Update on Pharmacists Intervening on Migraine Pain

Jill E. Martin-Boone, Pharm.D., FASHP, FFIP, FNAP

Clinical Professor and Interim Chair, Division of Pharmacy Practice and Administrative Sciences

Director of Interprofessional Education

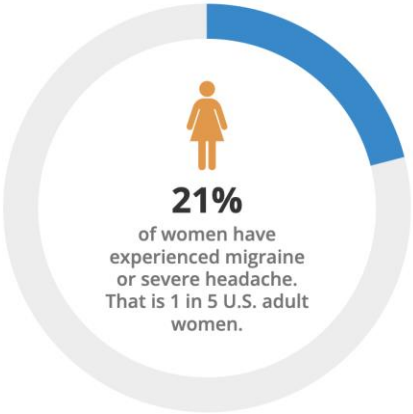
University of Cincinnati James L Winkle College of Pharmacy

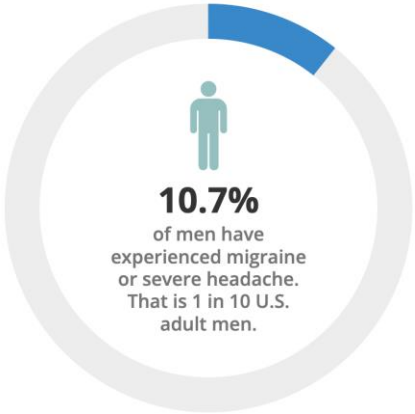
Overview

- Migraine Overview
- Acute pharmacologic management of migraines
- Preventive pharmacologic management of migraines
- Summary

Migraine Epidemiology

- Approximately 1.1 billion people globally in 2019
- In the US, migraines affect ~40 million people
  - Nearly 1 in every 7 Americans
  - Prevalence is highest among women





Lancet Neurol 2018;17:954-976.
Headache 2021. DOI: 10.1111/head.14024.
Front Neurol. 2021;12:800605.
Plast Reconstr Surg Glob Open. 2020;8:e2790.

Economic Impact

- Migraine-related loss of productive time in the US workforce is more than $13 billion per year
- Annual direct and indirect costs = ~$9000 in people with migraine
- 2019 Global Burden of Disease study
  - Second-leading cause of years lived with disability
  - Leading cause among women aged 15-49 yr
- Healthcare utilization
  - Migraine accounts for 3% of annual ED visits in the United States
  - Fourth to fifth most common reason for ED visits
  - Third most common reason for ED visits among women of childbearing age

J Headache Pain **21**, 137 (2020). https://doi.org/10.1186/s10194-020-01208-0;

Burch. Headache. 2018;58:496. Fan. J Headache Pain. 2023;24:79.

Migraine

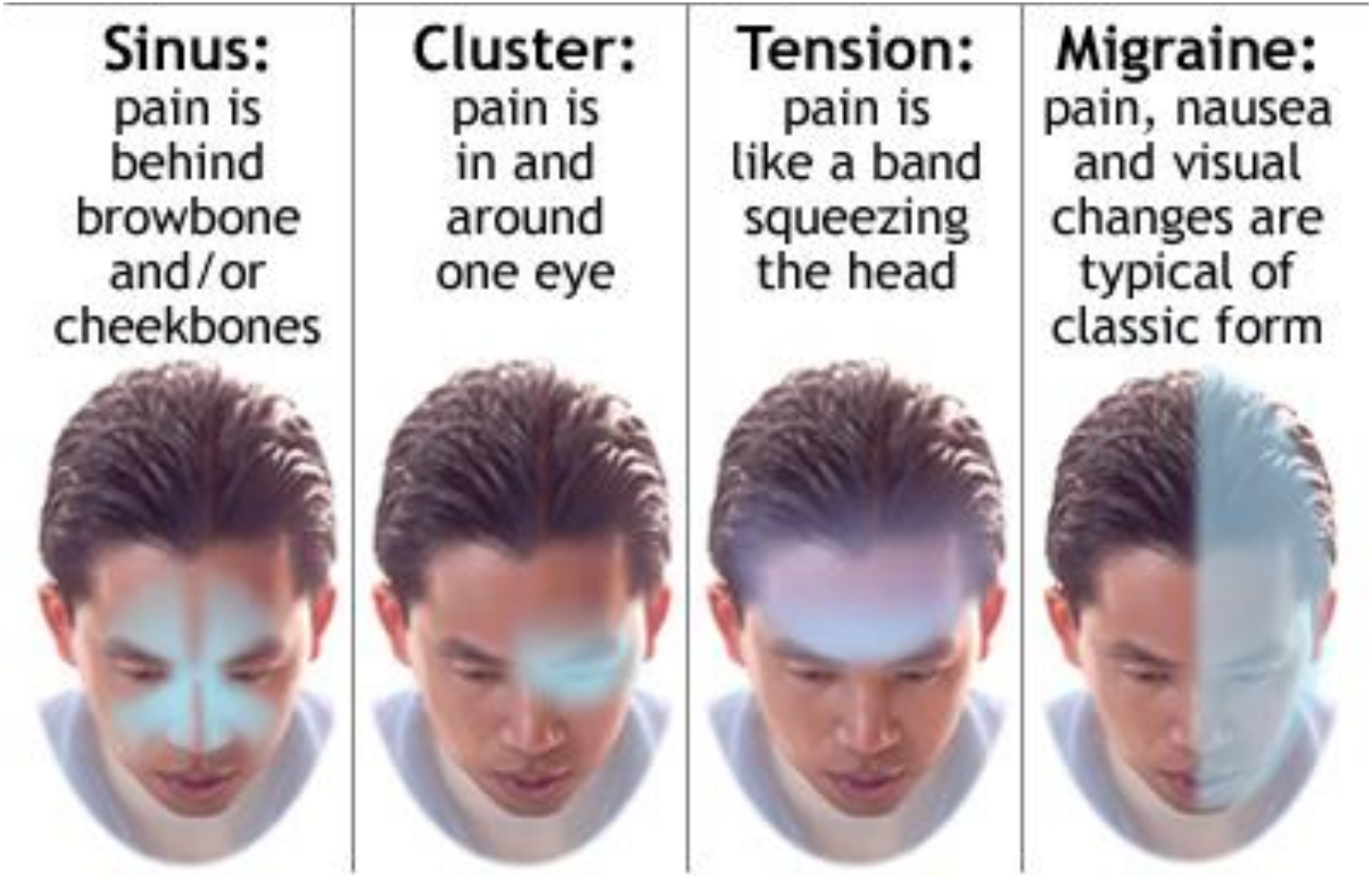
- Migraine headache
  - severe throbbing pain or a pulsing sensation
  - unilateral or bilateral
  - 4-72 hours
  - exacerbated by activity

- Accompanied by:
- nausea, vomiting
- Photo/phonophobia

https://www.who.int/news-room/fact-sheets/detail/headache-disorders

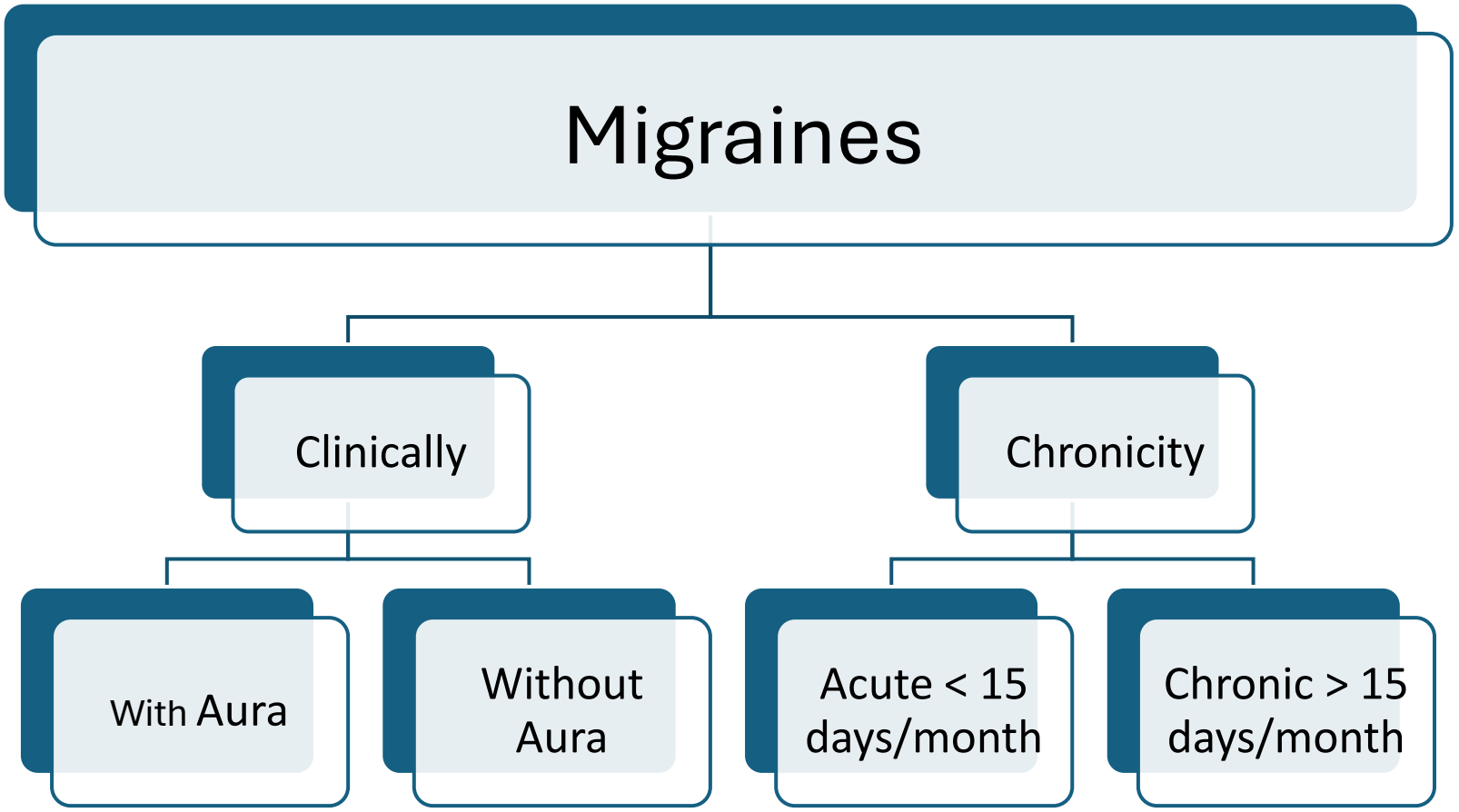
https://hmccentre.com/headache-and-migraines/

Comparison of Headache Symptoms



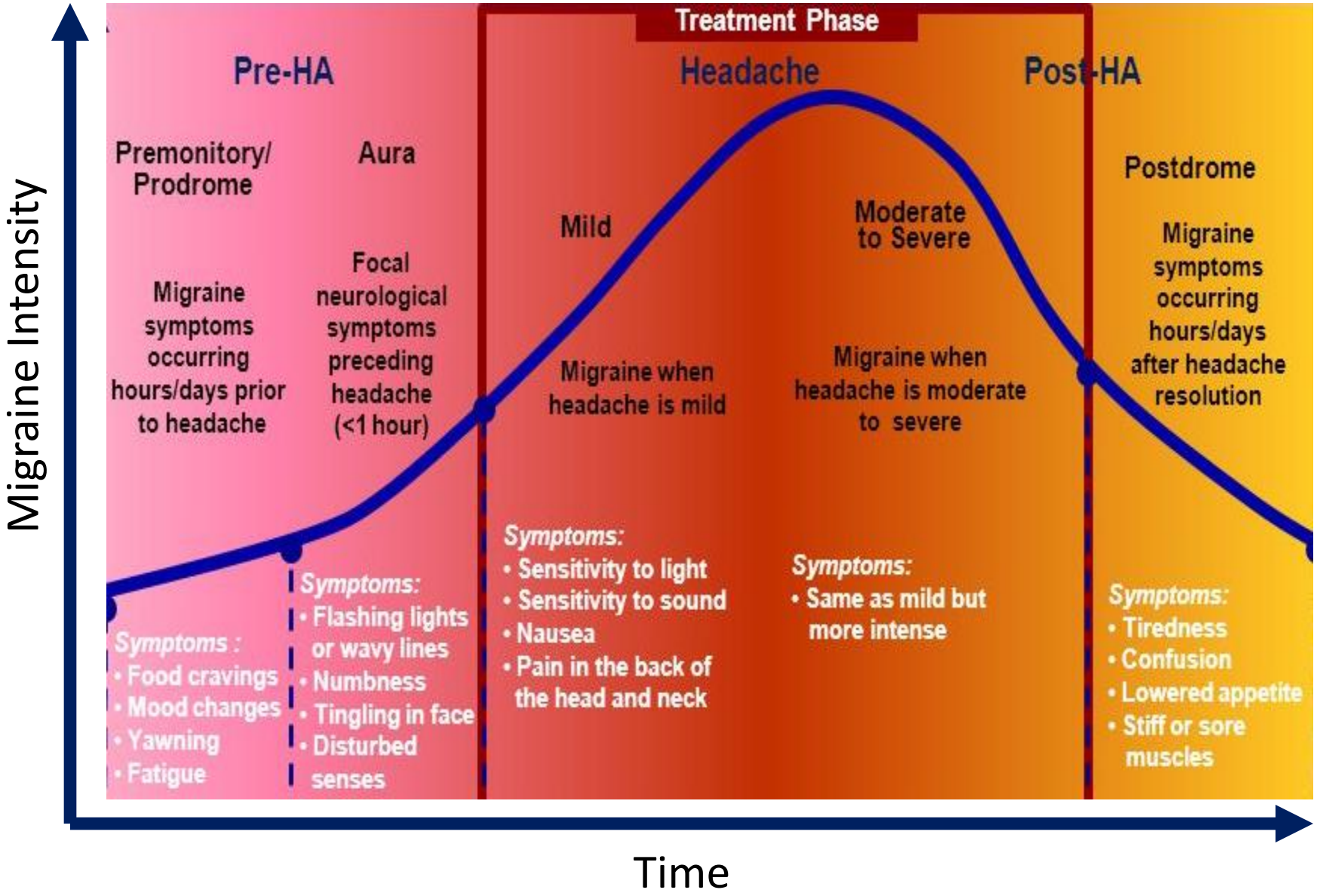
https://medlineplus.gov/ency/imagepages/17204.htm

ICHD-3 criteria for migraine and chronic migraine

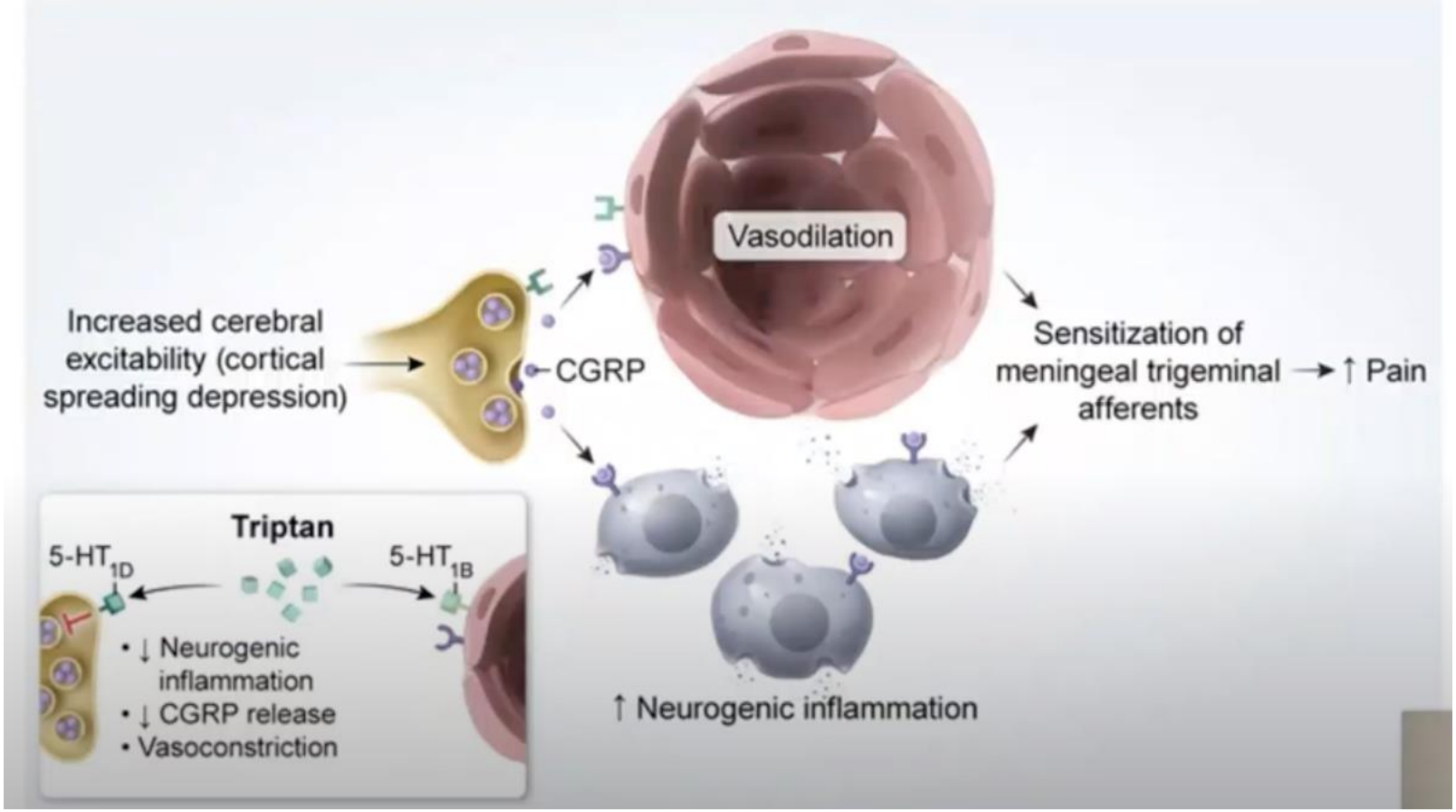


https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14153Gawde P, Shah H, Patel H, et al. (February 02, 2023) Revisiting Migraine: The Evolving Pathophysiology and the Expanding Management Armamentarium. Cureus 15(2): e34553. DOI 10.7759/cureus.34553

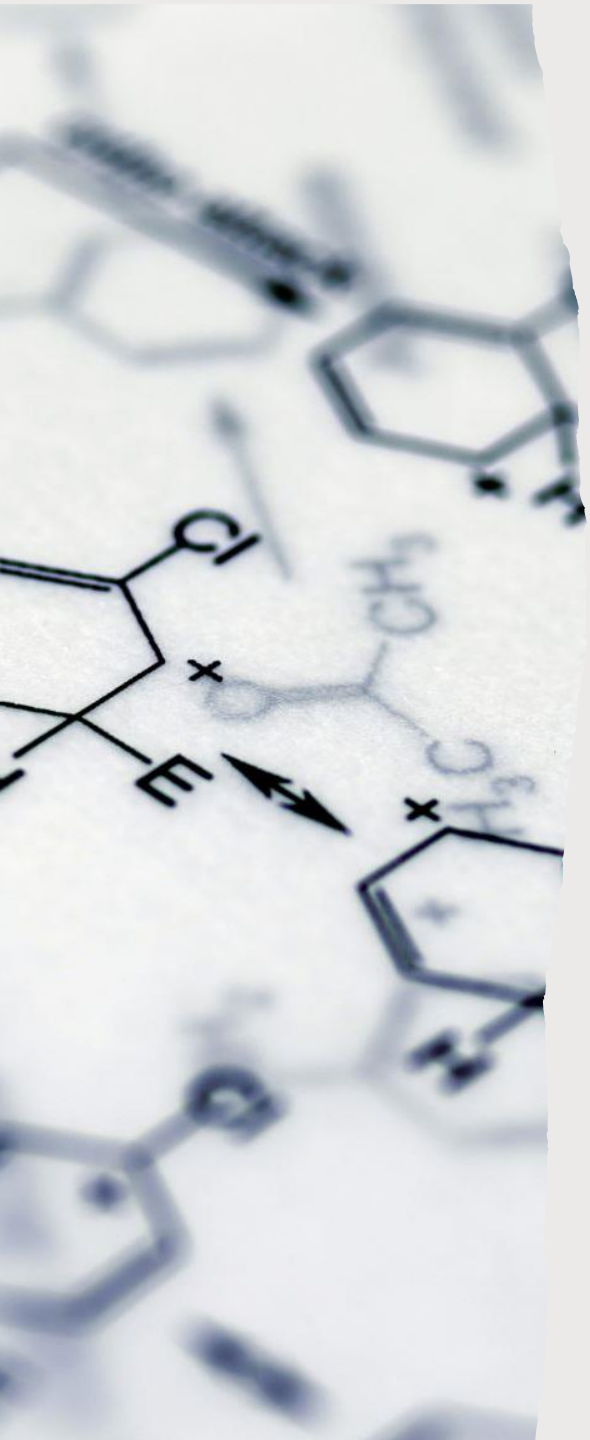
Phases of Migraine Attack



Pathophysiology of Migraines



https://www.ncbi.nlm.nih.gov/books/NBK560787/

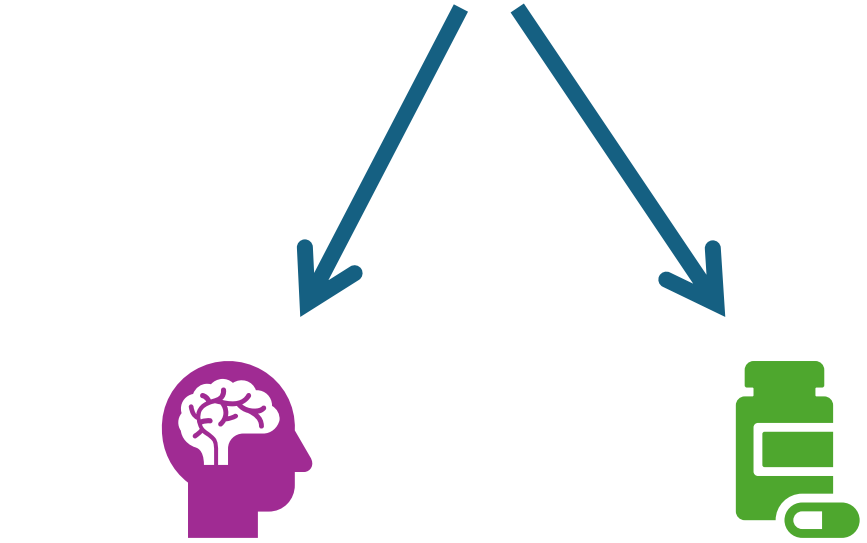


Select Neuropeptides in Migraine

- Serotonin 5-HT1B/1D & 5-HT1F
- Calcitonin gene-related peptide (CGRP)
- Dopamine
- Inflammatory substance (substance P, prostaglandins, etc).

The Journal of Headache and Pain (2023) 24:76
Ann Indian Acad Neurol. 2016 Apr-Jun; 19(2): 175–182

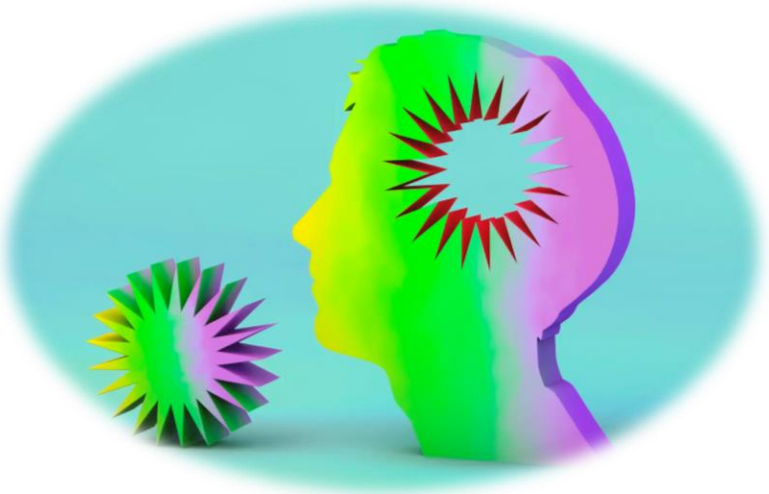
Pharmacologic Approach to Migraine



Acute Episodic Migraine Treatment

Preventative Therapy

Acute Migraine Treatment



General Approach to Managing Migraine

- Clinical Diagnosis
  - Evaluated to r/o other causes of HA
- Identify and eliminate triggers, if possible
  - Lifestyle changes
  - Patient log
  - Migraine triggers

J Headache Pain **21**, 137 (2020). https://doi.org/10.1186/s10194-020-01208-0;

Burch. Headache. 2018;58:496. Fan. J Headache Pain. 2023;24:79.

Acute Migraine Treatment Goals

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

The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice: https://doi.org/10.1111/head.14153

Developing an Acute Migraine Treatment Plan

- Use evidence-based treatments
  - Mild to moderate attacks
    - NSAIDs, nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations
  - Moderate to severe attacks
    - Migraine-specific agents

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** https://doi.org/10.1111/head.14153

Evidence for Acute Migraine Medications American Headache Society 2021 Consensus Statement

Established Efficacy

Nonspecific

- NSAIDs
  - ASA
  - Celecoxib oral solution
  - Diclofenac
  - Ibuprofen
  - Naproxen
- Combination analgesic
  - Acetaminophen/ ASA/caffeine

Migraine Specific

- Triptans
- Ergotamine derivatives
- Gepants
- Lasmiditan (Ditans)
- Nonpharmacologic: neuromodulation

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** https://doi.org/10.1111/head.14153

Evidence for Acute Migraine Medications American Headache Society 2021 Consensus Statement

Probably Effective

Nonspecific	Migraine Specific
▪ NSAIDs – Flurbiprofen – Ketoprofen – IV and IM ketorolac ▪ IV magnesium* ▪ Isometheptene-containing compounds ▪ Antiemetics – Metoclopramide – Prochlorperazine – Promethazine – Chlorpromazine – Droperidol	▪Ergotamine ▪Other forms of DHE

*In migraine with aura.

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** https://doi.org/10.1111/head.14153

Evidence for Acute Migraine Medications American Headache Society 2021 Consensus Statement

Recommended to
Avoid opioid- and butalbital-containing medications

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** https://doi.org/10.1111/head.14153

Individualized Acute Migraine Treatment Considerations

Selection should be individualized to the:

- Patient's symptoms
- Comorbidies
- Nausea and vomiting
- Pain intensity / disability
- Previous treatment
- Preferences
- Access

https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14153

Case of Katie

- Katie is a 28yo female that approaches you in obvious discomfort. She states she has occasional HA's over the last few years with pulsing pain on the right side of her head. She usually takes ibuprofen or Excedrin Migraine® and goes home to bed where it is quiet and dark. In about 6-8 hours, she begins to feel better.
- She's noticed that the meds haven't worked as well recently and would like you to recommend something?
- What questions do you have for Katie?

Triptan

- Triptan's – still a mainstay of therapy after OTC's
  - Less expensive than newer agents
  - Various routes of administration
  - Differ in onset and duration
  - May try multiple triptans with differing success
  - Contraindicated in CV disease

Recommended Dosing for Triptans

Triptan	Half-life (Hr)	Formulation(s)	Time to Onset (Min)	Dosing
Almotriptan (Axert®)	3-4	Oral tablet	30-60	12.5 mg
Eletriptan (Relpax®)	4	Oral tablet	30-60	20 or 40 mg
Rizatriptan (Maxalt ®)	2-3	Oral tablet, ODT, Oral film	30-45	5 or 10 mg
Sumatriptan (Imitrex®)	2-2.5	Oral tablet	30-60	25, 50, or 100 mg
		Nasal spray	10-15	20 mg
		Nasal powder	10-15	11 mg
		SC	10	3, 4, or 6 mg
Zolmitriptan (Zomig®)	3	Oral tablet, ODT nasal spray	30-60 10-15	2.5 or 5 mg
Frovatriptan (Frova®)	26	Oral tablet	120	2.5 mg
Naratriptan	6	Oral tablet	60-180	2.5 mg

- ~30% of patients given triptan have insufficient response

Ashina M, et al. Pharmacotherapies for Migraine and Translating Evidence From Bench to Bedside: VOLUME 99, ISSUE 2, P285-299, FEBRUARY 2024; OI:https://doi.org/10.1016/j.mayocp.2023.07.003
Medical Letter, June 12, 2023; chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/file:///Users/jillboone/Downloads/TML-article-1678b.pdf

Triptan	Features
Group I	
Sumatriptan Zolmitriptan Rizatriptan Almotriptan Eletriptan	Faster onset, 30-60min Nonoral routes faster
Group II	
Naratriptan Frovatriptan	Slower onset, longer lasting

Katie Recommendations?

Based upon the additional information that you learned about Katie, which of the following would you recommend for her to be prescribed to abort her next HA?

- Sumatriptan 6mg SQ
- Frovatriptan 2.5mg orally
- Rizatriptan 5mg orally

Important information for Katie

- Take medication when HA pain is mild
- May repeat dose in 2 hours if need
- Limit acute medication use to 2 headache days/wk (average) or 10 days/mo
- Other options available if needed

Katie Follow-up

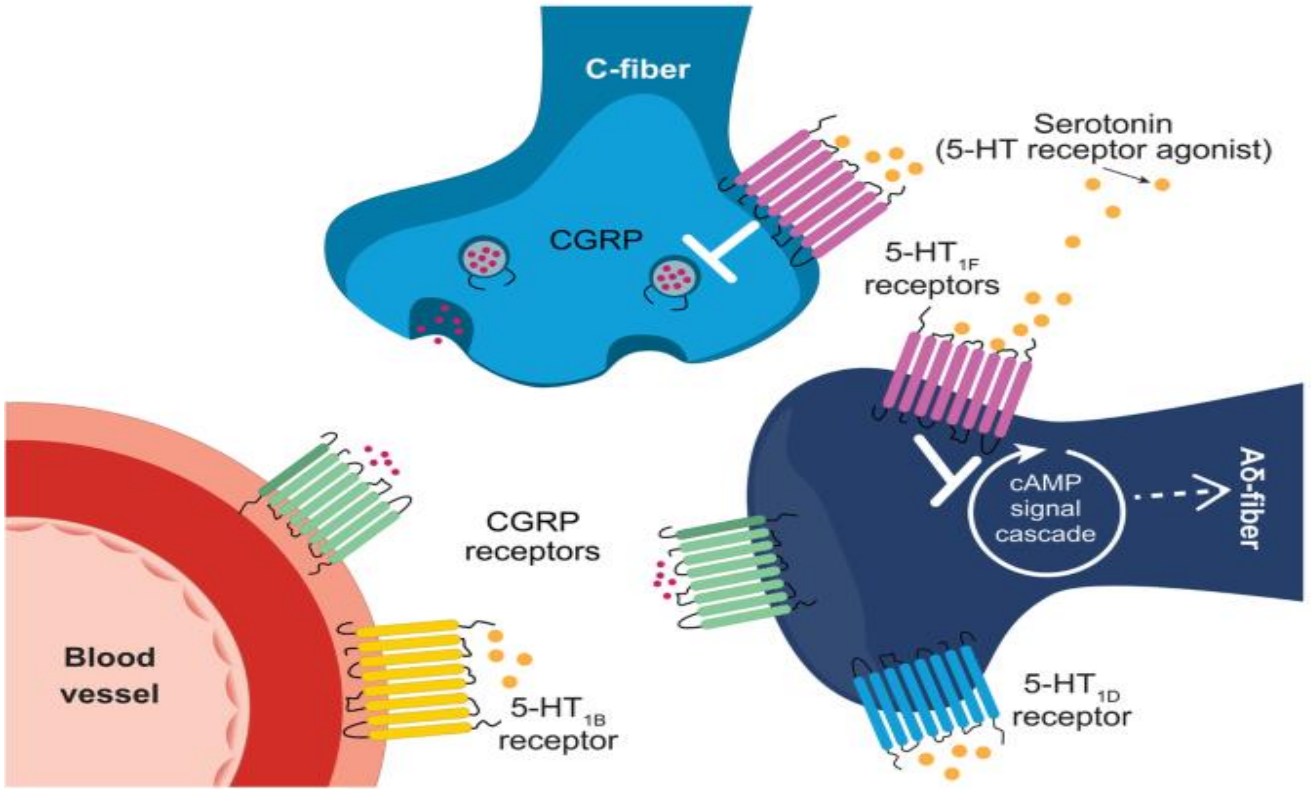
Two years later, Katie tells you that the medication she has been prescribed worked well, but it losing it's effectiveness. Should she

- Try another triptan
- Add an NSAID
- Go to a different class of medication
- Two of the above

New Acute Therapies

- Ditans (5-HT_{1F} receptor agonist)
- Gepants (CGRP antagonist)

Ditan: Lasmiditan MOA–5-HT_{1F} agonist



Clemow, D.B., Johnson, K.W., Hochstetler, H.M. *et al.* Lasmiditan mechanism of action – review of a selective 5-HT_{1F} agonist. *J Headache Pain* **21**, 71 (2020). https://doi.org/10.1186/s10194-020-01132-3

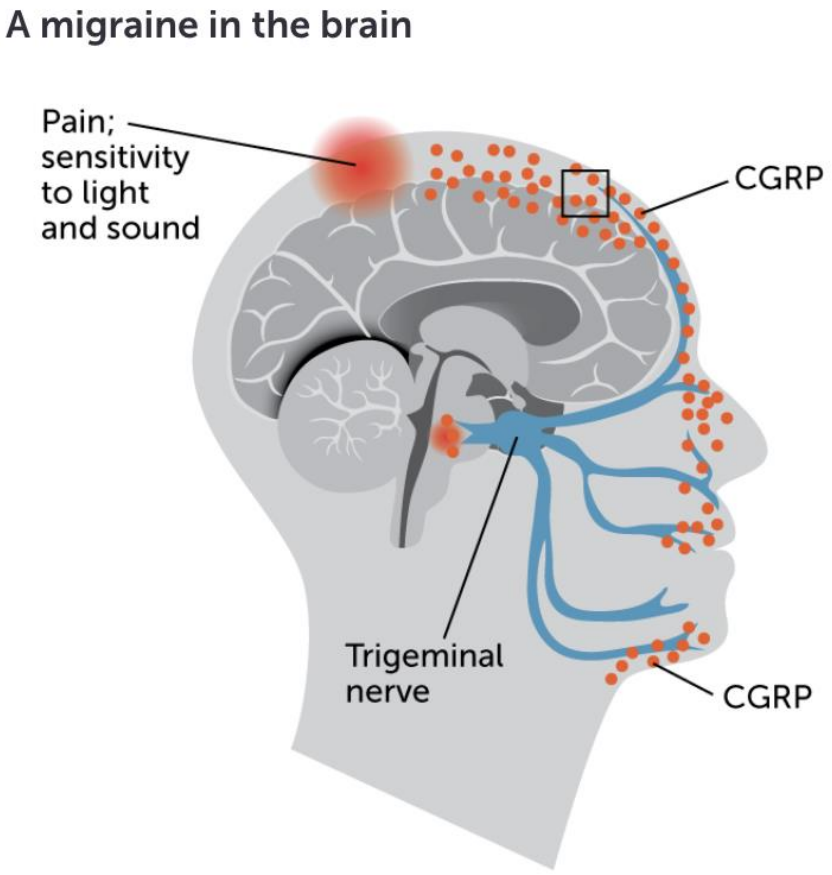
New Acute Therapies - Lasmiditan (Reyvow®)

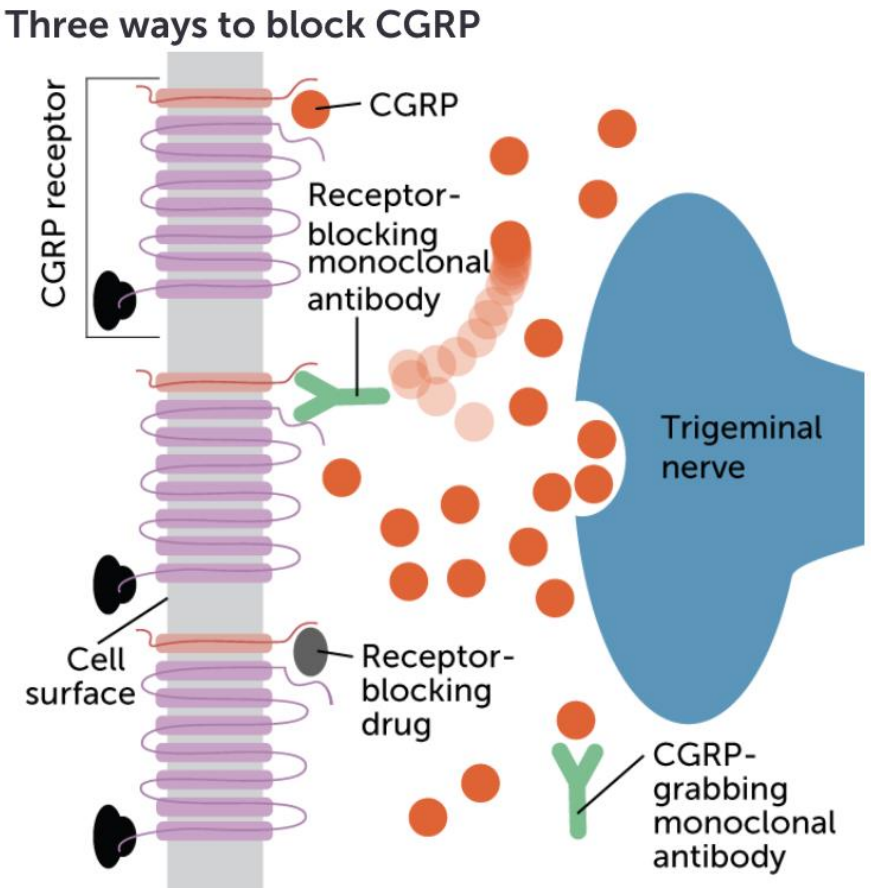
Mechanism of action	▪ 5-HT_{1F} receptor agonist ▪ 1st "ditan" approved (Oct, 2019)
Data	▪ Little or no cardiovascular issues, thus useful in patients with cardiovascular or cerebrovascular disease ▪ 2 hours pain free 28-38% of patient's vs 15-21% placebo ▪ Onset within 30 min
Dosing	▪ 50-mg, 100-mg, or 200-mg oral tablets ▪ **Not to exceed 1 dose in 24 hr** – A second dose has not been shown to be effective for the same migraine attack
Adverse events	▪ Dizziness ▪ Fatigue ▪ Paresthesia ▪ Sedation ▪ Driving or machinery impairment for 8 hrs ▪ Schedule V controlled

New Acute Therapies: Gepants

- Calcitonin gene-related peptide monoclonal antibodies and receptor blockers have recently revolutionized migraine treatment and prevention.
- Gepants are small molecules that block the CGRP docking station or CGRP receptor
- This mechanism does not cause vasoconstriction, so safe in CV disease

CGRP Antagonism





Adapted From F.A. Russell *Et Al*/*Physiol. Rev.* 2014; British Pharmacol. Soc. By T Tibbits: Https://Www.Sciencenews.Org/Article/Migraine-headache-new-drugs-block-brain-chemical

New Acute Therapies: Gepants

	Ubrogepant (Ubrelvy®)	Rimegepant (Nurtec ODT)	Intranasal Zavegepant (Zavzpret®)
Dosing	▪ 50 mg or 100 mg orally, as needed ▪ May take second dose ≥2 hr later ▪ **Not to exceed 200 mg in 24 hr**	▪ 75 mg orally or sublingual, as needed ▪ **Not to exceed 1 dose in 24 hr**	▪ 10-mg single spray in 1 nostril as needed ▪ Not to exceed 10 mg (1 spray) in 24 hr ▪ Onset 15 min
Adverse events	▪ Nausea ▪ Somnolence ▪ Contraindicated with potent 3A4 inhibitor	▪ Nausea ▪ Avoid potent inhibitors/inducers of 3A4 iP-gp or BCRP	▪ Unusual taste ▪ Nausea/vomiting ▪ Nasal discomfort ▪ Avoid intranasal decongestant within 1 hr
Indication	▪ Acute	▪ Acute and Preventative (QOD)	▪ Acute

Rissardo, J.P.; Caprara,A.L.F. Gepants for Acute and Preventive Migraine Treatment: A Narrative Review. Brain Sci. 2022, 12, 1612. https://doi.org/10.3390/brainsci12121612
CMAJ 2023 January 30;195:E153-8. doi: 10.1503/cmaj.211969

When to Consider Gepants or Ditans

Use is appropriate when ALL of the following are met

A. Prescribed/recommended by licensed healthcare professional
B. Patient is at least 18 yr of age
C. Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine
D. Either of the following
    a. Contraindications to or inability to tolerate triptans
    b. Inadequate response to 2 or more oral triptans, as determined by
    EITHER of the following
        i. Validated acute treatment patient-reported outcomes questionnaire
        ii. Healthcare professional attestation

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** **https://doi.org/10.1111/head.14153**

Cost of Acute Migraine Treatments

Drug Name	Brand Name	Package Size	Price Estimate
New Medications			
Lasmiditan	Reyvow®	8 tablets	$734
Rimegepant	Nurtec®	8 tablets	$941
Ubrogepant	Ubrelvy®	10 tablets	$973
Atogepant	Qulipta®	15 tablets	$517
Zavegepant	Zavzpret®	6 nasal sprays	$1,088
Oral Triptans			
Sumatriptan Oral	Imitrex	100mg, 9 tablets	$16
Zolmitriptan	Zomig	5mg, 3 tablets	$24
Naratriptan	Amerge	2.5mg, 9 tablets	$22
Rizatriptan	Maxalt	10mg, 9 tablets	$15
Eletriptan	Relpax	40mg, 6 tablets	$46
Almotriptan	Axert*	12.5 mg, 12 tablets	$229
Frovatriptan	Frova	2.5mg, 9 tablets	$16
Other			
DHE Nasal	Migranal	4mg/ml, 8 vials	$1,150
Sumatriptan SQ	Imitrex®	2 inj kits (4 doses)	$143
Sumatritpan Nasal Powder	Onzentra®	16 nosepieces	$977
Sumatriptan Nasal	Generic	6 units	$128

GoodRx List Price 2023

Ditans vs Gepants vs Triptans in Acute Migraine

Limited data of direct comparisons			
Systematic review and meta-analysis, 64 randomized trials 9 (46442 participants) of ditans, gepants and triptans			
Key findings	Most triptans > pain relief compared to ditans and gepants	Ditans – highest risk of adverse effects among all treatments	Gepants – fewer adverse events compared with triptans.
Systematic review of Five RCTs rimegepant study 303 (n = 1,466), ubrogepant (n = 1,672 and n = 1,686, respectively), and lasmiditan (n = 2,231 and n = 3,005, respectively).			
Key findings	Pain freedom and pain relief at 1-2 hours: lasmiditan 100-200mg > rimegepant and ubrogent	Rimegepant pain freedom and relief > lower doses of lasmiditan and all doses of ubrogepant	CNS side effects more with lasmiditan

Comparison of New Pharmacologic Agents With Triptans for Treatment of Migraine, Oct 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8506232/
Relative efficacy of lasmiditan versus rimegepant and ubrogepant as acute treatments for migraine: network meta-analysis findings, Jul 2022: https://pubmed.ncbi.nlm.nih.gov/35790906/

Acute Medication Combinations

Add **antiemetics** for those with nausea/vomiting

- Metoclopramide
- Prochlorperazine
- Promethazine
- Chlorpromazine

Combination treatment for difficult-to-treat attacks

- NSAIDs
- Triptans
- Gepants
- Neuromodulation

Relivion MG

Cefaly

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** **https://doi.org/10.1111/head.14153**

Katie – 1 year later

Katie tells you that the medication you recommended last year has is working. She is hoping to get pregnant in the near future. Can she continue her current medication or should she change?

Acute treatment options in Pregnancy

- Acetaminophen is safest.
- NSAIDs should not be used in first or third trimesters.
- Prochlorperazine, diphenhydramine and metoclopramide are relatively safe.
- Current research shows triptans may be a safe option.
- Nerve blocks with lidocaine.
- Neuromodulation devices
- CGRP receptor antagonist not recommended at this time

https://americanheadachesociety.org/news/treating-migraine-during-pregnancy/

Acute Migraine Therapy Summary

- All patients with migraine should have an acute treatment strategy
- Acute treatment strategies should be individualized to the patient
- Combinations may be required

Prevention of Migraines

Goals of Preventive Therapy

- Reduce attack frequency, severity, duration, and disability
- Improve responsiveness to and avoid escalation in use of acute treatment
- Improve function and reduce disability
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute treatments
- Reduce overall cost associated with migraine treatment
- Enable patients to manage their own disease to enhance a sense of personal control
- Improve health-related quality of life (HRQoL)
- Reduce headache-related distress and psychological symptoms

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** https://doi.org/10.1111/head.14153

Indications for Prophylaxis

Attacks significantly interfere with patients' daily routines despite acute treatment

Frequent attacks (#, depending upon disability)

Contraindication to, failure, or overuse of acute treatments, with overuse defined as:

- 10 or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused
- 15 or more days per month for nonopioid analgesics, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs [including aspirin])

AEs with acute treatments

Patient preference

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** https://doi.org/10.1111/head.14153

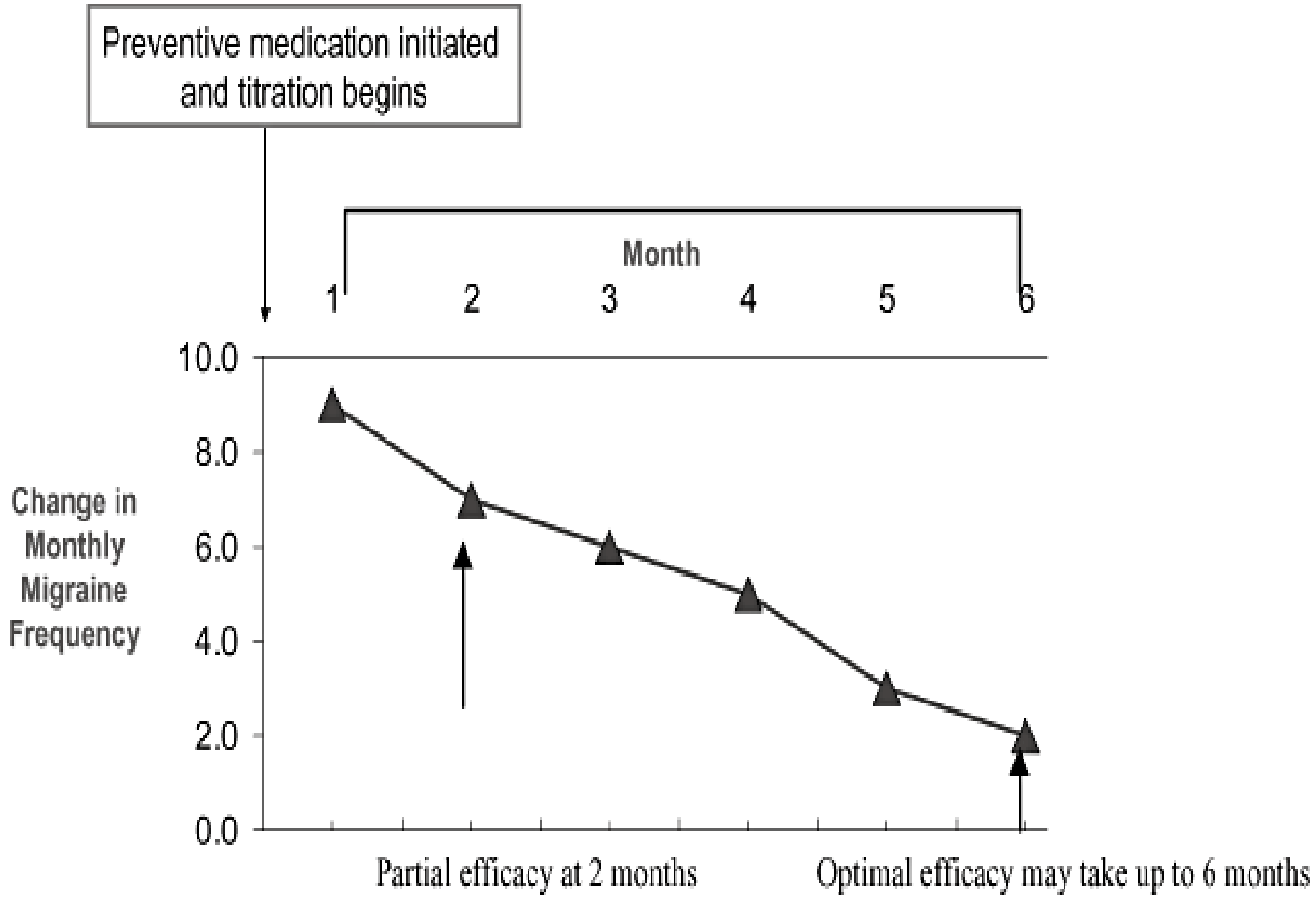
Migraine Prophylaxis

Success – defined as

- 50% reduction in the frequency of days with headache or migraine
- Significant decrease in attack duration as defined by patient
- Significant decrease in attack severity as defined by patient
- Improved response to acute treatment
- Reduction in migraine-related disability and improvements in functioning in important areas of life
- Improvements in HRQL and reduction in psychological distress due to migraine

Time to effect – allow 2 months after the minimally effective dose or maximally tolerated dose

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** https://doi.org/10.1111/head.14153



Medications With Evidence of Efficacy in Migraine Prevention

Established Efficacy		Probable Efficacy	
Oral	**Parenteral**	**Oral**	**Parenteral**
Topiramate [a]	Eptinezumab	Amitriptyline	OnabotulinumtoxinA + CGRP mAb
Divalproex sodium/ valproate sodium[a]	Erenumab	Venlafaxine	
Frovatriptan*	Fremanezumab	Lisinopril	
Metoprolol	Galcanezumab	Atenolol	
Propranolol[a]	OnabotulinumtoxinA**	Nadolol	
Timolol[a]		Memantine	
Candesartan			
Atogepant			
Rimegepant			

*Menstrual Migraine
**Chronic Migraine
[a]FDA Approved

Ailani J, et al: The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. https://doi.org/10.1111/head.14153

Lattanzi S, Trinka E, Altamura C, Del Giovane C, Silvestrini M, Brigo F, Vernieri F. Atogepant for the Prevention of Episodic Migraine in Adults: A Systematic Review and Meta-Analysis of Efficacy and Safety. Neurol Ther. 2022 Sep;11(3):1235-1252. doi: 10.1007/s40120-022-00370-8. Epub 2022 Jun 15. PMID: 35705886; PMCID: PMC9338214.

Silberstin SD, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. https://www.neurology.org/doi/10.1212/wnl.0b013e3182535d20

Preventive Therapy for Migraine

Oral agents are still considered first line
Tailor to Individual
Communicate expectations
Caution about adherence

Medication class		Most common side effects	Contraindications	Consider for
Antiepileptics	Topiramate	Paresthesia, weight loss, memory impairment, somnolence, GI upset	Renal impairment, nephrolithiasis, metabolic acidosis	Patients who are overweight
	Divalproex sodium/ sodium valproate	Weight gain, nausea, alopecia, somnolence, tremor	Liver impairment, pancreatitis, childbearing potential	
Antidepressants	TCAs - Amitriptyline - Nortriptyline	Hypersomnolence, dry mouth, weight gain, constipation, fatigue, sleepiness	Arrythmia (tachycardia), cardiac conduction abnormalities, suicidal behavior/thinking	Patients with comorbid depression, or insomnia
	SNRIs - Venlafaxine	Nausea, dizziness, insomnia, drowsiness, diaphoresis, dry mouth	Suicidal behavior/thinking, renal or hepatic impairment, poorly controlled HTN	Patients with comorbid depression, anxiety, postmenopausal hot flashes
Antihypertensives	Beta blockers - Propranolol - Metoprolol - Timolol	Orthostatic intolerance, exercise intolerance, fatigue	Bradycardia, asthma, hypotension, heart failure	Patients with hypertension, essential tremor
	Candesartan	Hypotension, dizziness	Hyperkalemia	Patients with hypertension

Ailani J, et al: **The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice.** https://doi.org/10.1111/head.14153
Hepp Z, ,Bloudek LM, Varon, SF. Systematic Review of Migraine Prophylaxis Adherence and Persistence. Journal of Managed Care Pharmacy JMCP January 2014 Vol. 20, No. 1 www.amcp.org

Natural/Herbal Products that have been used for Migraine Prevention

Level A Recommendation (established data):

- Butterbur extract (Petasites hybridus 75mg bid) – *removed for safety concerns*

Level B Recommendation (probably effective)

- Oral magnesium supplements (400-500mg/daily)
- Riboflavin (200mg bid)
- Feverfew (Tanacetum parthenium 50-82mg daily)
- Coenzyme Q10 (100mg tid)

Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039. doi: 10.1111/head.14153. Epub 2021 Jun 23. PMID: 34160823.

Level A: Botox - FDA Approved

FDA Approved, 2010 to treat chronic migraines.
LEVEL A: Efficacy to increase migraine free days in chronic migraine
Use: For refractory chronic migraine that has failed 2-3 prophylactic approaches
Administration: Series of tiny Botox injections administered around the head and neck every 12 weeks
in office
Adverse effects: neck pain and muscle weakness

Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039. doi: 10.1111/head.14153. Epub 2021 Jun 23. PMID: 34160823.

Rachel

Rachel is a 25yo that has 4-7 migraine headaches/month with mixed response to acute therapy. It is impacting her ability to work. She trialed propranolol with some success, but could not tolerate higher doses. Topiramate seemed to help some, but made her “loopy” and caused memory issues. She has no other health issues. She’s heard about new agents. Afraid of needles, but willing to try something to help her.

Newer Migraine Prevention Agents

- Four human monoclonal antibodies antagonizing CGRP function.
  - Erenumab (Aimovig®) 2018
  - Fremanezumab (Ajovy®) 2018
  - Galcanezumab (Emgality®) 2018
  - Eptinezumab – (VYEPTI™) 2020
- Two Oral CGRP receptor antagonists
  - Rimegepant (Nurtec®) 2021
  - Atogepant (Qulipta®) 2021

What is their place in migraine prevention?

American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice

Specific criteria for use and continuation of use based upon

- Headache classifications
- Lack of response to previous prophylactic therapies
- Functional assessment

ICHD-3 migraine with or without aura**		**ICHD-3** chronic migraine**
4–7 monthly headache days	8–14 monthly headache days	
and ***both*** of the following: •Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the level A or B treatments* •At least moderate disability (MIDAS>11, HIT-6>50)	•Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the A or B treatments according to AAN-AHS guideline*	***EITHER*** a or b: 1.Inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the A or B treatments according to AAN-AHS guideline* 2.Inability to tolerate or inadequate response to a minimum of 2 quarterly injection (6 months) of onabotulinumtoxinA

*AAN-AHS guideline treatments

1. Topiramate

2. Divalproex sodium/valproate sodium §

3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol

4. Tricyclic antidepressant: amitriptyline, nortriptyline

5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine

6. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline

**The International Classification of Headache Disorders 3rd edition

Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039. doi: 10.1111/head.14153. Epub 2021 Jun 23. PMID: 34160823

Reauthorization after initial use is approved when EITHER of the following criteria are met:

1. Reduction in mean monthly headache days of ≥50% relative to the pretreatment baseline (Diary documentation or healthcare provider attestation)

2. A clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures:

a. MIDAS
- Reduction of ≥5 points when baseline score is 11–20
- Reduction of ≥30% when baseline scores >20

b. MPFID
- Reduction of ≥5 points

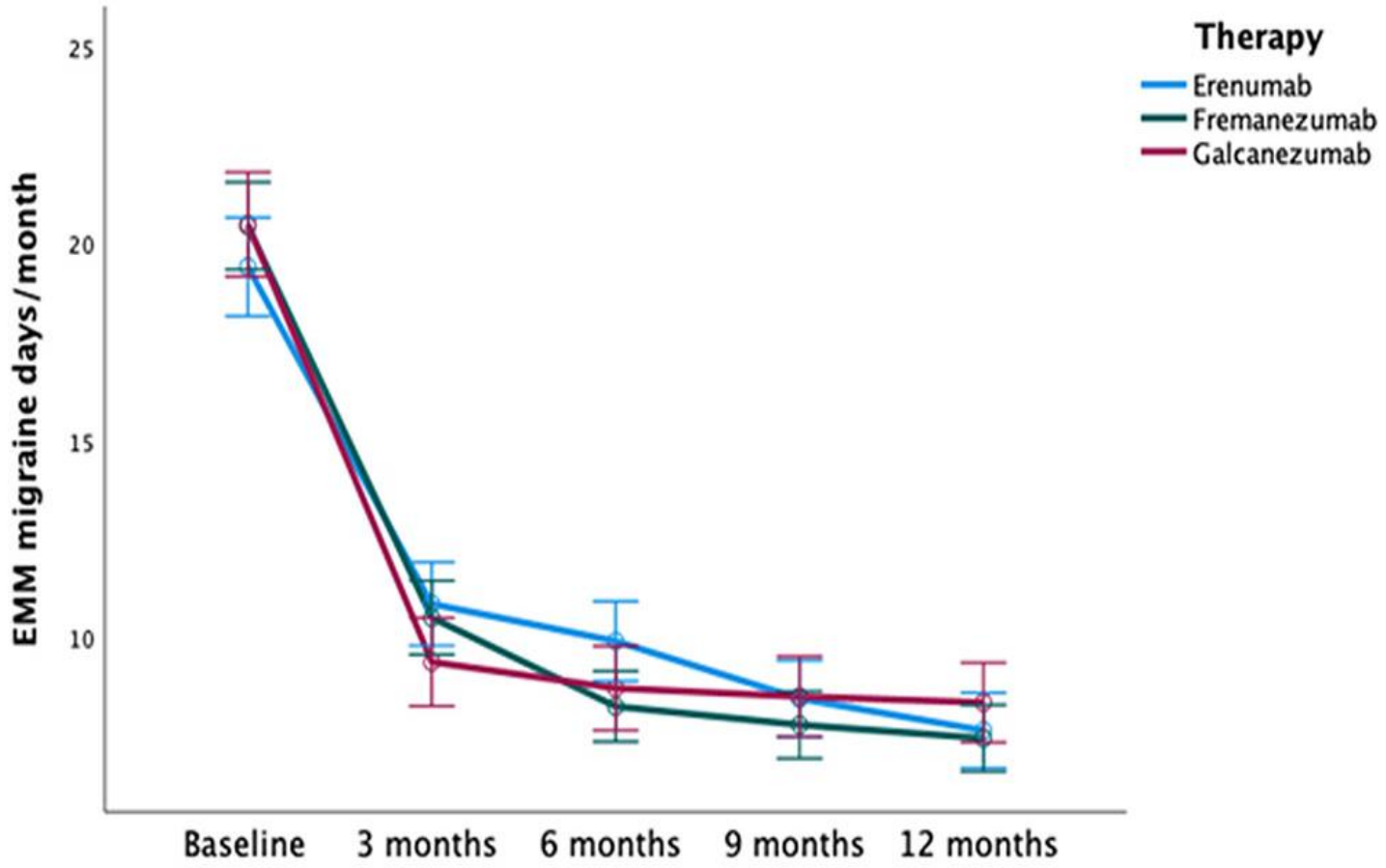
c. HIT-6
- Reduction of ≥5 points
- HIT, Headache Impact Test; MHD

Anti-CGRP Monoclonal Antibodies: Migraine Prevention

CGRP mAb	Target	Indication	Admin Route	T_{max}	$T_{1/2}$	Dosing	Adverse Effects	Est Cost / Dose
Erenumab Aimovig®	CGRP receptor	EM, CM	SC	6 days	28 days	70 or 140 mg monthly	Injection-site reactions, constipation, HTN	$600
Galcanezumab Emgality®	CGRP molecule	EM, CM, eCH	SC	5 days	27 days	240 mg loading dose, followed by 120 mg monthly	Injection-site reactions	$600
Fremanezumab Ajovy®	CGRP molecule	EM, CM	SC	7 or 5 days	32 days	225 mg monthly or 675 mg quarterly	Injection-site reactions	$500
Eptinezumab Vyepti®	CGRP molecule	EM, CM	IV	100% bioavail	27 days	100 or 300 mg quarterly	Nasopharyngitis, hypersensitivity	$1500

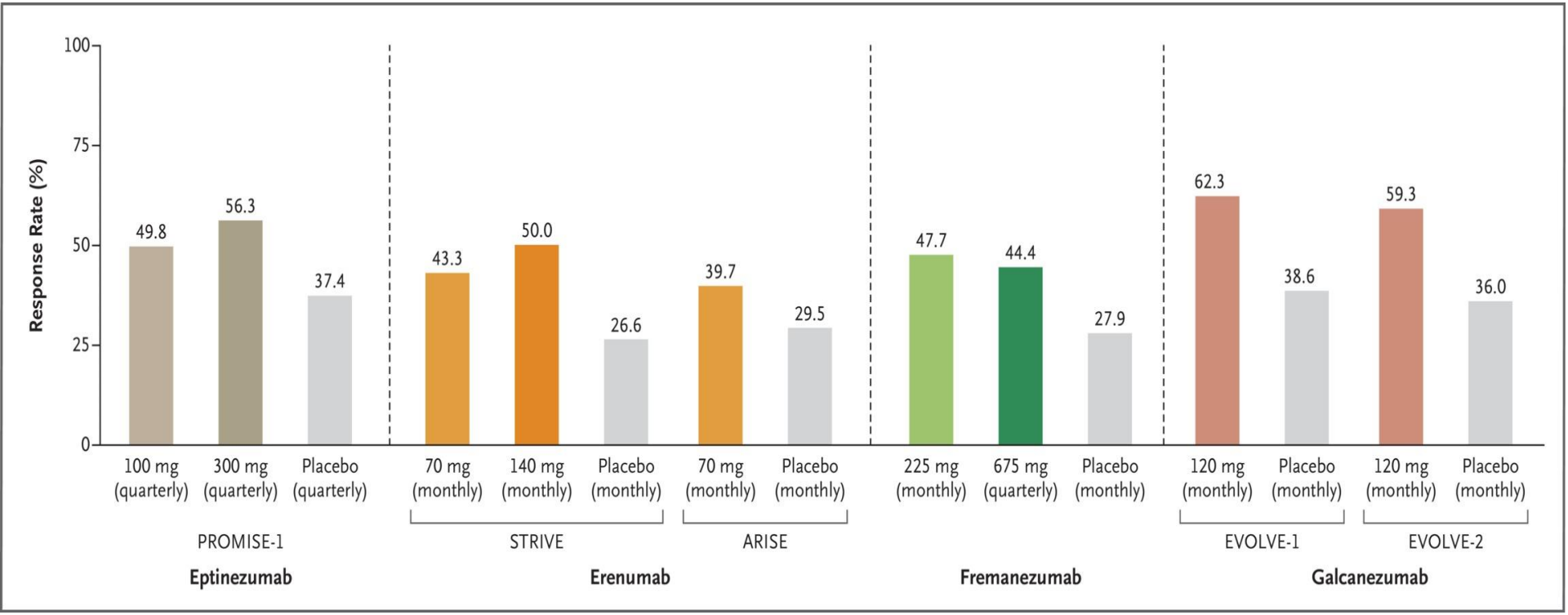
CMAJ 2023 February 6;195:E187-92. doi: 10.1503/cmaj.221607
Asawavichienjinda T, Sathitratanacheewin S, Chokesuwattanaskul R. "Wearing-off" efficacy of CGRP monoclonal antibodies for migraine prevention: A meta-analysis of randomized controlled trials. *Cephalalgia*. 2023;43(4). doi:10.1177/03331024231161261

A head-to-head observational cohort study on the efficacy and safety of monoclonal antibodies against CGRP for chronic and episodic migraine



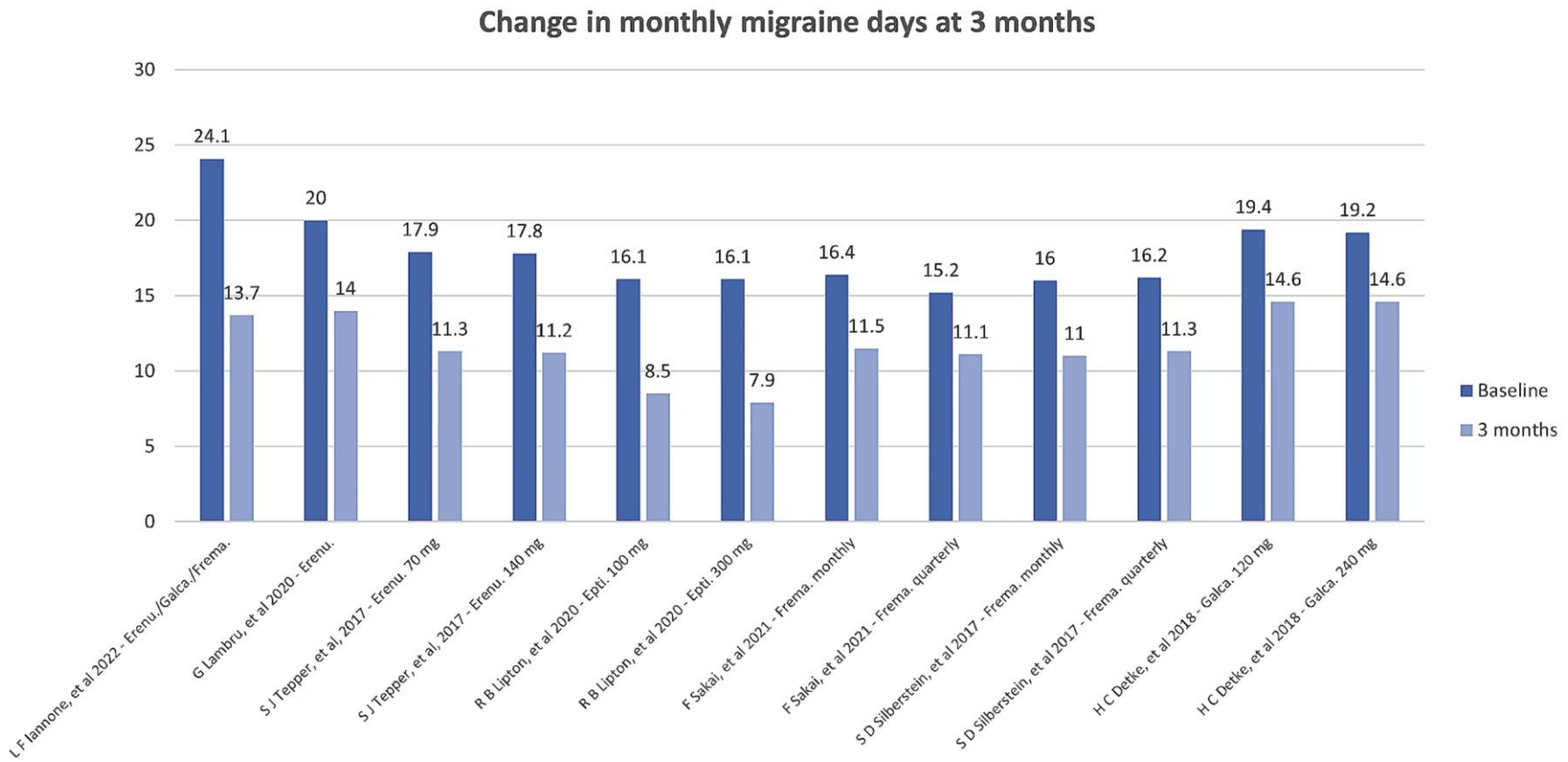
Headache, Volume: 63, Issue: 6, Pages: 788-794, First published: 31 May 2023, DOI: (10.1111/head.14528)

CGRP mAB Response Rates in Phase 3 Randomized Trials Episodic Migraine Prevention



Ashina M. Migraine. N Engl J Med 2020 Nov 5;383(19):1866-1876.doi: 10.1056/NEJMra1915327.

Overall efficacy of anti-CGRP mAbs in chronic migraine



Change in monthly migraine days after 3 months of treatment with anti-CGRP mAb. Legend: Epti: eptinezumab; Erenu: erenumab; Frema: fremanezumab; Galca: galcanezumab

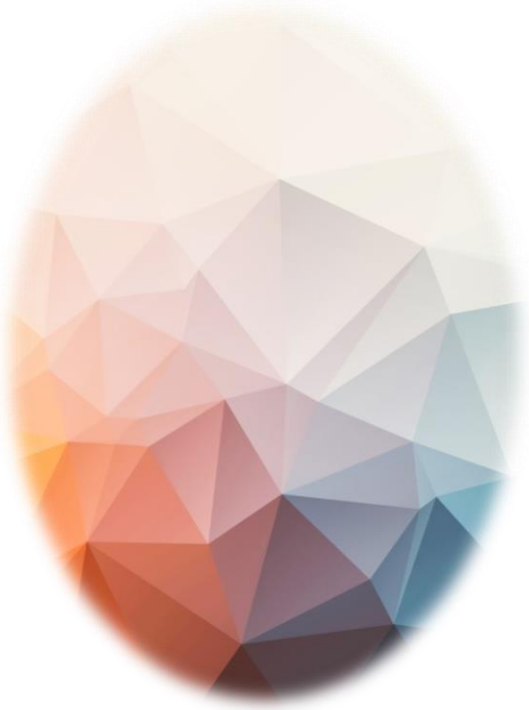
Oliveira, R., Gil-Gouveia, R. & Puledda, F. CGRP-targeted medication in chronic migraine - systematic review. *J Headache Pain* **25**, 51 (2024). https://doi.org/10.1186/s10194-024-01753-y

Anti-CGRP mAbs vs Standard Migraine Prophylactic Medications

RCTs of Anti-CGRP mAbs vs Standard Migraine Prophylactic meds with Level A evidence analyzed for comparison

mAbs at least comparable if not higher than those of the currently used preventive medications (topiramate, valproate, candesartan, beta blockers, amitriptyline)

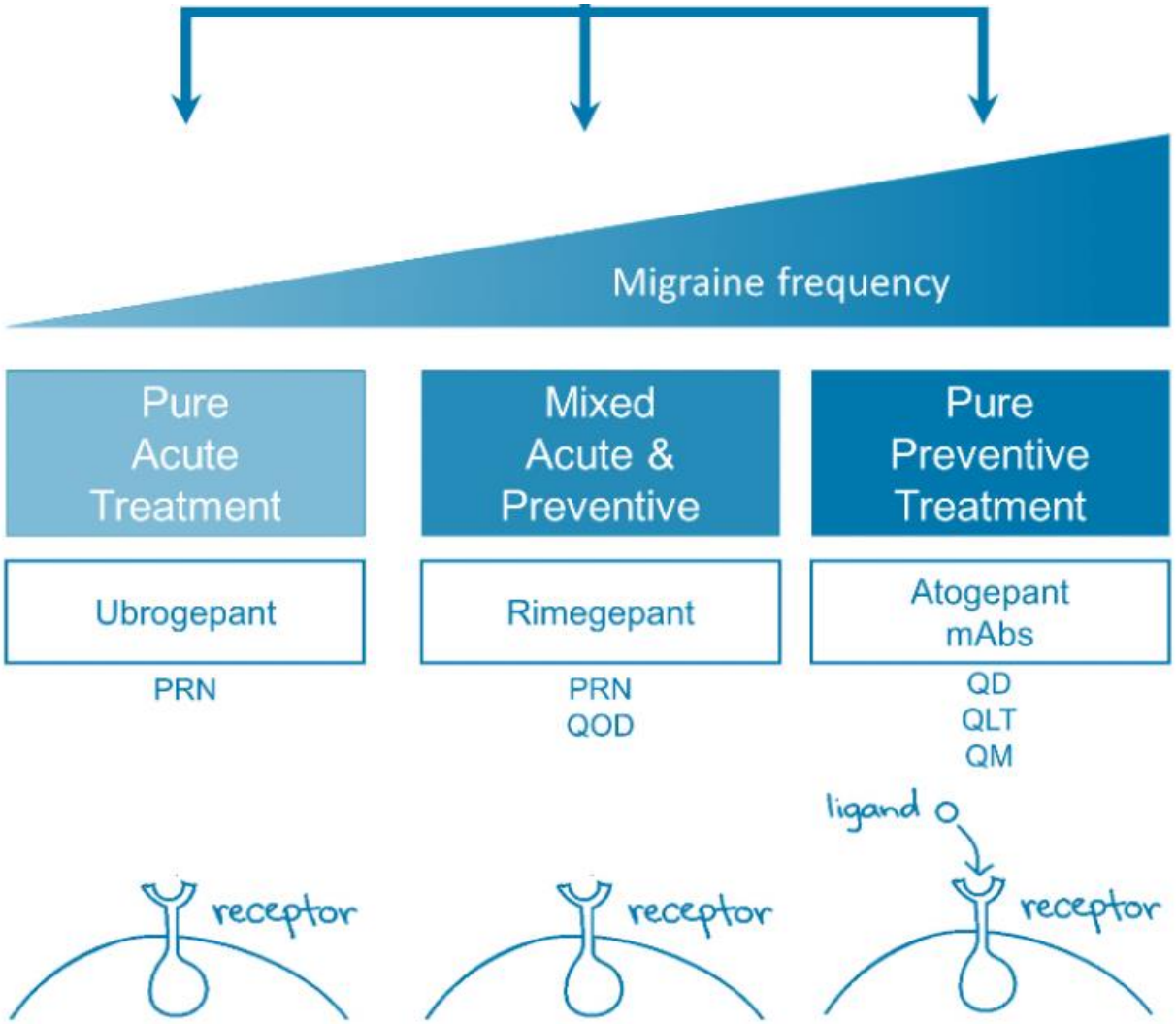
Dropouts due to adverse effects significantly higher in standard medications vs mAbs, suggesting better tolerability with mAbs



Vandervorst F, Van Deun L, Van Dycke A, Paemeleire K, Reuter U, Schoenen J, Versijpt J. CGRP monoclonal antibodies in migraine: an efficacy and tolerability comparison with standard prophylactic drugs. J Headache Pain. 2021 Oct 25;22(1):128. doi: 10.1186/s10194-021-01335-2. PMID: 34696711; PMCID:

Gepants for Migraine Prevention

CGRP Antagonists Spectrum



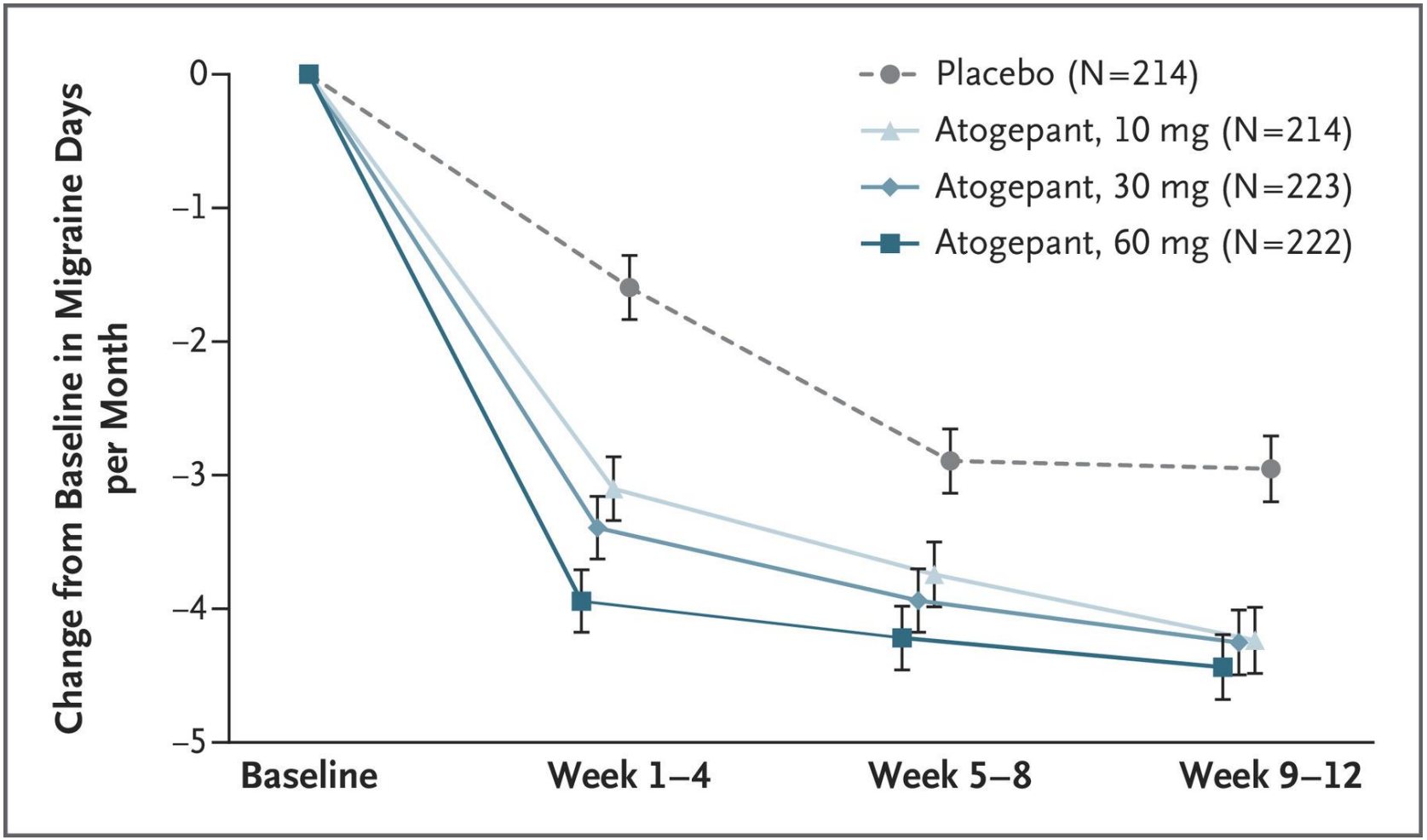
Rissardo, J.P.; Caprara, A.L.F. Gepants for Acute and Preventive Migraine Treatment: A Narrative Review. Brain Sci. 2022, 12, 1612. https://doi.org/10.3390/ brainsci12121612

Gepants for Migraine Prevention

CGRP mAb	Target	Indication	Admin. Route	T_{max}	$T_{1/2}$	Dosing	Adverse Effects
Rimegepant Nurtec# May 27, 2021	CGRP receptor	EM prevention	SL	1.5 hr	11 hr	75 mg every other day	Nausea, stomach pain/indigestion Avoid potent inhibitors/inducers of 3A4 iP-gp or BCRP n
Atogepant Qulipta® September 28, 2021	CGRP molecule	EM/CM prevention only	Oral	2 hr	11 hr	10, 30, or 60 mg daily	Constipation, nausea, fatigue/ somnolence CYP3A4.P-gp or BCRP strong intrxn

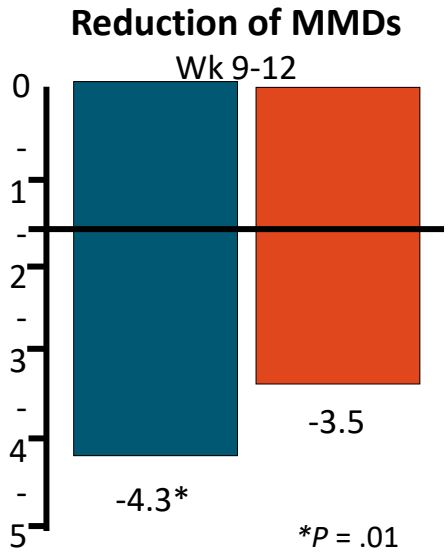
Tassorelli C et al. Cephalalgia 2024, Vol. 44(2) 1–11. International Headache Society 2024. DOI: 10.1177/03331024241235156
Medical Letter, June 12, 2023; chrome extension://efaidnbmnnnibpcajpcglclefindmkaj/file:///Users/jillboone/Downloads/TML-article-1678b.pdf
Rissardo JP, Caprara ALF. Gepants for Acute and Preventive Migraine Treatment: A Narrative Review. Brain Sci. 2022 Nov 24;12(12):1612. doi: 10.3390/brainsci12121612. PMID: 36552072; PMCID: PMC9775271.

Time Course of Efficacy vs Placebo



Ailani et al. Atogepant for the Preventive Treatment of Migraine. NEJM, Aug 2021
https://www.nejm.org/doi/full/10.1056/NEJMoa2035908

Rimegepant: Efficacy in Migraine Prevention vs Placebo



49% (171/348) decreased their moderate to severe MMDs by **≥50%** vs 42% (144/347) of those taking placebo; *P* = .044

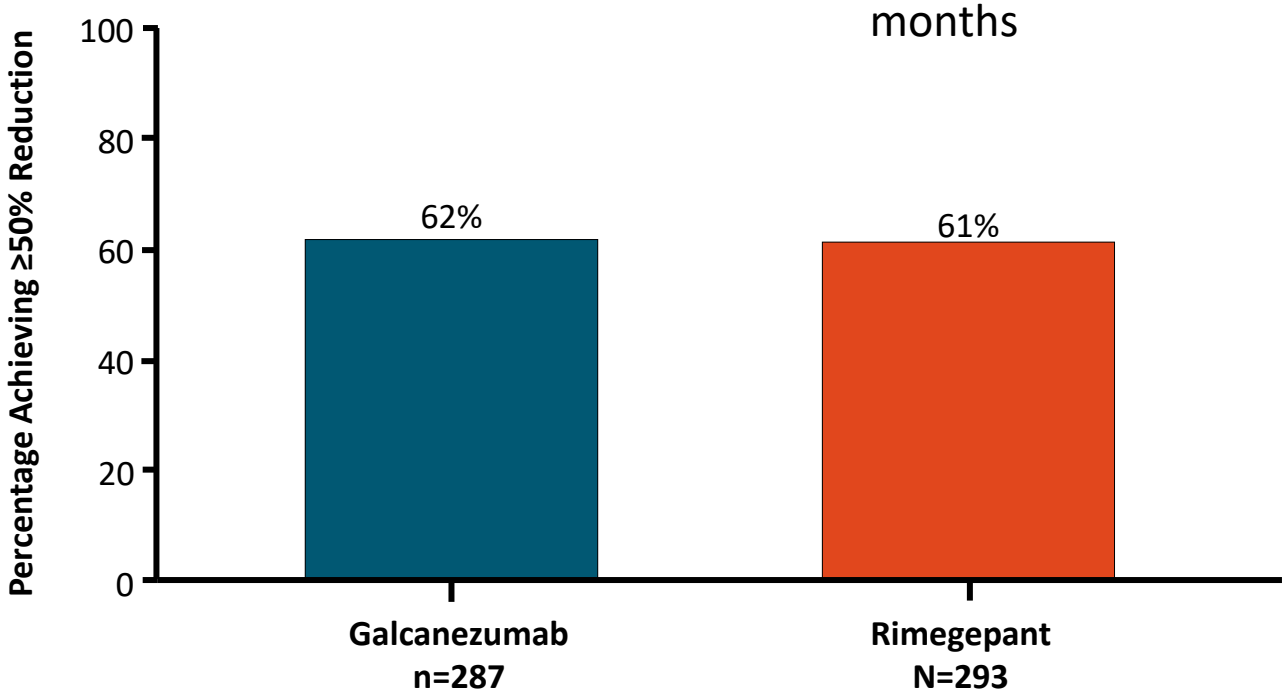
Rimegepant 75 mg (n = 348)
Placebo (n = 347)

The beneficial effects of rimegepant in reducing migraine frequency and improving quality of life were maintained over the longer term (up to 52 weeks).

Croop R et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet 2021 Jan 2;397(10268):51-60. doi: 10.1016/S0140-6736(20)32544-7. Epub 2020 Dec 15.
Blair HA. Rimegepant: A Review in the Acute Treatment and Preventive Treatment of Migraine. CNS Drugs. 2023 Mar;37(3):255-265. doi: 10.1007/s40263-023-00988-8. Epub 2023 Feb 4. Erratum in: CNS Drugs. 2023 Jul;37(7):661. PMID: 36739335; PMCID: PMC10299922.

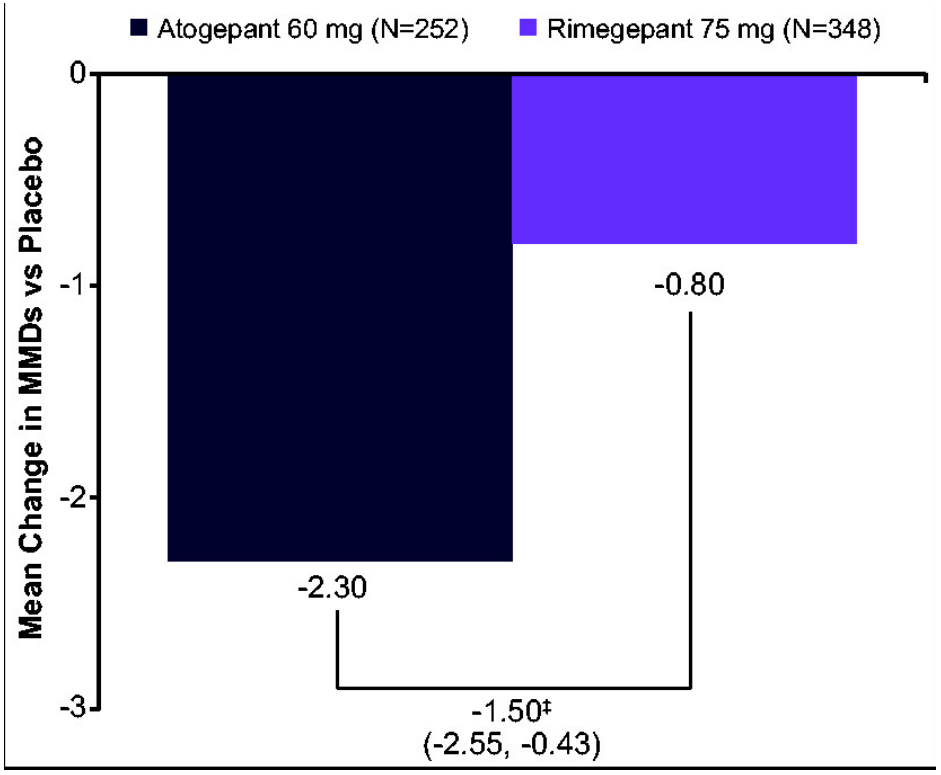
Efficacy of Galcanezumab vs Rimegepant in Reduction of Monthly Migraine Headache Days

Proportion of patients with >50% reduction in migraine headache days similar in both groups at 3 months



Schwedt, T.J., Myers Oakes, T.M., Martinez, J.M. *et al.* Comparing the Efficacy and Safety of Galcanezumab Versus Rimegepant for Prevention of Episodic Migraine: Results from a Randomized, Controlled Clinical Trial. *Neurol Ther* **13**, 85–105 (2024). https://doi.org/10.1007/s40120-023-00562-w.

Comparison of atogepant and rimegepant in migraine prevention



Atogepant 60 mg once daily demonstrated a significantly greater reduction in monthly migraine days compared with rimegepant 75 mg orally disintegrating tablet once every other day

Tassorelli C et al. **Comparative efficacy, quality of life, safety, and tolerability of atogepant and rimegepant in migraine prevention: A matching-adjusted indirect comparison analysis** *Cephalagia* 2024 Feb;44(2):3331024241235156. doi: 10.1177/03331024241235156.

Back to Rachel

Rachel is a 25yo that has 4-7 migraine headaches/month with mixed response to acute therapy. It is impacting her ability to work. She trialed propranolol with some success, but could not tolerate higher doses. Topiramate seemed to help some, but made her “loopy” and caused memory issues. She has no other health issues. She’s heard about new agents. Afraid of needles, but willing to try something to help her.

Practical Considerations – Combinations

mAb + acute abortive agents, triptans, ditans

- Standard practice

mAb + previous oral therapies if patient tolerated and had some benefit

- Standard practice

mAb preventive + gepants

- Gepant acute – case reports
- Gepant preventive – no studies

Gepant preventive + gepant acute

- Rimegepant QOD prevention - with the option to dose as needed for acute therapy if not taken that day for prevention
- Study planned to assess efficacy and safety of combining daily atogepant for migraine prevention with ubrogepant as needed for acute therapy

Shah T, Bedrin K, Tinsley A. Calcitonin gene relating peptide inhibitors in combination for migraine treatment: A mini-review. Front Pain Res (Lausanne). 2023 Mar 17;4:1130239. doi: 10.3389/fpain.2023.1130239. PMID: 37006413; PMCID: PMC10064089..
Asawavichienjinda T, Sathitratanacheewin S, Chokesuwattanaskul R. "Wearing-off" efficacy of CGRP monoclonal antibodies for migraine prevention: A meta-analysis of randomized controlled trials. *Cephalalgia*. 2023;43(4). doi:10.1177/03331024231161261
Alsaadi, T., Suliman, R., Santos, V. *et al.* Safety and Tolerability of Combining CGRP Monoclonal Antibodies with Gepants in Patients with Migraine: A Retrospective Study. *Neurol Ther* **13**, 465–473 (2024). https://doi.org/10.1007/s40120-024-00586-w

Practical Considerations – Other

Switching anti-CRGP mAb's

- Change due to insurance – mixed responses
- Decreased efficacy of current agent – may try another
- Intolerable side effects – may try another

Switching Gepants for prevention

- Limited data for switching

Pregancy:

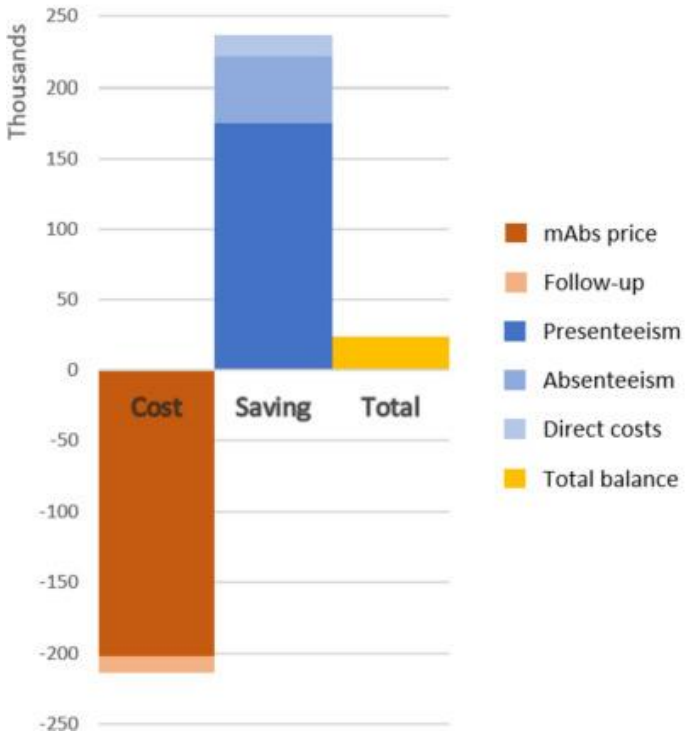
- CGRP is suspected to play a possible role in regulating uteroplacental blood flow, myometrial and uterine relaxation, and in maintaining normal gestational blood pressure.
- mAbs have a long half-life and can last in the system for 5 months, it is recommended to stop it about 6 months prior to pregnancy planning.
- mAbs are also not recommended to use during breast-feeding since we do not have enough safety data at this time.

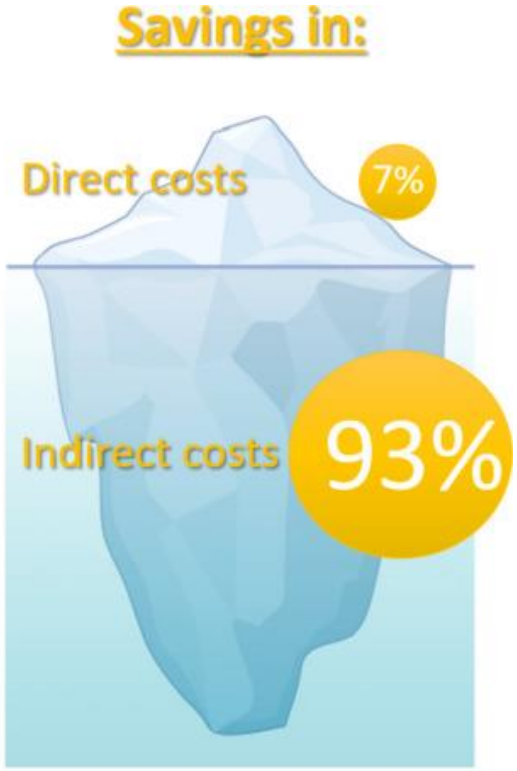
Lee MJ, Al-Karagholi MA-M, Reuter U. New migraine prophylactic drugs: Current evidence and practical suggestions for non-responders to prior therapy. *Cephalalgia*. 2023;43(2). doi:10.1177/03331024221146315

Asawavichienjinda T, Sathitratanacheewin S, Chokesuwattanaskul R. "Wearing-off" efficacy of CGRP monoclonal antibodies for migraine prevention: A meta-analysis of randomized controlled trials. *Cephalalgia*. 2023:43(4). doi:10.1177/03331024231161261

Cost-effectiveness?

- The annual economic burden of migraine in the US is high, with indirect costs due to lost productivity accounting for 36–56% of these costs among patients with episodic migraine (EM) and 40–70% of these costs among patients with chronic migraine (CM).
- Despite the high costs of the newer preventive agents, pharmacoeconomic analysis suggest overall cost-effectiveness





J Headache Pain. 2024 Feb 12;25(1):21. doi: 10.1186/s10194-024-01727-0. PMID: 38347485; PMCID: PMC10860274
Siersbæk, N., Kilsdal, L., Jervelund, C. *et al.* Real-world evidence on the economic implications of CGRP-mAbs as preventive treatment of migraine. *BMC Neurol* **23**, 254 (2023). https://doi.org/10.1186/s12883-023-03302-7

American Headache Society (AHS) New Position Statement on CGRP-targeting therapies, March, 2024

The new guidance encourages clinicians to consider CGRP-targeting therapies as a first-line approach for migraine prevention along with previous first-line treatments, without a requirement for prior failure of other classes of migraine preventive treatment

- Charles, AC et al. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. The American Headache Society.. https://americanheadachesociety.org/
- J of Head and Face Pain, Volume64, Issue4; 333-34, April 2024. https://doi.org/10.1111/head.14692

Key Summary Points

- Preventive therapies tailored to individual needs
- CGRP-targeted therapies increasingly used in eligible patients and may be considered first line in near future
- Combination of therapies including CGRP therapies may be used for some patients
- Many new therapies on the horizon to consider

The End