Migraine:

Pharmacists' Opportunities to Improve Care Via Evidenced-Based Treatments and New Medications

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Disclosures

Dr. Wenzel in the past 12 months has the following financial relationship with a manufacturer of a commercial product discussed in this CE activity:

- Consultant – Impel Pharmaceuticals

This presentation will include mention of off-label drugs:

- flurbiprofen, ketoprofen, ketorolac, amitriptyline, atenolol, lisinopril, venlafaxine, nadolol, memantine

All relationships have been mitigated

At the completion of this activity, the participant will be able to:

1. define migraine's presentation, diagnosis, and impact;

2. use algorithms and validated tools to assess whether an individual may have migraine, is appropriate for over-the-counter medications, or requires a referral;

3. recommend treatment goals and medications endorsed by evidence-based guidelines as well as the discontinuation of drugs that can exacerbate migraine;

4. describe the indications, dose/frequency, administration, and warnings and precautions of recently FDA-approved migraine medications; and

5. outline a treatment regimen given a patient case scenario.

Migraine is common

Worldwide, affects more than 1 BILLION individuals

World's 2nd leading cause of disability

- Leading cause in individuals younger than 50 years old
  - *"Disability" = unable to perform normal work, school, or social functions or ability reduced by at least 50%*

6th most prevalent disease worldwide, affecting:

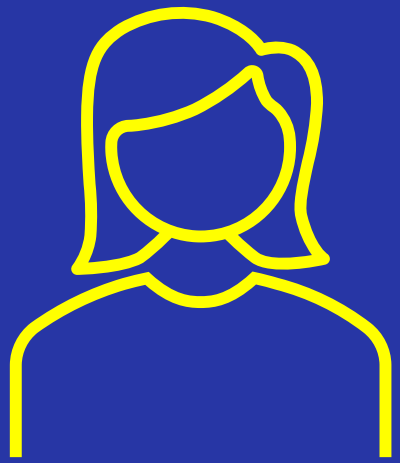
- Every ethnicity, region, culture, and socioeconomic status
- Disproportionately women
- Marital/romantic relationships
- Parenting decisions
- Family relationships
- Career/financial achievement and stability
- Overall health

Cureus. 2022 Aug 24;14(8):e28347.; Lancet. 2021 Apr 17;397(10283):1485-1495.; Lancet. 2017 Sep 16;390(10100):1211-1259.; Headache. 2013 Mar;53(3):427-36.; Headache. 2019 Sep;59(8):1286-1299.; J Pain Manag Med. 2017;3(2):126.; Medicine (Baltimore). 2016 Apr;95(17):e355.;

U.S. 1-year Migraine Prevalence

12% of adults = 30+ million people

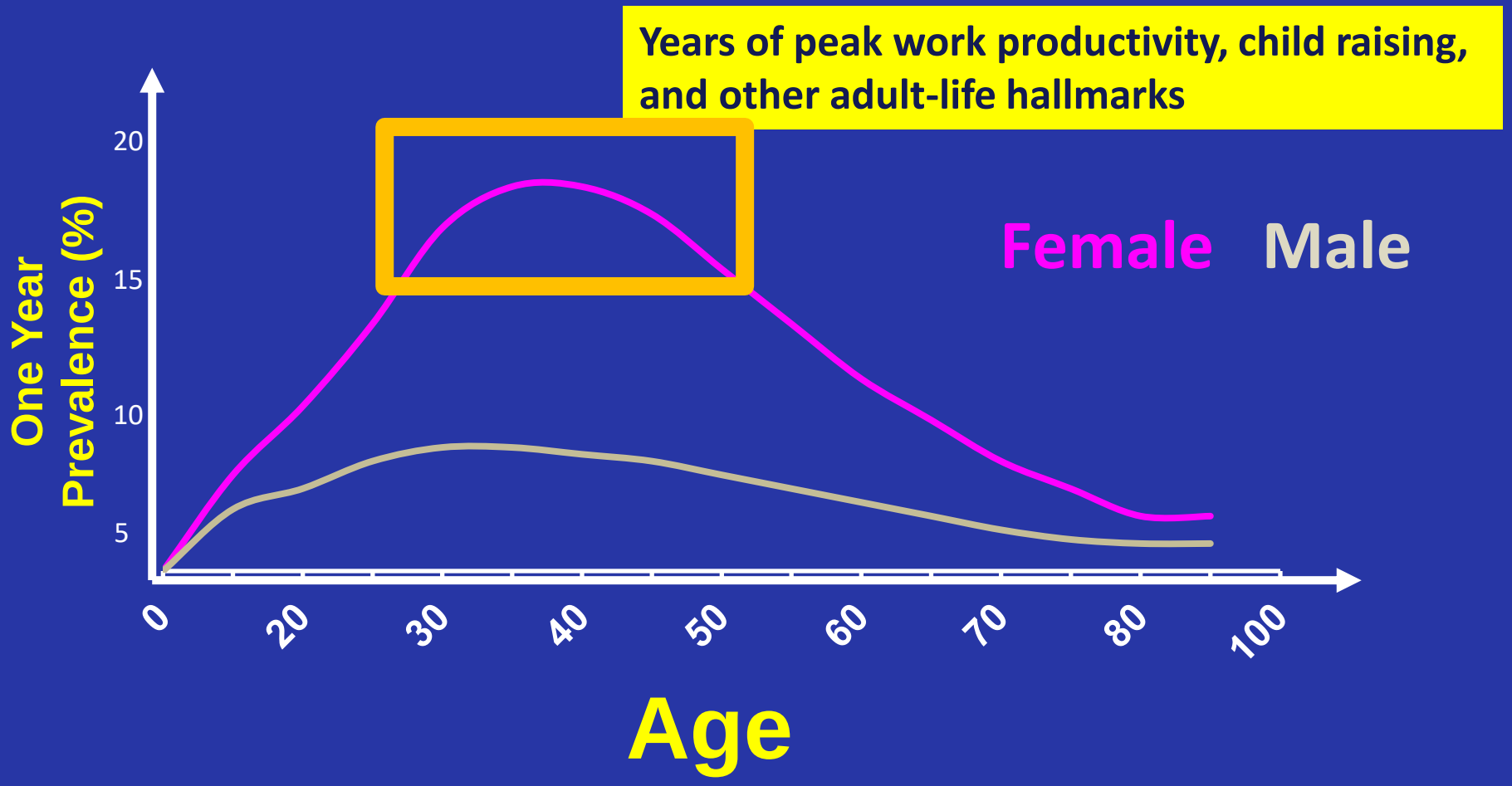
17% women



6% men

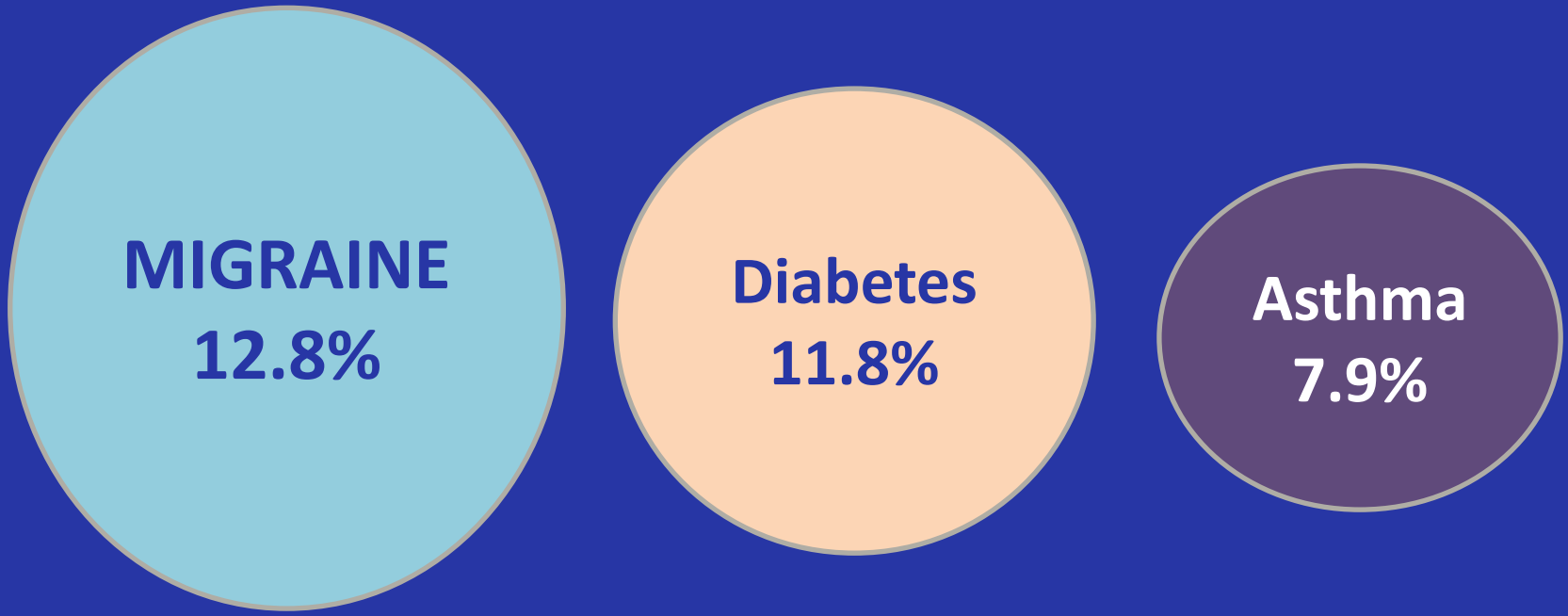
Neurology. 2007;68(5):343-349.
Images courtesy of Microsoft PowerPoint Version 2211

Prevalence



Lancet 2021; 397: 1485–95

Prevalence



www.cdc.gov/diabetes/health-equity/diabetes-by-the-numbers.html; /www.cdc.gov/asthma/data-visualizations/prevalence.htm

International Headache Society Diagnostic Criteria (ICHD-3)

Migraine without aura

A. At least five attacks fulfilling criteria B-D:

B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:

1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

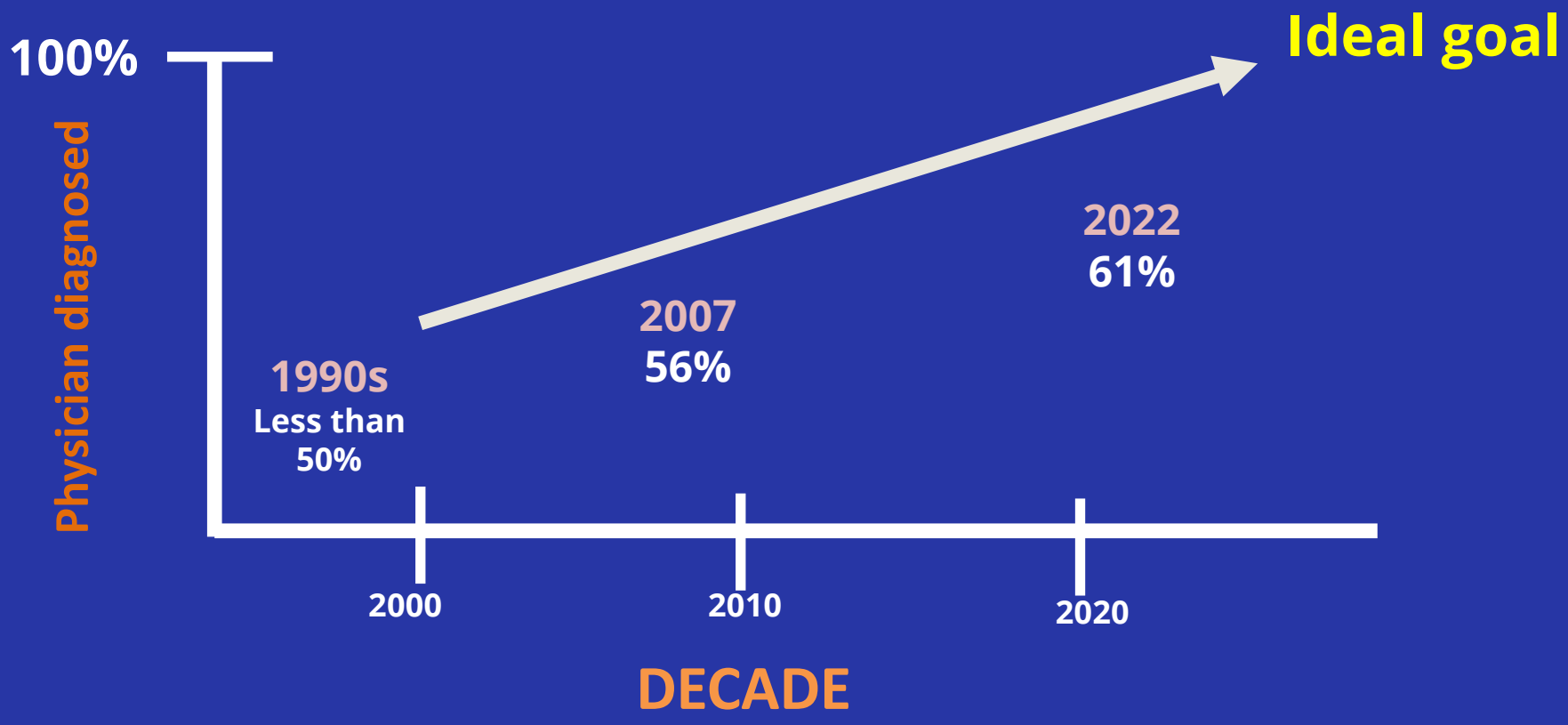
D. During headache at least one of the following:

1. Nausea and/or vomiting
2. Photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

Gobel H. 1.1 Migraine without aura. ICHD-3.

Migraine diagnosis remains low



Headache. 2022 Feb;62(2):122-140.; Neurology. 2007 Jan 30;68(5):343-9.

World Health Organization statements

Lack of providers' knowledge = principal barrier to improved migraine care

Poor awareness among the general public

Payers, seeking to constrain costs, do not acknowledge headaches' societal burdens

WHO. Headache Disorders. World Health Organization. April 8, 2016.; Lancet. 2021;397(10283):1485-1495.

PharmD candidates' migraine education

Only 55% of programs teach evidence-based migraine treatment guidelines

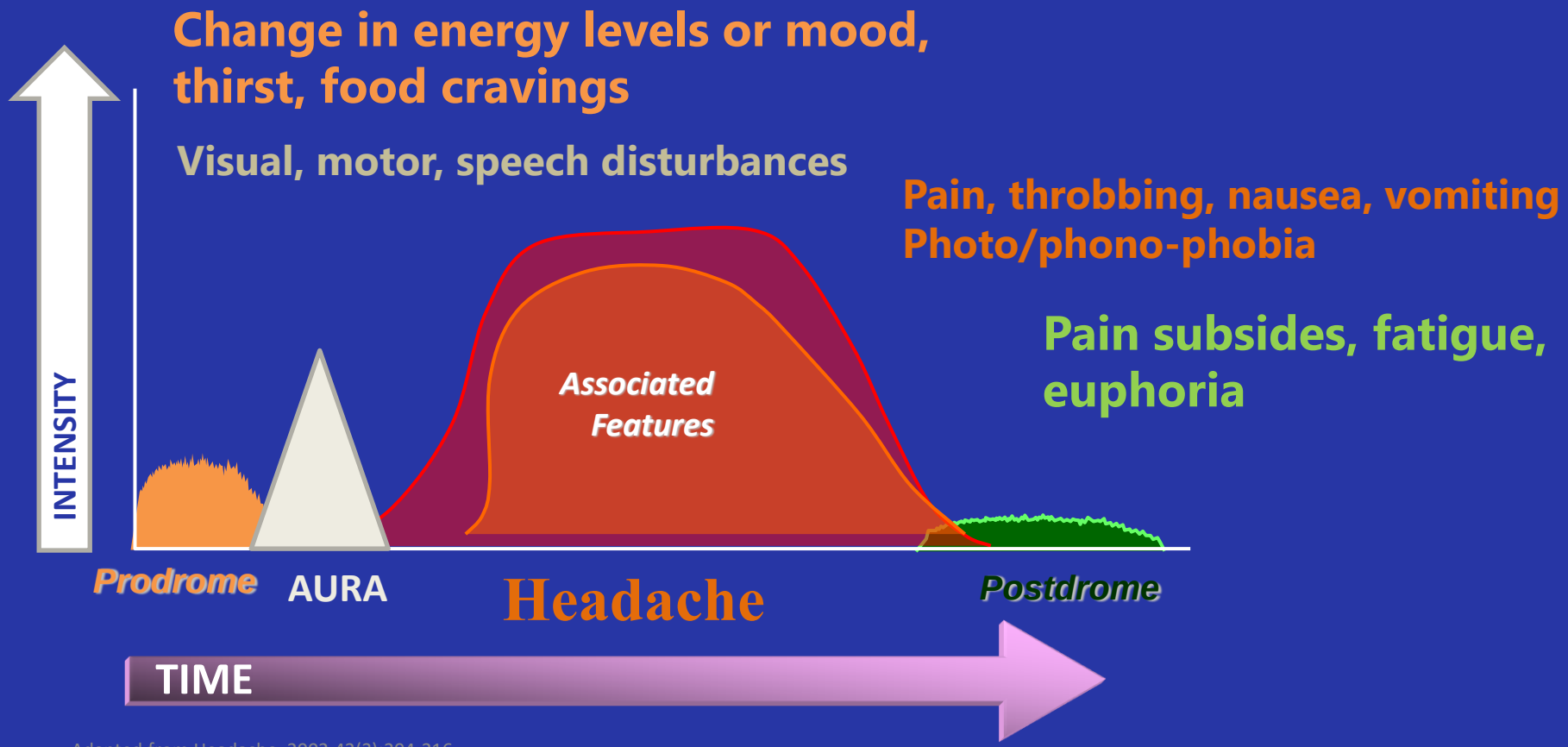
45% recommend a butalbital-containing product as treatment

49% discuss the selection of nonprescription versus prescription agents

Only 20% educated students about validated tools for assessing migraine

Wenzel et al. AJPE 2010;74:Article 4

DISTINCT PHASES



Adapted from Headache. 2002;42(3):204-216.

Pathophysiology remains poorly elucidated

- Many mechanisms proposed, none completely explain
  - Major obstacle to research and treatment
- Current understanding = hyperexcitability of trigeminal nucleus/cranial nerves
  - Subsequent neurotransmitter release
    - calcitonin gene related peptide
    - substance P
    - nitrous oxide
- Pain = neurogenic inflammation at peripheral nerve/blood vessel junction

Int J Mol Sci. 2022 Oct 27;23(21):13002., Headache: The Journal of Head and Face Pain. 2018;58:4-16.

Calcitonin Gene Related Peptide (CGRP)

CGRP levels are elevated in during ictal and interictal spans in migraine patients.

Levels do not correspond to disease severity

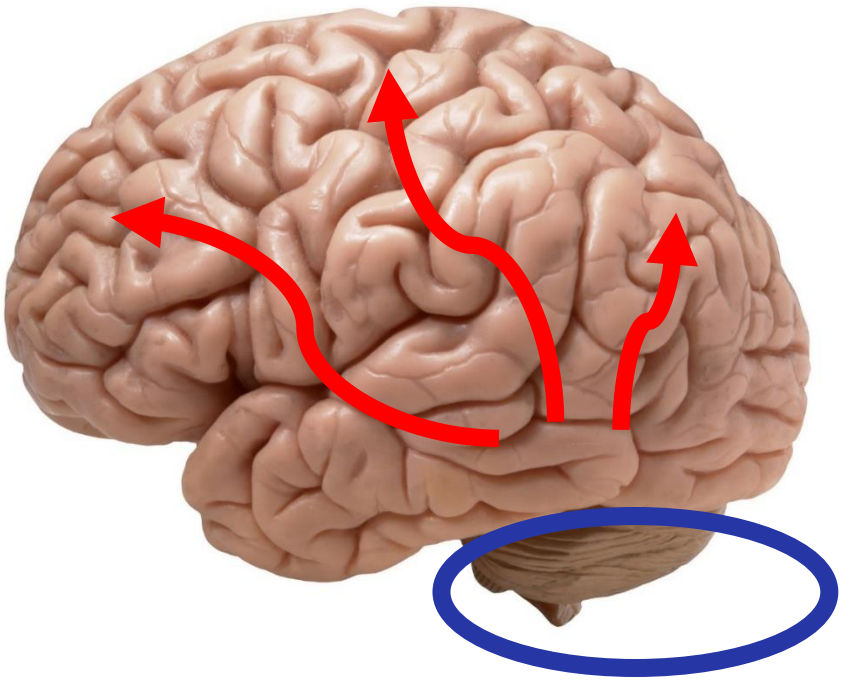
Infusion of CGRP can induce migraine-like headaches in individuals with a migraine history

CGRP levels are reduced after acute and preventive therapy (with non-CGRP drugs)

Phase III studies demonstrate CGRP medications' effectiveness

Front Neurol. 2022 Jul 27;13:930383.

Pathogenesis



Trigeminal Nucleus Caudalis

Sensory input and relay center

J Headache Pain. 2023 Jan 10;24(1):3., Int J Mol Sci. 2022 Oct 27;23(21):13002., Headache. 2018 May;58 Suppl 1:4-16.
Image courtesy of https://www.flickr.com/photos/flamephoenix1991/8376271918. Accessed February 4, 2023.

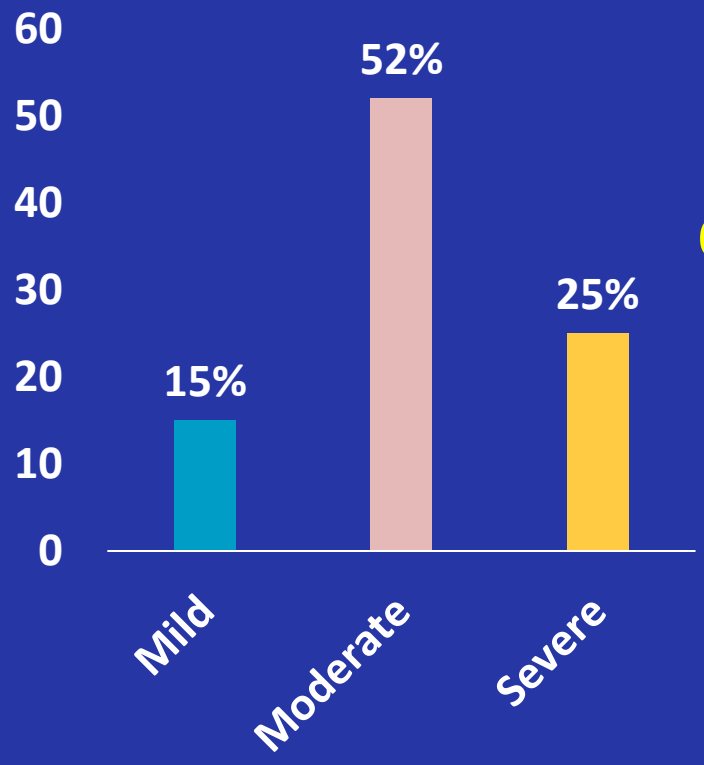
Central sensitization

- Migraine attack represents nervous system hyperexcitability
  - What initiates this process? How to prevent?
- Normally non-noxious stimuli are perceived as noxious
  - for example, light, sound, movement
- Hyperexcitability is called “central sensitization”

Acute medications’ efficacy depends on promptly disrupting this process

Headache 2003;43(7):704-14.; J Neurol 2008;15(12):1279-85.; Headache 2006;46 (Suppl 4):S182-91.; Rev Neurol 2005;161:658-60.

Pain Intensity When Medication Taken



Reason for Delaying

69% - Wait to see if really a migraine attack

46% - Only want to take medication if headache is severe

9% - Cost of medication

2.5% - Advised by provider to wait

Adapted from Headache. 2005;45:538-545.

“TRIGGERS” - a misunderstood idea

STOP!

Providing patient with a long list of “triggers” to avoid is NOT supported by research/data

N Engl J Med 2020;383:1866-76

Neurol 2021 May;268(5):1885-1893

Headache. 2023;63(1):51-61.

Headache 2022 Nov;62(10):1406-1415

Headache 2020 Jul;60(7):1300-1316

- ***“….suggesting, contrary to popular belief, that the role of these triggers is limited.”***

Diary is essential

- Headache diaries, maintained for at least 1-month's duration, are validated for:
  - Diagnosis
  - Treatment evaluation
  - Note – multiple months are even more informative
- Can utilize e-diaries
- Diaries are the best tool to identify **PATIENT-SPECIFIC** factors contributing to attacks

Lancet 2021; 397: 1485–1495.

Pharmacists' over-the-counter recommendations

- "Headache product" = 2,262,891 times per month
  75,000 times daily

- "Migraine product" = 1,673,077 times per month
  - 56,000 times daily

- *Over-the-counter acute meds' use not optimized in majority of people*

www.pharmacytimes.com/otcguide/paininflammation/migraine-headache-products; www.pharmacytimes.com/otcguide/paininflammation/headache-products;
Headache. 2022 Jun;62(6):755-765.
J Pharm Pract. 2015 Aug;28(4):413-8; Pharmacotherapy 2003:23:494-505.

“Excuse me, can you recommend something for my headache?”

1. What percentage of your headache attacks are debilitating?
2. How many days per month are you completely headache free?
3. Describe the symptoms of your attacks?
4. Prior response to OTC products?

J Pharm Pract. 2015 Aug;28(4):413-8; Pharmacotherapy 2003:23:494-505.

Assessment Tools

Diagnosis
ID MIGRAINE

Medication efficacy
Migraine-ACT
Migraine-Treatment Optimization Questionnaire
Migraine Functional Impact Questionnaire

Work-related disability
HEADWORK

Headache related disability
Migraine Disability Assessment Scale(MIDAS)
Headache Impact test (HIT-6)
Migraine Quality of Life Questionnaire

Neurology. 2003;61:375-382.; Headache. 2001;41:854-861.; Headache. 2020 Oct;60(9):1982-1994.; Qual Life Res. 2003;12:963-974.; Headache. 2020 Feb;60(2):497-504.; Headache. 2019 Sep;59(8):1253-1269.; Cephalalgia. 2009 Jul;29(7):751-9.; Headache. 2006 Apr;46(4):553-62.; Arq Neuropsiquiatr. Published online October 27, 2022:s-0042-1756490.

MIGRAINE-ACT

“Yes” or “no”, when you take your treatment:

1. Does your migraine medication work consistently in the majority of your attacks?
2. Does the headache pain disappear within 2 hours?
3. Are you able to function normally within 2 hours?
4. Are you comfortable enough with your medication to be able to plan your daily activities?

One or more “no” answers may indicate need to change treatment.

An increasing number of “no” answers indicate increasing treatment needs.

Headache. 2006 Apr;46(4):553-62.

Use of Migraine Medications

Medications	Lifetime (%)	Current (%)
Any (prescription or non)	97	94
Triptans	35	23
Opioids	48	19

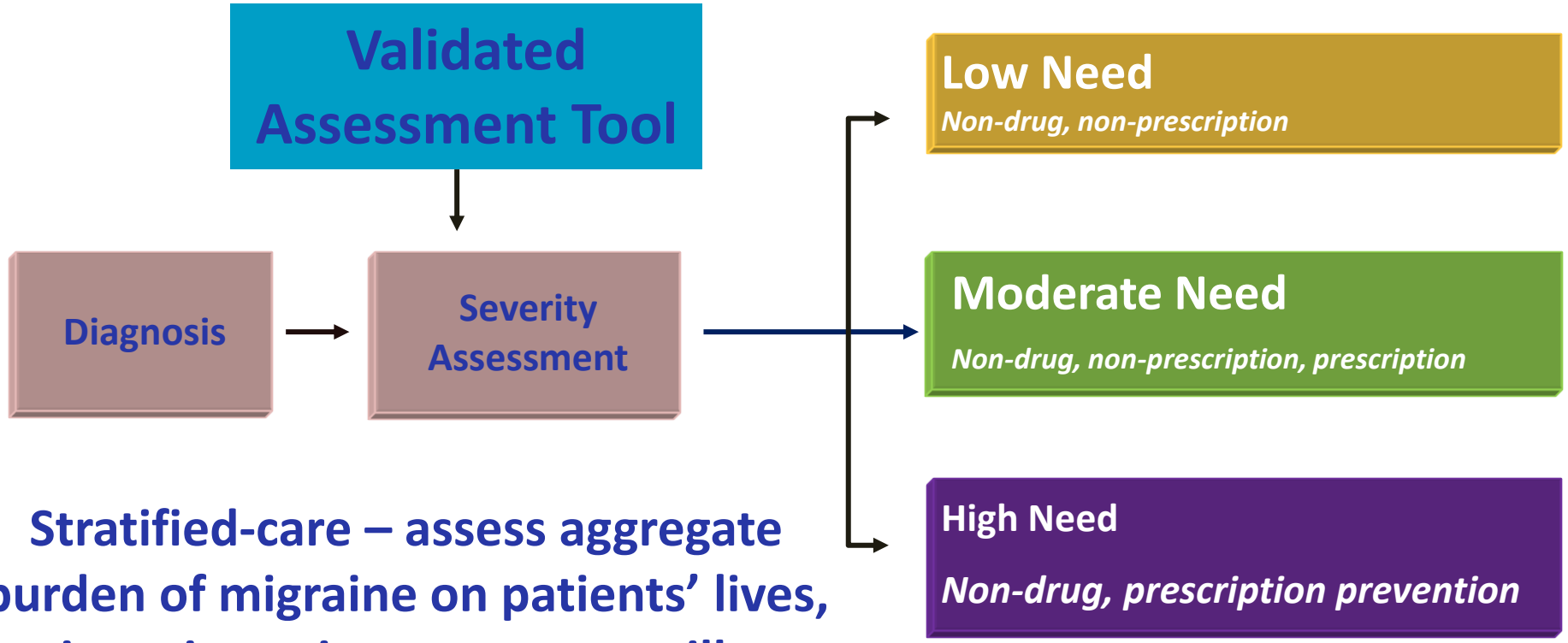
Headache. 2022 Feb;62(2):122-140.

Discontinuing Acute Medications

- N = 13,624
- 42% had moderate to severe disability (as per MIDAS)
- Reasons for prescription medication discontinuation
  - 46% were switching to non-prescription medication
  - 28% concerns about efficacy
  - 25% concerns tolerability

Headache. 2019;59(10):1762-1772.

STRATIFIED CARE



Stratified-care – assess aggregate burden of migraine on patients' lives, patients incurring most severe illness are prescribed migraine specific drugs from the onset

JAMA. 2000;284:2599–2605.; Am J Med. 2005 Mar;118 Suppl 1:18S-27S.

Overall goals per guidelines

- Establish diagnosis
- Educate patient
  - Preventive/acute drugs, devices, limits of use
- Set realistic expectations
  - No cures, only management
- Create formal management plan
- Avoid precipitating causes
  - Diary

Behavioral therapies are effective

- Grade A evidence supporting their use
  - example: biofeedback

- Well suited for patients who:
  - Prefer nonpharmacologic interventions
  - Have inadequate response, poor tolerance, or medical contraindications to specific pharmacologic treatments
  - Are pregnant, lactating, or planning to become pregnant
  - Have a history of acute medication overuse or medication-overuse headache
  - Exhibit significant stress or deficient stress-coping skills
  - Have high migraine-related disability, and/or low Health Related Quality of Life, and/or comorbidities.

Cleve Clin J Med. 2010;77(Suppl 3):S72–S76.

Acute Treatment Goals

- **Restored ability to function**
- Rapid and consistent freedom from pain and associated symptoms, especially the most bothersome symptom, without recurrence
- Minimal need for repeat dosing or rescue medications
- Optimal self-care and reduced subsequent use of resources (e.g., emergency room visits)
- Minimal or no adverse events (early intervention can reduce adverse events)
- Cost considerations

Headache. 2021 Jul;61(7):1021-1039

Acute Meds Limits

- Guidelines endorse “2 days” per week (multiple doses allowed)
  - Educate patient to seek clinician’s help if exceeding
- Overuse of acute medications is associated with
  - Increased risks of migraine progression
  - Greater headache-related disability
  - Comorbid anxiety and depression

Headache. 2021 Apr;61(4):628-641.

Guideline Endorsed Acute Treatment

Established Efficacy	Probably Effective
Triptans*	Ergotamine*
Dihydroergotamine*	NSAIDS (flurbiprofen, ketoprofen, ketorolac)
Gepants*	Intravenous magnesium
Lasmiditan*	Isometheptene compounds
NSAIDS (aspirin, celecoxib oral solution, diclofenac, ibuprofen, naproxen)**#	Antiemetics
Combination acetaminophen/aspirin/caffeine*#	
* FDA-approved ** Some drugs in this class FDA-approved # Some drugs for mild-to-moderate migraine	

Headache. 2021;61:1021-1039.

Consider Preventive Medication

- Attacks significantly interfere with daily routines despite acute treatment
- Frequent attacks **(see next slide)**
- Contraindication to, failure of, or overuse of acute treatments
- Intolerable adverse events with acute treatments
- Patient preference

Headache. 2021 Jul;61(7):1021-1039.

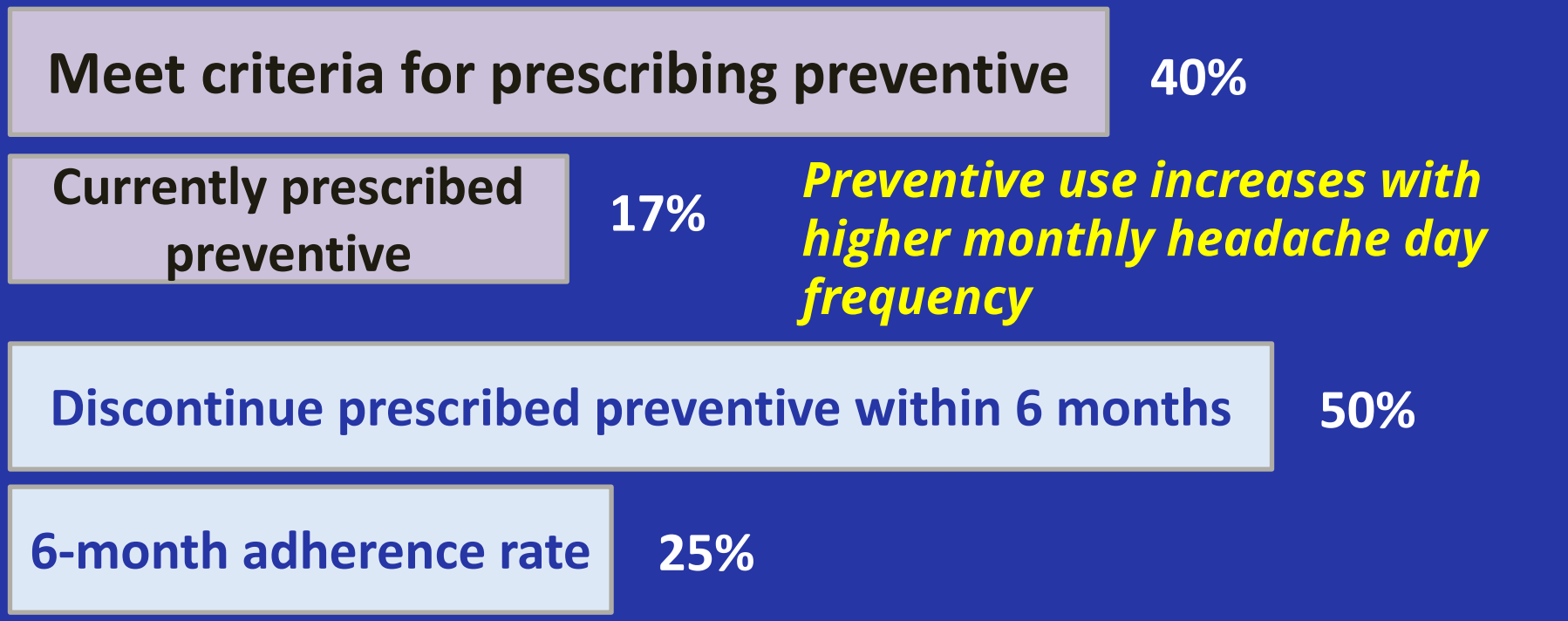
Prevention Should Be:	Headache Days per Month	Disability (Per Migraine Disability Assessment Scale, Migraine Physical Function Impact Diary, or Headache Impact Test)
Offered	6 or more	None
	4 or more	Some
	3 or more	Severe
Considered	4 or 5	None
	3	Some
	2	Severe

Preventive goals

- **Reduce attack frequency, severity, duration, and disability**
- Improve responsiveness to/avoid escalation of acute treatments
- Improve function and reduce disability
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute treatments
- Reduce overall costs
- Empower patients to manage their disease
- Improve health-related quality of life

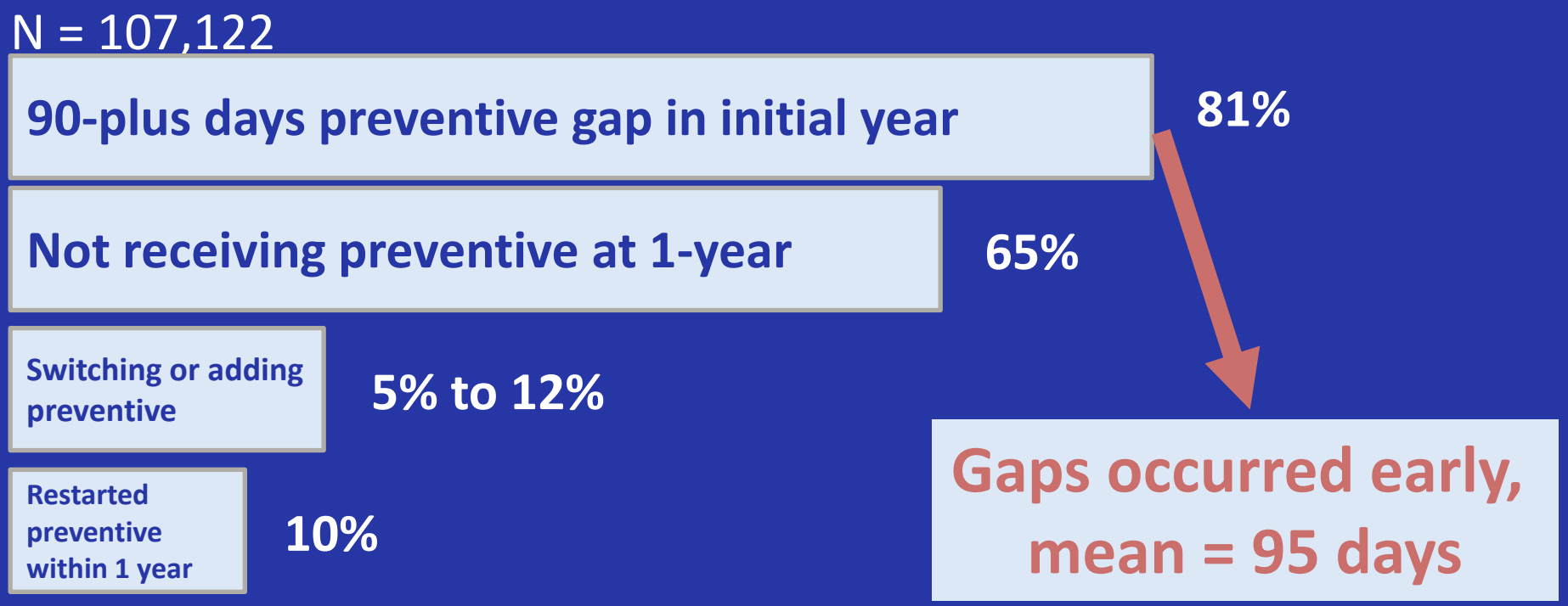
Headache. 2021;61:1021-1039.

Migraine Preventive Medications



Headache. 2022 Feb;62(2):122-14.; Patient Prefer Adherence. 2022 Mar 29;16:821-839.

Preventive Drugs: Adherence and persistence



Headache. 2017 Oct;57(9):1399-1408.

Guideline Endorsed Preventives

Established Efficacy		Probably Effective	
ORAL	**PARENTERAL**	**ORAL**	**PARENTERAL**
Divalproex*	Erenumab-aooe*	Amitriptyline	OnabotulinumtoxinA + CGRP mAbs (for chronic)*
Topiramate*	Fremanezumab-vfrm*	Atenolol	
Propranolol*	Galcanezumab-gnlm*	Lisinopril	
Timolol*	Eptinezumab*	Venlafaxine	
Metoprolol	OnabotulinumtoxinA (for chronic)*	Nadolol	*FDA Approved
Frovatriptan (short-term menstrual migraine)*		Memantine	

Headache. 2021 Jul;61(7):1021-1039.

FDA Approval & Indication

- Erenumab-aooe, Fremanezumab-vfrm, Galcanezumab-gnlm
  - Approved 2018
- Eptimezumab-jjmr
  - Approved 2020

- Indicated for migraine prevention in adults
  - First preventive medications specifically developed (“research bench to bedside”) specifically for migraine

Aimovig (erenumab-aooe). Prescribing information. Amgen. Sep 2022.; Ajovy (fremanezumab-vfrm). Prescribing information. Teva. Sep 2021.; Emgality (galcanezumab-gnlm). Prescribing information. Eli Lilly. Sep 2018.; Vyepti (eptinezumab-jjmr). Prescribing information. Lundbeck Seattle BioPharmaceuticals, Inc. Feb 2020.

Name	Pharmacology	Route	Dose	Frequency	Comment
Erenumab	CGRP receptor antagonist	Subcutaneous, Self-administered	70mg Some patients may benefit from 140mg	Monthly	140mg autoinjector available Refrigerated
Fremanezumab	Binds to CGRP ligand	Subcutaneous, Self-administered	225mg or 675mg	Monthly (225mg) or every 3 months (675mg)	675mg = three 225mg injections
Galcanezumab	Binds to CGRP ligand	Subcutaneous, Self-administered	240mg loading, then 120mg	Monthly	240mg = two 120mg injections
Eptimezumab	Binds to CGRP ligand	Intravenous infusion	100mg or 300mg	Every three months	Administered by trained personnel

BioDrugs. 2022 May;36(3):341-358.

Name	Pharmacology	Route	Dose	Frequency	Comment
Erenumab					
Fremanezumab					
Galcanezumab					
Eptimezumab					

BioDrugs. 2022 May;36(3):341-358.

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Erenumab	CGRP receptor antagonist	Subcutaneous, Self-administered	70mg Some patients may benefit from initial 140mg dose	Monthly	140mg autoinjector available Refrigerated
Fremanezumab					
Galcanezumab					
Eptimezumab					

BioDrugs. 2022 May;36(3):341-358.

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BioDrugs. 2022 May;36(3):341-358.

FDA Adverse Events Reporting System (FAERS) Public Dashboard

Administration issues reported for erenumab, fremanezumab, galcanezumab

Example

Galcanezumab-gnlm

- 9% = product dose omission issue
- 2.7% = Incorrect dose administered
- 2% = accidental underdose
- 1% = inappropriate schedule of product administration
- 1% = product storage error
- 0.7% = prescribed underdose

17% are for reasons that pharmacists can resolve

FDA Adverse Events Reporting System (FAERS) Public Dashboard, search term = emgality. www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers.

Drug	Trials' Duration	Primary Outcome	Secondary Outcomes	Comment
Erenumab	EM = one study 3 months, one study 6 months CM= 3 months	EM = CFB over months 4 to 6 (one study), at month 3 (one study) CM= CFB at month 3	50% reduction MHD Acute medication reduction Migraine Physical Function Impact Diary	Medication overuse headache patients excluded
Fremanezumab	EM & CM =3 months	EM= CFB over 3 months CM = CFB of at least moderate MHD over 3 months	50% reduction MHD Acute medication reduction CFB MHD 1st month	EM & CM = subset allowed to use one concurrent preventive
Galcanezumab	EM = 6 months CM = 3 months	EM=CFB over months 1 to 6 CM = CFB over months 1 to 3	100%, 75%, 50% reduction (CM = 50% only) Acute medication reduction EM & CM= Migraine Specific Quality of Life	
Eptimezumab	EM = 12 months CM = 6 months	EM = CFB over months 1 to 3 CM = CFB over months 1 to 3	75%, 50% reduction	

EM = episodic migraine; CM = chronic migraine; CFB = change from baseline; MHD = monthly headache days

BioDrugs. 2022 May;36(3):341-358.

Drug	Trials' Duration	Primary Outcome	Secondary Outcomes	Comment
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BioDrugs. 2022 May;36(3):341-358.

Drug	Trials' Duration	Primary Outcome	Secondary Outcomes	Comment
Fremanezumab	EM & CM =3 months	EM= CFB over 3 months CM = CFB of at least moderate MHD over 3 months	50% reduction MHD Acute medication reduction CFB MHD 1st month	EM & CM = subset allowed to use one concurrent preventive

EM = episodic migraine; CM = chronic migraine; CFB = change from baseline; MHD = monthly headache days

BioDrugs. 2022 May;36(3):341-358.

Drug	Trials' Duration	Primary Outcome	Secondary Outcomes	Comment
Galcanezumab	EM = 6 months CM = 3 months	EM=CFB over months 1 to 6 CM = CFB over months 1 to 3	100%, 75%, 50% reduction (CM = 50% only) Acute medication reduction EM & CM= Migraine Specific Quality of Life	

EM = episodic migraine; CM = chronic migraine; CFB = change from baseline; MHD = monthly headache days

BioDrugs. 2022 May;36(3):341-358.

Drug	Trials' Duration	Primary Outcome	Secondary Outcomes	Comment
Eptimezumab	EM = 12 months CM = 6 months	EM = CFB over months 1 to 3 CM = CFB over months 1 to 3	75%, 50% reduction	

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BioDrugs. 2022 May;36(3):341-358.

Drug	Trials' Duration	Primary Outcome	Secondary Outcomes	Comment
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Fremanezumab	EM & CM =3 months	EM= CFB over 3 months CM = CFB of at least moderate MHD over 3 months	50% reduction MHD Acute medication reduction CFB MHD 1st month	EM & CM = subset allowed to use one concurrent preventive
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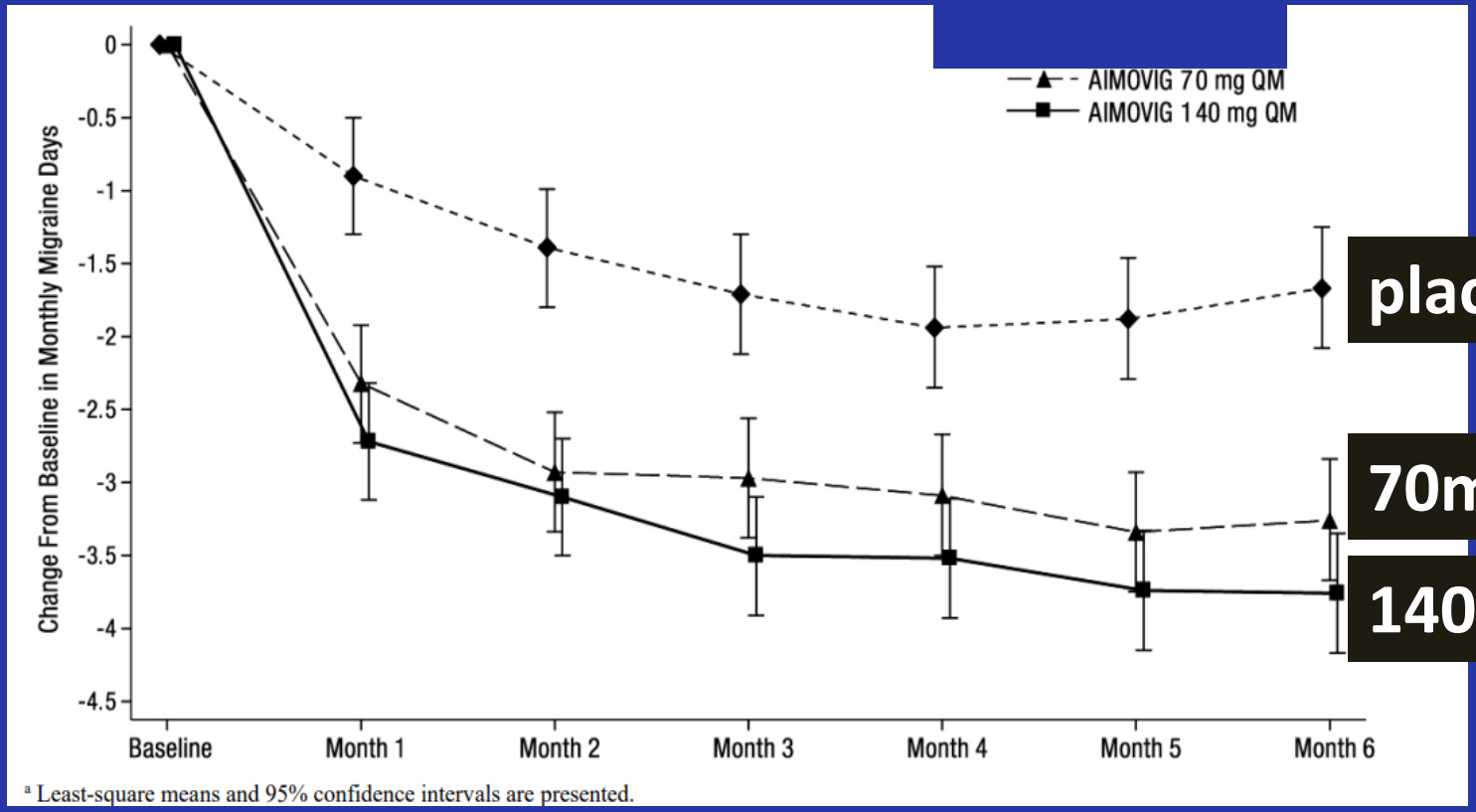
BioDrugs. 2022 May;36(3):341-358.

Erenumab-aooe Change from baseline in Monthly Migraine Days



[a] Least-square means and 95% confidence intervals are presented.

Adapted from Aimovig (erenumab-aooe). Prescribing information. Amgen. Sep 2022.

Preventive Trials' Results

	MMD with Active Drug	Difference Versus Placebo (days)
Erenumab-aooe	-1.8 to -6.6	-1 to -2.5
Fremanezumab-vfrm	-3.4 to -5	-1.3 to – 3.5
Galcanezumab-gnlm	-4.1 to -4.8	-1.8 to – 3.1
Eptinezumab	-3.9 to - 8.2	-0.7 to -2.6

MMD: monthly migraine days

N Engl J Med. 2021;385(8):695-706.; Cephalalgia. 2020;40:241-254.; Neurology. 2018;91:e2211-e2221.; Lancet. 2021;397(10268):51-60.; Cephalalgia. 2018;38:1026-1037.; JAMA. 2018c;319:1999-2008.; Lancet. 2019;394(10203):1030-1040.; N Engl J Med. 2017;377:2123-2132.; Neurology. 2020;94:e1365-e1377.; Lancet Neurol. 2020;19:814-825.; Lancet. 2018;392:2280-2287.; N Engl J Med. 2017;377:2113-2122.; Cephalalgia. 2018;38:1442-1454.; JAMA Neurol. 2018;75:1080-1088.; Lancet Neurol. 2017;16:425-434.

Summary

- All CGRP mAbs statistically significantly ($p<0.001$) reduced monthly migraine headache days by approximately 1 to 2 days versus placebo

- All secondary 50% reduction and acute medication reduction outcome measures were statistically significant versus placebo

Headache 2018;58:276-290.

CGRP mAbs & Gepants

Completed post-hoc, open-label, and real-world data studies

- favorable safety and tolerability, including in sub-populations
- additional studies on-going

Head-to-head studies?

- On-going topiramate versus erenumab-aooe for chronic migraine
- Unlikely: CGRP mAb versus CGRP mAb? Gepant versus gepant?

Cephalalgia. 2023 Feb;43(2):3331024221137091., BioDrugs. 2022 May;36(3):341-358.; Cephalalgia. 2022;42(2):108-118.

AHS Criteria for Initiating CGRP mAbs

Four to seven Migraine Monthly Days and both of the following:

- Intolerant to or inadequate response **to an 8-week trial** of two or more of the following:
  - Level A or B treatments according to guidelines
- At least moderate disability (MIDAS ≥ 11 or HIT-6 > 50)

Eight to 14 Monthly Migraine Days

Intolerant to or inadequate response **to an 8-week trial** of two or more of the following:

- Level A or B treatments according to guidelines

Headache. 2021;61:1021-1039.

Erenumab-aooe	70mg	140mg	placebo
At least 2% AND at least 2% greater than placebo during first 3 months			
Injection site reaction	6%	5%	3%
Constipation	1%	3%	1%

Fremanezumab-vfrm	225mg	675mg	placebo
At least 2% AND at least 2% greater than placebo			
Injection site reaction	43%	45%	48%

Galcanezumab-gnlm	240mg	120mg	placebo
At least 2% AND at least 2% greater than placebo			
Injection site reaction	Not recorded	18%	13%

Eptimezumab-jjmr	100mg	300mg	placebo
Nasopharyngitis	6%	8%	6%
Hypersensitivity	1%	2%	0%

Aimovig (erenumab-aooe). Prescribing information. Amgen. Sep 2022.; Ajovy (fremanezumab-vfrm). Prescribing information. Teva. Sep 2021.; Emgality (galcanezumab-gnlm). Prescribing information. Eli Lilly. Sep 2018.; Vyepti (eptinezumab-jjmr). Prescribing information. Lundbeck Seattle BioPharmaceuticals, Inc. Feb 2020.

FDA Updates to Erenumab-aooe Label

- 2019, Warning/Precaution,
  - Constipation with serious complications
- 2020, Warning/Precaution,
  - New-onset or worsening of preexisting hypertension

www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=1894

FDA Approval & Indication

- Ubrogepant
  - Approved 2019
  - **Acute treatment of migraine with or without aura**
- Rimegepant
  - Approved 2020
  - Acute treatment of migraine with or without aura in adults
  - Migraine prevention in adults
- Atogepant
  - Approved 2021
  - Migraine prevention in adults

First drug with both indications

Ubrelvy (ubrogepant). Prescribing information. Allergan. Dec 2019.; Nurtec (rimegepant). PFirst drug with BOTH indications rescribing information. Biohaven Pharmaceuticals. Apr 2022.; Qulipta (atogepant). Prescribing information. Allergan. Sep 2021.

Name	Pharmacology	Route	Dose	Frequency	Comment
Ubrogepant	CGRP receptor	Oral	50mg or 100mg	As needed; May repeat two hours after first dose, maximum 200mg per day	50mg for hepatic or renal impairment
Rimegepant	CGRP receptor	Oral	75mg	Prevention: every-other-day; Acute: as needed; maximum 75mg per day	Only drug FDA approved for both acute and prevention; oral disintegrating tablet
Atogepant	CGRP receptor	Oral	10mg, 30mg, or 60mg	Daily, maximum 60mg per day	10mg for renal impairment

Name	Pharmacology	Route	Dose	Frequency	Comment
Ubrogepant	CGRP receptor	Oral	50mg or 100mg	As needed; May repeat two hours after first dose, maximum 200mg per day	50mg for hepatic or renal impairment

BioDrugs. 2022 May;36(3):341-358.

Name	Pharmacology	Route	Dose	Frequency	Comment
Rimegepant	CGRP receptor	Oral	75mg	Prevention: every-other-day; Acute: as needed; maximum 75mg per day	Only drug FDA approved for both acute and prevention; oral disintegrating tablet

Name	Pharmacology	Route	Dose	Frequency	Comment
Atogepant	CGRP receptor	Oral	10mg, 30mg, or 60mg	Daily, maximum 60mg per day	10mg for renal impairment

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Atogepant	CGRP receptor	Oral	10mg, 30mg, or 60mg	Daily, maximum 60mg per day	10mg for renal impairment

Name	Change in MMD	ADVERSE EFFECTS
Rimegepant	-3.5 to – 4.3	Nausea (2%), hypersensitivity (including delayed)
Atogepant	- 2.4 to - 4.2	Nausea (5–9%), constipation (6%), somnolence (4–6%), elevated AST/ALT (1%)

MMD = Monthly migraine days

Brain Sci. 2022 Nov 24;12(12):1612

Name	Contraindications	Adverse Effects
Ubrogepant	Concomitant use with strong CYP3A4 inhibitors	Nausea (2–4%) Somnolence (2–3%) Dry mouth (2%
Rimegepant	History of hypersensitivity	Nausea (2%) Hypersensitivity (including delayed)
Atogepant	None	Nausea (5–9%) Constipation (6%) Somnolence (4–6%) Elevated AST/ALT (1%)

MMD: monthly migraine days

Brain Sci. 2022 Nov 24;12(12):1612.

On-going debate

Require “failure” of traditional (and cheaper) preventives **<u>prior to</u>** prescribing CGRP mAbs or gepants?

Headache. 2021;61:1021-1039. Image courtesy of Microsoft PowerPoint Version 2211.

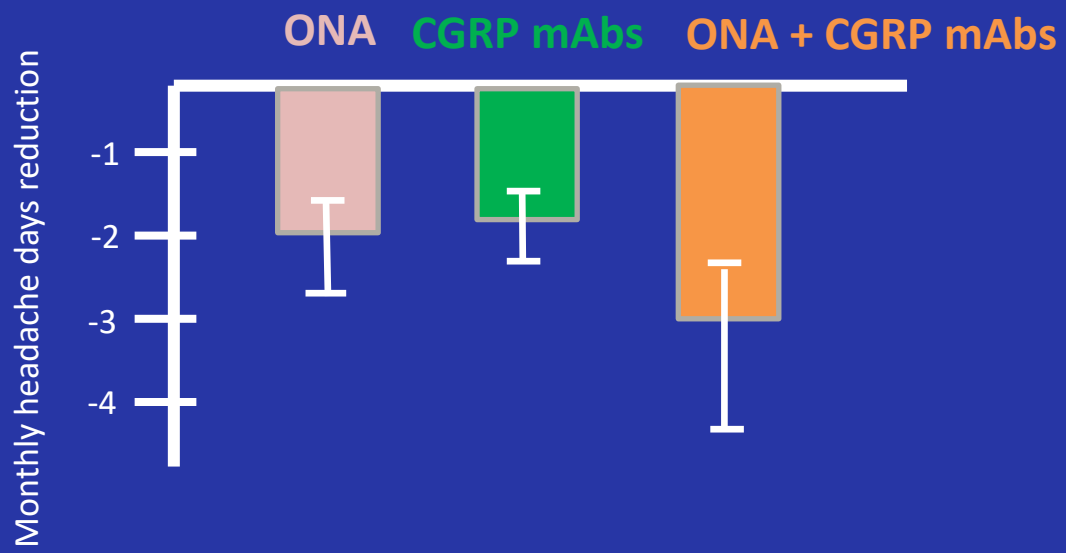
	Pre-2018 Preventives	CGRP mAbs	Gepants
Frequency of Administration	Daily/multiple times daily	Loading dose for some, then monthly or quarterly	Daily or every other day
Adverse Events	Drug dependent, but are common and can cause significant patient dissatisfaction or discontinuation	Generally well-tolerated, mainly injection site events	Generally well-tolerated
Assess Efficacy	Titrate to stable dose, then 2 to 3 months	3 months after initiation for monthly, 6 months for quarterly Efficacy can occur within days/weeks	3 months after initiation Efficacy can occur within days/weeks
Drug Interactions	Depends on drug	No known/clinically consequential	Ubrogepant with CYP3A4
Pregnancy/ Breast feeding	Some agents teratogenic/ contraindicated	Little data	Little data

N Engl J Med. 2021;385(8):695-706.; Headache. 2021;61:1021-1039.; N Engl J Med. 2020;383:1866-1876.; Lancet. 2021;397(10268):51-60.; Headache. 2010;50:921-936.; Neurology. 2012;78:1337-1345.

Limited data supports combination

- AHS Consensus Statement
  - "Probably effective, OnabotulinumtoxinA + CGRP mAb"
- Systematic review

Studies still needed



Headache. 2021 Jul;61(7):1021-1039., Toxins 2022 Aug 1;14(8):529.

Drug interactions

Few clinically significant drug interactions

with **FDA-approved** acute and preventive

migraine drugs

Headache. 2021 Jun;61(6):838-853.; Image courtesy of Microsoft PowerPoint Version 2211.

Co-prescriptions of Triptans and SSRIs

- **2006 FDA serotonin syndrome alert based on 27 case reports of dubious quality gathered over 5 years**
  - NONE MET SEROTONIN SYNDROME CRITERIA!

- **Per American Headache Society POSITION STATEMENT:**
  - *Currently available evidence does not support limiting the use of triptans with SSRIs or SNRIs, or the use of triptan monotherapy, due to concerns for serotonin syndrome*

Annals of Pharmacotherapy 2008;42:1692-1696.; Headache 2012;52:198-203.; Headache 2010;50:1089-1099.

Pregnancy

The use of erenumab for migraine prophylaxis during pregnancy: a case report and narrative review

Sierra J Vig PharmD, BCOP, BCPS, Julia Garza, PharmD candidate, Yunting Tao, PharmD candidate

Headache 2022 Nov;62(10):1256-1263.

Narcotics & Butalbital

Choosing wisely in headache medicine: the American Headache Society's list of five things physicians and patients should question:

- ***Don't prescribe opioid- or butalbital-containing medications as a first-line treatment for recurrent headache disorders; and***
- ***Don't recommend prolonged or frequent use of over-the-counter pain medications for headache.***

- Consider referral to headache specialist
- Narcotics and butalbital should be used sparingly and exclusively in conjunction with comprehensive assessment and integration of psychological treatment

Curr Pain Headache Rep. 2016 Sep;20(9):51.; Headache. 2012 Jan;52(1):18-36.; Headache. 2013 Nov-Dec;53(10):1651-9.