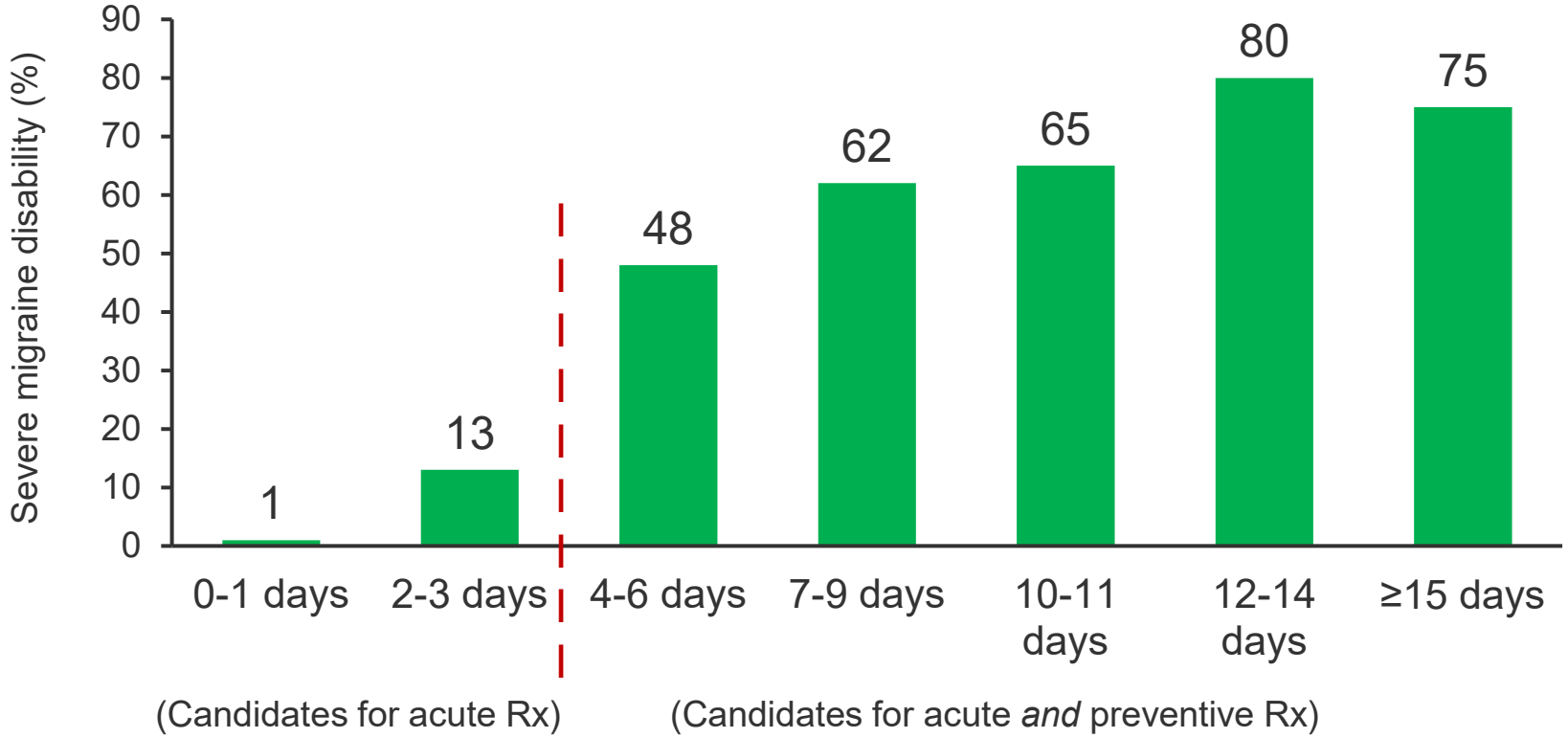
Migraine: Disability *Jumps Dramatically* at ≥4 Headache Days/Month



Blumenfeld AM, et al. *Cephalalgia*. 2011;31(3):301-315.

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Migraine: When Should Neurology Be Consulted?

- Chronic migraine
- Medication overuse
  - Especially when refractory to weaning
- Multiple comorbidities
- Refractory to acute or preventive medications
- Atypical presentation
- Hemiplegic migraine

Part Two: Dr. Yacoub

Migraine Therapy

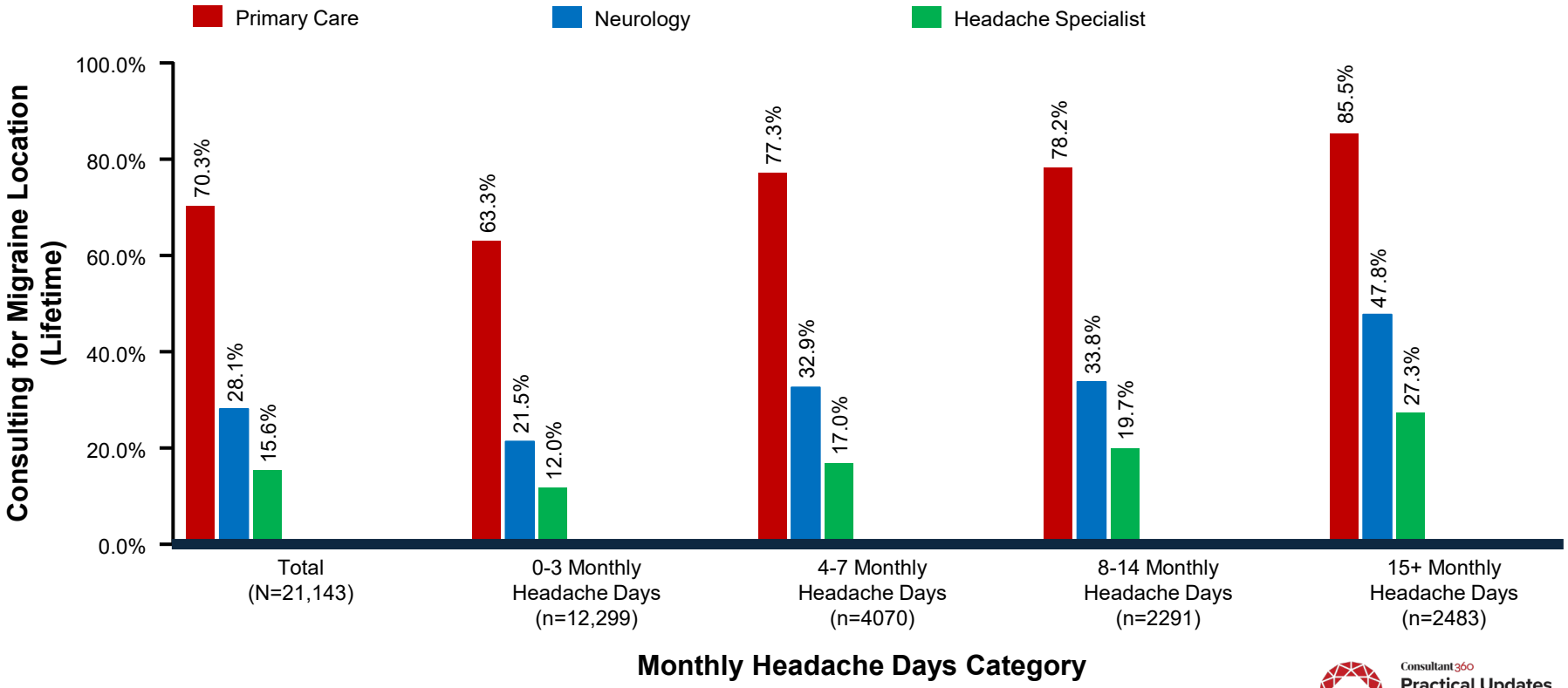
Acute Therapy

Acute Medications Are Underutilized

Medication type	Lifetime use (%)	Current use (%)
Acute treatment* (prescription/OTC)	97.1%	94.2%
Triptans	35.0%	22.7%
Opioids	47.7%	19.1%

***Acute medications, prescription and OTC, used for the acute treatment of migraine included specific names (brand/generic) of triptans, opioids, barbiturates, ergot alkaloids, NSAIDs, and simple/combination analgesics.**
OTC = over-the-counter; NSAIDs = nonsteroidal anti-inflammatory drugs.
Lipton RB, et al. *Headache*. 2022;62(2):122-140.

Lifetime Consultation by Specialty



Lipton RB, et al. *Headache*. 2022;62(2):122-140.

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Acute Therapies…
More Than Just Medications

Behavioral interventions

Pharmacotherapy

Neuromodulation

Factors Influencing Selection of Acute Therapy

- Time to peak intensity
- Presence of nausea or vomiting
- Attack stage
- Patient comorbidities
- Headache-related disability
- Attack frequency

Acute Therapy

TABLE 3-2 Select Summary of American and Canadian Headache Societies Guidelines for Acute Migraine Treatment

Medication	American Headache Society	Canadian Headache Society
Acetaminophen 1000 mg for nonincapacitating attacks	Strong evidence (Level A)	Strong evidence
Aspirin 500 mg, diclofenac 50 mg or 100 mg, ibuprofen 200 mg or 400 mg, naproxen 500 mg or 550 mg	Strong evidence (Level A)	Strong evidence
Triptans	Strong evidence (Level A)	Strong evidence
Dihydroergotamine nasal spray	Strong evidence (Level A)	Weak evidence but may be first line in some cases
Dihydroergotamine IV/IM/subcutaneous	Medium evidence (Level B)	Weak evidence but may be first line in some cases
Acetaminophen/aspirin/caffeine	Strong evidence (Level A)	Not addressed
Butorphanol nasal spray	Strong evidence (Level A)	Weak evidence, should not use
Codeine	Medium to weak evidence (Level B/C)	Weak evidence, should not use
Tramadol	Medium evidence (Level B)	Weak evidence, should not use

IM = intramuscular; IV = intravenous.

Ailani J. *Continuum* (Minneap Minn). 2021;27(3):597-612.

Triptan Therapy

- Similar in action
  - 5HT 1B and 1D agonists
- Differences
  - Onset
  - Duration
  - Side effects
  - Delivery mechanisms
  - Metabolism

- Consider treatment early in headache cycle
- Dose appropriately
- May have synergistic effect with NSAIDs
  - Naproxen

Triptans

Drug	Tmax (hours)	Half-life (hours)
Almotriptan	2.1	3.1
Eletriptan	1.8	5
Frovatriptan	2.5	26
Naratriptan	3-5	6
Rizatriptan	2-3	5
Sumatriptan	2	2
Zolmitriptan	2.5	3

Silberstein SD (ed), et al. *Wolff's Headache and Other Head Pain*. 8th ed. Oxford; 2007 (print) & 2023 (online).

Contraindications to Triptans

- History of stroke, aneurysm, or myocardial infarction

- Uncontrolled hypertension

- History of ischemic bowel disease or severe peripheral vascular disease

- Serotonin syndrome?

- Overall, triptans are very safe!
- Standard of care for migraine

Silberstein SD (ed), et al. *Wolff's Headache and Other Head Pain*. 8th ed. Oxford; 2007 (print) & 2023 (online).

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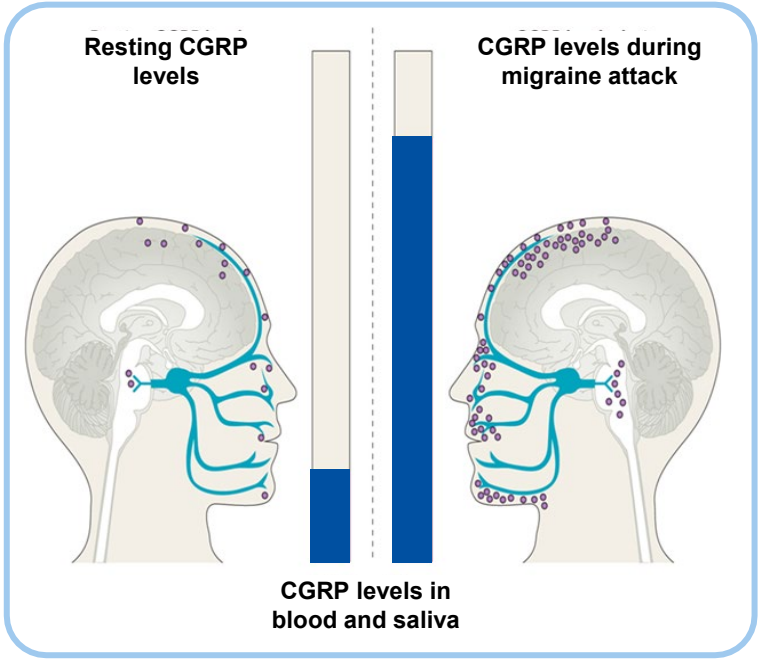
CGRP and Migraine Connection



- **CGRP receptor** activation plays a critical role in the peripheral and central mechanisms that ultimately lead to migraine pain
  - Serum CGRP levels are elevated in migraine
  - CGRP infusion evokes migraine
- CGRP receptor antagonist small-molecule gepants effectively terminate migraine attacks
- Anti-CGRP and anti-CGRP receptor monoclonal antibodies are approved for the prevention of episodic migraine (EM) and chronic migraine (CM)

Edvinsson L, et al. *J Cereb Blood Flow Metab*. 1987;7(6):720-728. Edvinsson L, et al. *Neurosci Lett*. 1985;58(2):213-217. McCulloch J, et al. *Proc Natl Acad Sci USA*. 1986;83(15):5731-5735. Edvinsson L. *Trends Neurosci*. 1985;8:126-131. Lassen LH, et al. *Cephalalgia*. 2002;22(1):54-61. Goadsby PJ, et al. *Brain*. 1994;117(Pt 3):427-434. Olesen J, et al. *N Engl J Med*. 2004;350(11):1104-1110. Ho TW, et al. *Neurology*. 2008;70(16):1304-1312. Voss T, et al. *Cephalalgia*. 2016;36(9):887-898. Tso AR, et al. *Curr Treat Options Neurol*. 2017;19(8):27. Levy D. *Brain*. 2023;146(12):4796-4798.

Acute Migraine Clinical Trial Endpoints

Co-primary endpoints

- Pain freedom at 2 hours
  - Treat at moderate to severe must go to NO PAIN in 2 hours
  - More in line with patient needs and prescriber wishes
- Freedom from most bothersome symptom (MBS) at 2 hours
  - Patient chooses from list of nausea, photophobia, or phonophobia as most bothersome associated symptom they will treat at start of attack
  - Epidemiology studies show ~50% of people with migraine state photophobia is MBS

Different from past endpoints

- Pain relief from moderate to severe pain to mild to none
- Triptan/NSAID/ergot studies all prior to 2009/2010 were using this as primary endpoint

Focus on patient-reported outcomes

- Return to normal function
- Satisfaction with treatment
- Reduction in disability

Lasmiditan

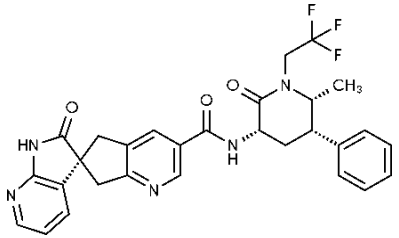
- Presumed mechanism of action: Peripheral and central activation of 5-HT_{1F} receptors
- Lacks vasoconstrictive activity
- Dose 50, 100, or 200 mg
- 2-hour pain freedom: ~30% vs ~18% placebo
- Most common adverse events (AEs): Dizziness, paresthesia, and somnolence
- Schedule V (controlled medication, same category as pregabalin)
  - Patients advised not to drive/operate machinery for 8 hours after dosing, even if no central nervous system AEs (somnolence, dizziness)

Kuca B, et al. *Neurology*. 2018;91(24):e2222-e2232. Goadsby PJ, et al. *Brain*. 2019;142(7):1894-1904. Oswald JC, Schuster NM. *J Pain Res*. 2018;11:2221-2227.

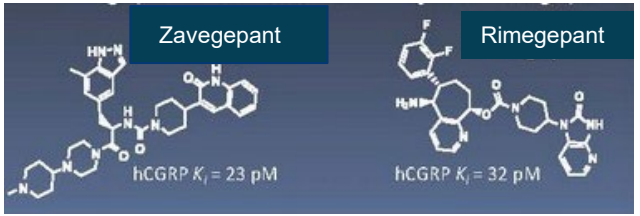
The Gepants for Acute Treatment of Migraine

ACUTE treatment of migraine

- Gepants, a newer class of migraine therapy, are CGRP receptor antagonists
- 7 gepants have demonstrated efficacy in acute migraine treatment
- Early gepants were liver-toxic; new ones are not
- **Ubrogepant tablets approved Dec 2019 for acute migraine treatment in adults**
- **Rimegepant orally dissolvable tablets approved Feb 2020 for acute migraine treatment (and approved 2021 for EM prevention) in adults**
- **Zavegepant** nasal spray gepant for acute migraine treatment in adults (FDA approved in March 2023)
- Gepants do not cause blood vessels to constrict; so, unlike triptans, should be safe in people with vascular disease



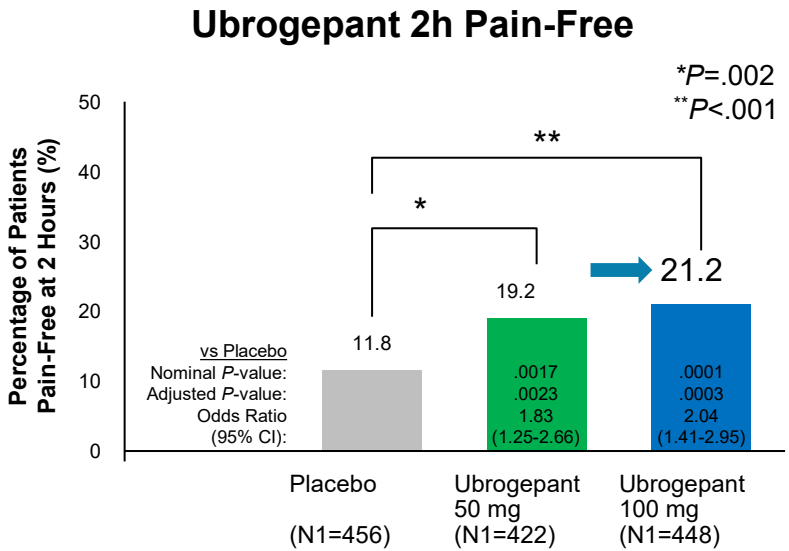
Ubrogepant

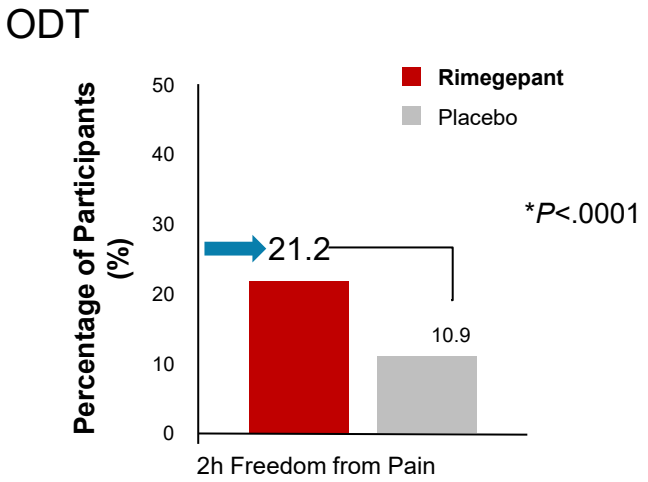


EM = episodic migraine.

Tepper SJ. *Headache*. 2018;58(Suppl 3):238-275. Tepper SJ. *Headache*. 2018;58(Suppl 3):276-290. Croop R, et al. *Neurology*. 2021;96(15 Suppl):4976. FDA. October 9, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211765s000lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212728s006lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216386s000lbl.pdf.

Representative Regulatory Gepant Trials: 2-Hour Pain-Free vs Placebo, Phase 3 Studies Side by Side – Same Efficacy





- For the 2 approved gepant tablets: Adverse events drowsiness, nausea, dry mouth, allergic reactions ≤2% over placebo
- Zavegepant (formerly vazegepant) nasal spray 10 mg also resulted in 2h pain-free of 22.5% in Phase 2/3 study

ODT = oral disintegrating tablet.

Dodick DW, et al. *N Engl J Med.* 2019;381(23):2230-2241. Croop R, et al. *Lancet.* 2019;394(10200):737-745. Croop R, et al. *Neurology*. 2021;96(15 Suppl):4976.

Rimegepant

Effects of Rimegepant 75 mg on Monthly Migraine Days: a 52-Week, Open-Label Extension Study (P10-12.010)

Robert Croop, Jessica Ailani, David Kudrow, Timothy Smith, Richard Lipton, Alexandra Thiry, Christopher Jensen, and Lisa Kamen

Treatment with rimegepant every other day plus as-needed on nonscheduled dosing days led to a ≥50% reduction in monthly migraine days in >80% of subjects and a 100% reduction in monthly migraine days in ~50% of subjects

Croop R, et al. *Neurology*. 2023;100(17 Suppl 2):P10-12.010.

Zavegepant

- FDA-approved CGRP receptor antagonist for the acute treatment of migraine in adults
  - The first gepant nasal spray
- Helpful for patients who need a non-oral medication and have a triptan contraindication
- Pain freedom at 2 hours: 24% (vs 15% placebo, *P*<.001)
- Freedom from most bothersome symptom: 40% (vs 31% placebo, *P*=.0012)
- Benefit was seen as early as 15 minutes from first dose
- Most common adverse effects were dysgeusia, nasal discomfort, and nausea

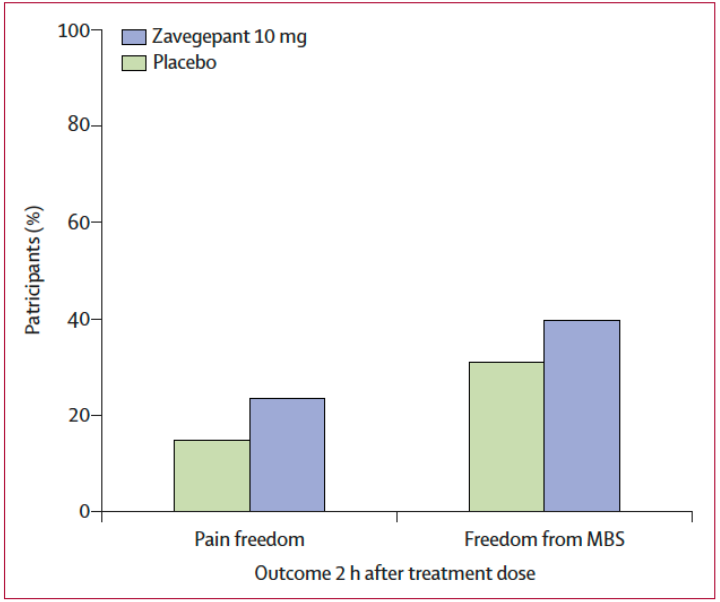


Figure 2: **Zavegepant versus placebo for pain freedom and freedom from the most bothersome symptom (MBS) at 2 h after treatment dose**
Pain freedom was defined as a pain intensity of none. Freedom from the MBS was defined as an absence of the MBS reported immediately before dosing.

Lipton RB, et al. *Lancet Neurol*. 2023;22(3):209-217.

Safety Concerns Associated with Acute Migraine Treatments

Triptans and Ergots/DHE	• Contraindicated in patients with vascular disease • Eletriptan and DHE metabolized by CYP3A4
NSAIDs	• Contraindicated in PUD and renal disease • May worsen hypertension • Risk of medication overuse
Lasmiditan	• 8-hour driving restriction • Schedule V medication • CYP3A4, P-gp, and BCRP interactions
Gepants	• CYP3A4 interaction
Narcotics and Butalbital	• Lead to medication overuse, overdose, sedation, abuse, and myriad bad patient outcomes • Reduce efficacy of both preventive and other acute medications • **<u>Should not ever be used in acute treatment of migraine!</u>**

PUD = peptic ulcer disease; BCRP = breast cancer resistance protein.
FDA. Accessed October 10, 2024. https://www.accessdata.fda.gov/scripts/cder/daf/.

Migraine Preventative Therapy

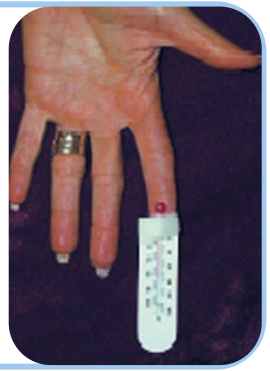
Behavioral Interventions That May Help Prevent Migraine

Regular exercise

Structured treatment plan—*follow the program!*

Consider biofeedback,

cognitive behavioral therapy



Caffeine—taper to 2 a day or less

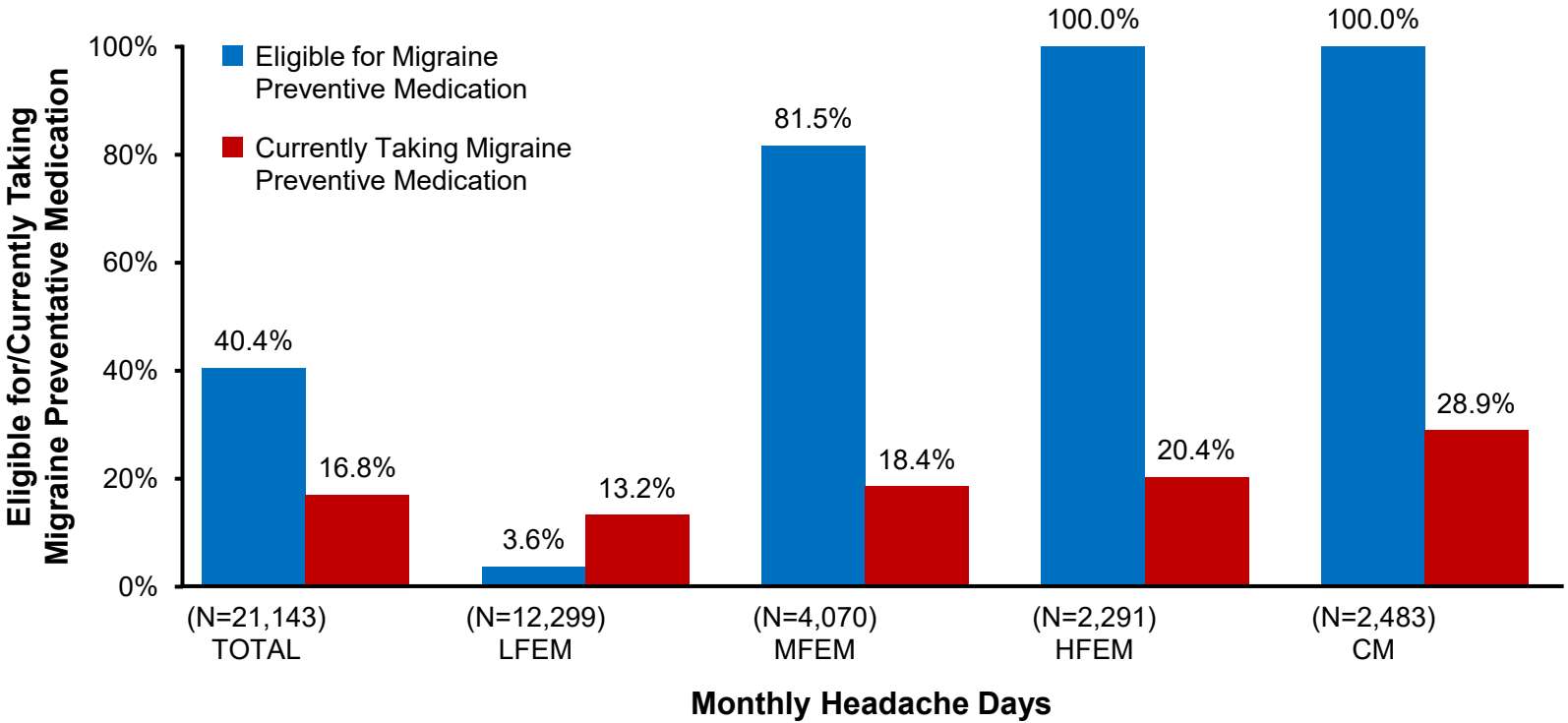
Fluids—maintain hydration

Regulate sleep

Don’t skip meals!

Especially breakfast

Preventive Medications Are Underutilized



LFEM = low-frequency EM; MFEM = moderate-frequency EM; HFEM = high-frequency EM; CM = chronic migraine.

Lipton RB, et al. *Headache*. 2022;62(2):122-140.

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Oral Preventive Therapies (Non-Specific) for Episodic Migraine before Monoclonal Antibodies: US Classification/Level of Evidence

Level of Evidence/Efficacy	Drug Class/Agent
LEVEL A Established Efficacy	• Antiepileptic drugs: Divalproex sodium[a], sodium valproate[a], topiramate[a] • Beta-blockers: Metoprolol, propranolol[a], timolol[a] • Angiotensin receptor blockers: Candesartan (studies now suggest level A efficacy)[b]
LEVEL B Probably Effective	• Antidepressants TCA/SNRI: Amitriptyline, venlafaxine • Beta-blockers: Atenolol, nadolol
LEVEL C Possibly Effective	• ACE inhibitors: Lisinopril • Beta-blockers: Nebivolol, pindolol • Alpha agonists: Clonidine, guanfacine • Antiepileptic drugs: Carbamazepine • Antihistamines: Cyproheptadine

The only FDA-approved medication for chronic migraine prior to 2018 was onabotulinumtoxin A

[a]FDA-approved; [b]Not in original paper.
TCA = tricyclic antidepressant; SNRI = selective norepinephrine reuptake inhibitor;
ACE = angiotensin-converting enzyme.
Silberstein SD, et al. *Neurology*. 2012;78(17):1337-1345.

Preventative Medications: Choices Based on Side Effects and Comorbidities

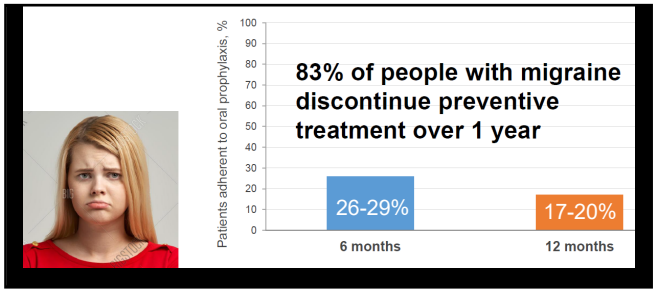
Area of concern	Consider	Avoid
Side effects[a]		
General	Verapamil and memantine well tolerated; lisinopril and candesartan if normal blood pressure	Valproate, topiramate, amitriptyline
Weight gain	Topiramate, venlafaxine	Valproate, amitriptyline, cyproheptadine
Fatigue/exercise intolerance	Topiramate, venlafaxine	Beta-blockers, amitriptyline, verapamil
Cognitive symptoms	Verapamil, lisinopril, candesartan, venlafaxine, memantine	Antiepileptic drugs
Contraindications		
Hypotension		Antihypertensive drugs
Nephrolithiasis		Topiramate, zonisamide
Possibility of pregnancy	Propranolol first line; amitriptyline, verapamil, coenzyme Q10 second line	Valproate, topiramate, lisinopril, candesartan, feverfew
Glaucoma		Topiramate (narrow-angle glaucoma), amitriptyline
Comorbidities		
Insomnia	Amitriptyline, melatonin	Memantine
Anxiety	Beta-blockers	Topiramate
Depression	Venlafaxine	Beta-blockers
Hypertension	Antihypertensive drugs	Erenumab, venlafaxine, duloxetine
Obesity	Topiramate	Valproate, amitriptyline
Frequent migraine aura	Verapamil, valproate, magnesium, topiramate	None identified

[a] Herbal and nutritional supplements and behavioral treatments are good choices for patients with side effect concerns.

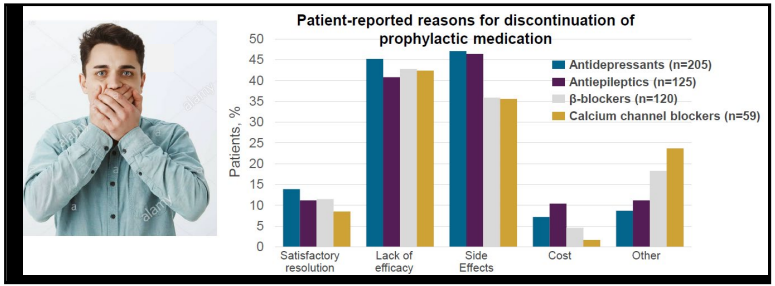
Burch R. *Continuum* (Minneap Minn). 2021;27(3):613-632.

Terrible Adherence to Oral Preventive Medication

- US claims database analysis: Insured patients with migraine (N=8688)
- Lack of efficacy and/or medication side effects are the most common reasons for discontinuation of preventive medication

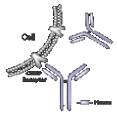
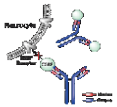
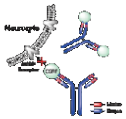
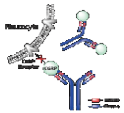


- International Burden of Migraine Study-II assessed preventive therapy patterns in 1165 patients with migraine



Hepp Z, et al. *Cephalalgia*. 2015;35(6):478-488. Blumenfeld AM, et al. *Headache*. 2013;53(4):644-655.

4 Monoclonal Antibodies to CGRP or its Receptor for Migraine

	Erenumab-aooe	Fremanezumab-vfrm	Galcanezumab-gnlm	Eptinezumab-jjmr
Approved in adults for	EM, CM	EM, CM	EM, CM, eCH	EM, CM
Route and dosing	 Monthly SC 70, 140 mg	 Monthly or quarterly SC; 225 mg monthly, or 675 mg Q3 months	 For migraine: Monthly SC; 240 mg loading dose, then 120 mg SC monthly thereafter; For eCH: 300 mg SC, then 300 mg monthly to cycle end	 100 mg or 300 mg Q3 months IV
Target	CGRP receptor	CGRP peptide or ligand	CGRP peptide or ligand	CGRP peptide or ligand

eCH = episodic cluster headache.

Tepper SJ. *Headache*. 2018;58(Suppl 3):238-275. Tepper SJ. *Headache*. 2018;58(Suppl 3):276-290. Edvinsson L. *Headache*. 2018;58(Suppl 1):33-47.

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Safety Considerations

	Erenumab (SC 70 or 140 mg once monthly)	Fremanezumab (SC 225 mg monthly; 675 mg quarterly)	Galcanezumab (SC 240 mg loading dose, then 120 mg monthly)	Eptinezumab (IV 300, 100 mg quarterly)
Treatment Groups	Injection site reactions Ph 3 RCTs (6, 5%) Constipation (1, 3%) Cramps, muscle spasms (<1, 2%)	Injection site reactions (43, 45% Ph 3 RCTs) (6, 4% FOCUS study)	Injection site reactions Ph 3 RCTs (18%)	URI (11, 7, 6, 7%) Dizziness (2, 10, 3, 12%) Nausea (7, 7, 3, 5%)
Placebo Group	Injection site reactions (3%) Constipation (1%) Cramps, muscle spasms (<1%)	Injection site reactions (38%)	Injection site reactions (13%)	URI (5%) Dizziness (7%) Nausea (7%)

- **Liver:** So far, LFT abnormalities have not been seen in excess of placebo

- **URI:** So far, not with every product and not always in excess of placebo

- **Constipation:** Warning in US erenumab prescribing information (PI); noted for galcanezumab in EU PI
- **Hypertension:** Warning in US erenumab prescribing information; debated in prospectively collected safety data

- **CV toxicity:** No signal across 5 years of safety data; one intravenous erenumab study in patients with angina

RCTs = randomized controlled trials; URI = upper respiratory infection; LFT = liver function test; CV = cardiovascular.

Camporeale A, et al. *BMC Neurol*. 2018;18(1):188. Dodick DW, et al. *Cephalalgia*. 2019;39(9):1075-1085. Ashina M, et al. *Cephalalgia*. 2019;39(11):1455-1464. Tepper SJ, et al. *Cephalalgia*. 2020;40(6):543-553. Goadsby PJ, et al. *Neurology*. 2020;95(18):e2487-e2499. Ashina M, et al. *Eur J Neurol*. 2021;28(5):1716-1725. Kudrow D, et al. *BMC Neurol*. 2021;21(1):126. Depre C, et al. *Headache*. 2018;58(5):715-723. Dodick D, et al. *Headache*. 2021;61(9):1411-1420.

Are mAbs an Improvement? Secondary Endpoints

- Areas of superiority to non-specific migraine-preventive medications
  - Onset of effect: All separate from placebo for EM and CM
  - Effectiveness in those with multiple previous preventive medication failures: 3 effective in RCTs in those for whom 2-4 preventive meds failed
  - Responder rates: 40-53% have ≥75% reduction in MMDs by 1 year
  - Conversion of CM to EM and from acute medication overuse and medication overuse headache to non-overuse in ~50% or more
  - Overall placebo-subtracted and direct-comparison risk/benefit analysis

MMDs = mean monthly migraine days.
Lipton RB, et al. *Neurology*. 2019;92(19):e2250-e2260.

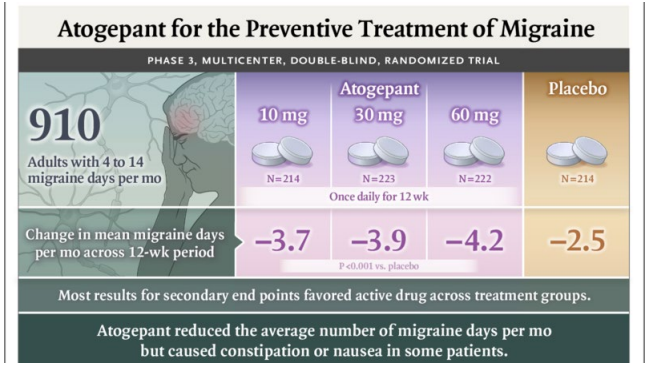
Gepants: Rimegepant and Atogepant for EM Prevention

Baseline: ~10 migraine days/month	Rimegepant (n=348)		Placebo (n=347)	
	n	Point estimate (95% CI)	n	Point estimate (95% CI)
Change in mean number of migraine days per month during weeks 9–12, days (primary efficacy outcome)	348	−4·3 (−4·8 to −3·9)	347	−3·5 (−4·0 to −3·0)

- Rimegepant studied for both EM and CM prevention
  - FDA-approved only for EM prevention in May 2021
  - Dose QOD 75 mg
- Atogepant FDA-approved for EM prevention Sept 2021
  - 3 doses: 10, 30, 60 mg QD

- Rimegepant adverse events: Nausea, allergy ≤2%
- Atogepant adverse events: Nausea, constipation, somnolence, anorexia <10%

Baseline 7.5 – 7.9 migraine days/month

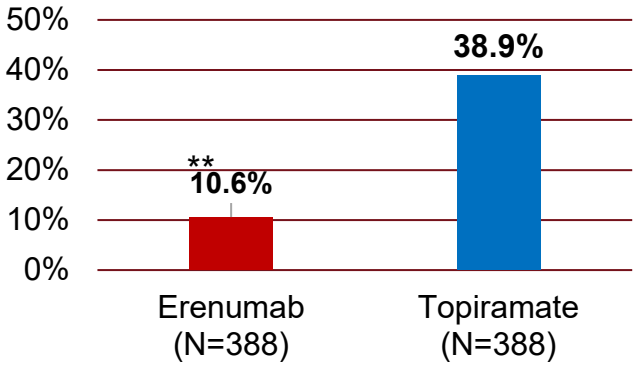


Croop R, et al. *Lancet*. 2021;397(10268):51-60. Ailani J, et al. *N Engl J Med*. 2021;385(8):695-706. FDA. Accessed October 10, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212728s006lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215206s004lbl.pdf.

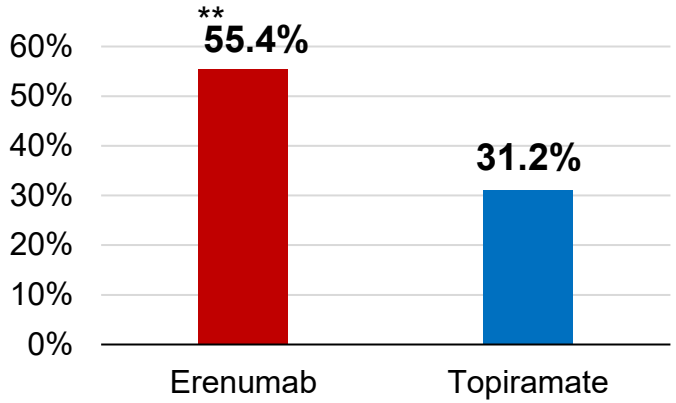
Direct Comparison of Erenumab to Topiramate

- HER-MES trial in Germany: 777 patients randomized to erenumab 70, 140, or TPM (6-week titration to 50-100 mg)
- Primary endpoint: Treatment discontinuation due to AEs during the double-blind treatment period

Treatment discontinuation due to adverse events



≥50% reduction of monthly migraine days over months 4-6



- All endpoints demonstrated superiority for erenumab over TPM, so for efficacy, tolerability, and adherence
- Post-hoc analysis of mean monthly migraine reduction

****P<.001 vs topiramate.**
TPM = topiramate.
Reuter U, et al. *Cephalalgia*. 2022;42(2):108-118.

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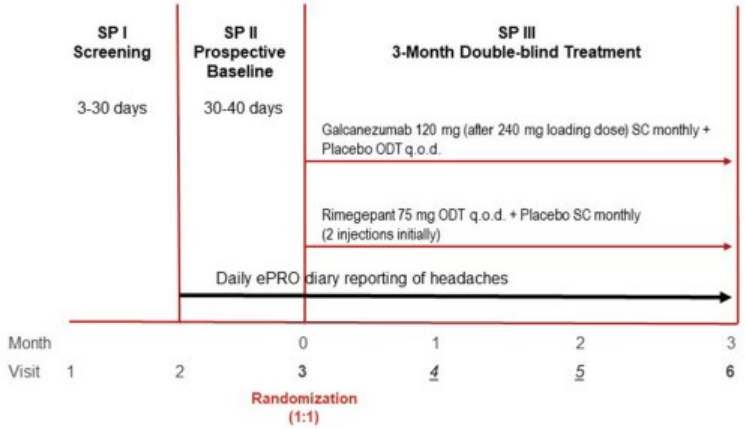
ORIGINAL RESEARCH

Comparing the Efficacy and Safety of Galcanezumab Versus Rimegepant for Prevention of Episodic Migraine: Results from a Randomized, Controlled Clinical Trial

Todd J. Schwedt · Tina M. Myers Oakes · James M. Martinez · Bert B. Vargas · Hitendra Pandey · Eric M. Pearlman · Diane R. Richardson · Oralee J. Varnado · Michael Cobas Meyer · Peter J. Goadsby



"Galcanezumab was not superior to rimegepant for the primary endpoint; however, both interventions demonstrated efficacy as preventive treatments in participants with episodic migraine."

Schwedt TJ, et al. *Neurol Ther*. 2024;13(1):85-105.

Who Should Receive New Acute Treatments?

AHS position statement, 2021

- Should be available to be prescribed by any licensed healthcare provider to patients who meet the following criteria
  - Patients with contraindications to triptans or
  - Patients with lack of adequate response to ≥2 oral triptans or
  - Patients with lack of tolerability with ≥2 oral triptans
  - Determined by either healthcare provider attestation or validated patient-reported outcome (PRO) questionnaire
- Treat with older meds for ≥2 attacks to evaluate efficacy and tolerability

NHF position statement, 2022

- The selection of a migraine therapy
  - *Should ultimately be* determined by the clinician, in collaboration with the patient, based on the individual needs of that patient and that patient's outcomes
  - *Should not* be determined solely by a step-care model
  - *Should not* be determined by a one-size-fits-all algorithm, including models focused predominantly on costs instead of outcomes

AHS = American Headache Society; NHF = National Headache Foundation.

Ailani J, et al. *Headache*. 2021;61(7):1021-1039. GlobeNewswire. January 19, 2022. Accessed October 10, 2024. https://www.globenewswire.com/news-release/2022/01/19/2369687/0/en/National-Headache-Foundation-Position-Statement-on-the-Treatment-of-Migraine.html.

FEATURE ARTICLE

Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update

Andrew C. Charles MD[1] | Kathleen B. Digre MD[2] | Peter J. Goadsby MD, PhD[1,3] | Matthew S. Robbins MD[4] | Andrew Hershey MD, PhD[5,6] | on behalf of The American Headache Society

Charles AC, et al. *Headache*. 2024;64(4):333-341.

Combination Therapy

ORIGINAL RESEARCH

Safety and Tolerability of Combining CGRP Monoclonal Antibodies with Gepants in Patients with Migraine: A Retrospective Study

Taoufik Alsaadi · Reem Suliman · Vanessa Santos · Ibrahim Al Qaisi · Princess Carmina · Batool Aldaher · Shadi Haddad · Yazan Bader

Received: December 25, 2023 / Accepted: January 29, 2024 / Published online: February 15, 2024

- The findings of this study demonstrate that combining CGRP mAbs with gepants is a safe and well-tolerated treatment approach for migraine
- Future studies are warranted to further validate these findings and explore long-term outcomes

Alsaadi T, et al. *Neurol Ther*. 2024;13(2):465-473.

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Part Three

Migraine: The Time Thief
It’s Time to Ask

Migraine: Consider and Ask…

Do you get headaches?
- In primary care, most will be migraine

Do you have associated symptoms with these headaches?
- 2/3 photophobia, nausea, impairment, and most will be migraine

How many days/month are you impacted by these headaches?
- 1 day/month – offer acute Rx
- 4 or more days/month – also offer prevention Rx

Can you schedule an appointment just to focus on these headaches?
- Over 1/3 patients with migraine think we will be dismissive

Partner with the patient in choosing their therapy
- Shared decision-making often leads to improved outcomes

Lipton RB, et al. *Neurology*. 2003;61(3):375-382. Ailani J, et al. *Headache*. 2021;61(7):1021-1039.

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Migraine in Primary Care: We Can Make a Difference…If We Ask

29% Of patients we see in primary care have migraine

50% Of patients with migraine don't have a migraine diagnosis

40% Of patients with migraine are candidates for prevention

77% Of candidates for migraine prevention are not taking Rx

Recognize and treat migraine EARLY AND EFFECTIVELY

MAXIMIZE

The chance of alleviating migraine symptoms

Functionality

REDUCE

Migraine frequency

PREVENT

Progression from episodic to chronic migraine

Couch JC, et al. *Headache*. 2003;43(5):570-571. Shapiro RE, et al. *Headache*. 2021;61:10. Ailani J, et al. *Headache*. 2021;61(7):1021-1039. Buse DC, et al. *Neurology*. 2020;94(Suppl 15):4154. Buse DC, et al. *Headache*. 2019;59(3):306-338.

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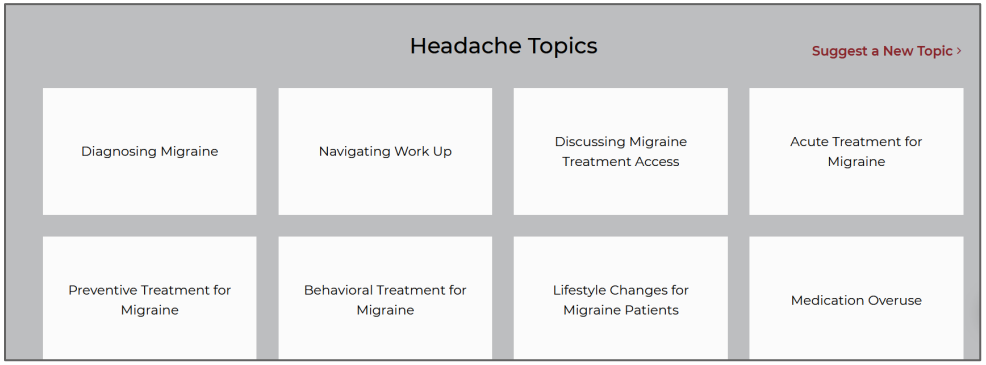
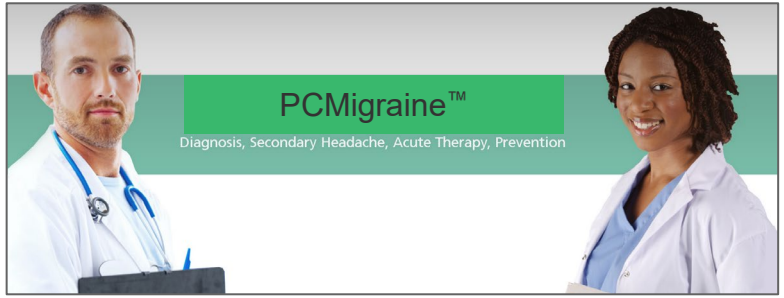
Migraine: If You Want to Learn More…
…We Suggest These Educational Resources

AHS: https://americanheadachesociety.org/primarycare



NHF's PCMigraine™: www.pcmigraine.com



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Key Learning Points

- Migraine is one of the most common medical conditions in the world
- Migraine is a leading cause of disability
- Migraine is both highly prevalent and highly underdiagnosed in PC
- Underdiagnosis and undertreatment leave significant unmet needs
- Straightforward algorithms exist to assist with diagnosing migraine in PC
- CGRP released from the trigeminal ganglion plays a critical role in both central and peripheral sensitization that leads to migraine
- Targeting the CGRP receptor or ligand can successfully treat acute migraine as well as help prevent migraine
- Many new medications targeting CGRP have been approved for acute treatment of migraine and prevention of migraine

Thank You!!

Q and A

You've Got Questions?
We've Got Answers