Mastering Migraine: Examining the Therapeutic Spectrum for Optimal Patient Outcomes

Supported by an educational from GSK

Michael J. Marmura, MD

BRAINWeek™

Title & Affiliation

Michael J. Marmura, MD

Associate Professor

Director of Outpatient Operations

Jefferson Headache Center

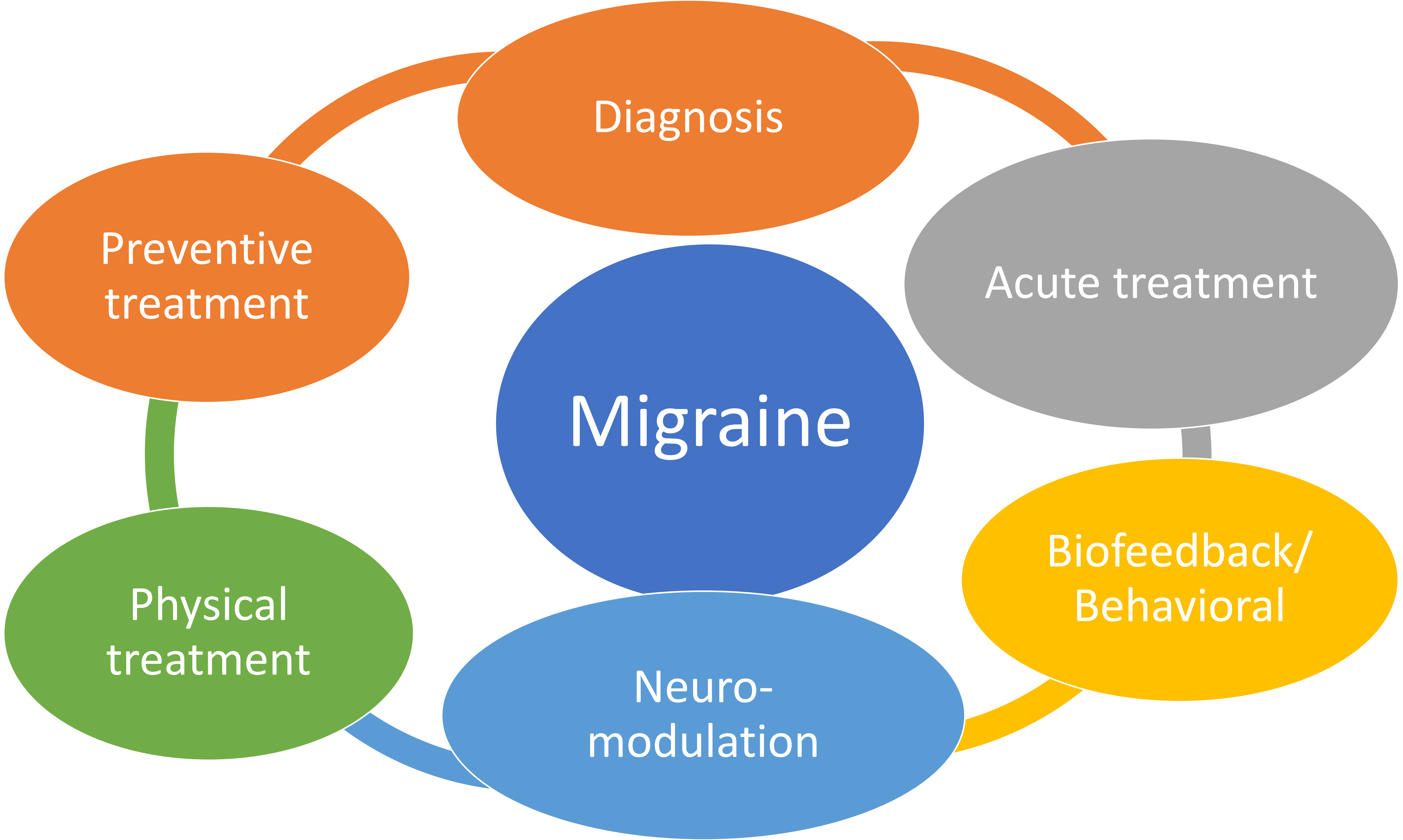
Co-Chief, Division of Headache

Disclosures

Role	Organization
Consulting Fee (eg, Advisory Board):	Theranica, electroCore, Lundbeck, Eli Lilly, Amgen, Novartis
Contracted Research (Principal Investigators must provide information, even if received by the institution):	Teva, Allergan/AbbVie
Honoraria	Lundbeck
Speakers Bureau:	Eli Lilly, Amgen, Novartis

Learning Objectives

- Recall tools and diagnostic criteria for accurate identification of migraine patients
- Review conventional therapies designed for acute and preventive migraine treatment
- Describe the OTC analgesic compounds and the non-pharmacological solutions available for migraine treatment
- Summarize the safety and efficacy of novel CGRP inhibitors as an emerging treatment option for migraine
- Outline individualized treatment plans that address the specific needs of migraine patients


Diagnosis
Preventive treatment
Acute treatment
Migraine
Biofeedback/ Behavioral
Physical treatment
Neuro- modulation

Initial Visit: Migraine

- Establish diagnosis (or need for further testing)
- Assess impact of migraine (including disability)
- Discuss and recommend acute and preventive treatment

Nausea + Light sensitivity + Disability = > 95% migraine diagnosis

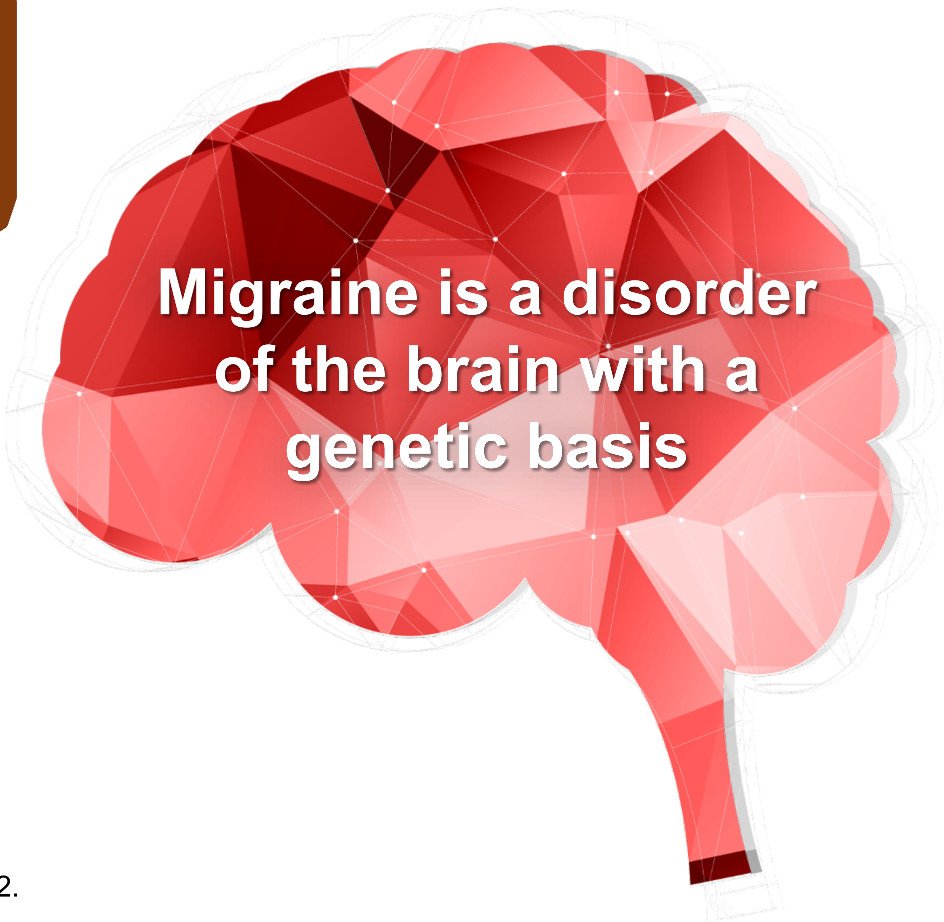
Most chronic headache, “sinus headaches,” stress headache are migraine.

Lipton et al Neurology 2003

What Causes Migraine?

But vasodilation is neither necessary nor sufficient for the symptoms of migraine to occur

Neuronal theories involving the central and/or peripheral nervous system are now the focus of migraine pathophysiology

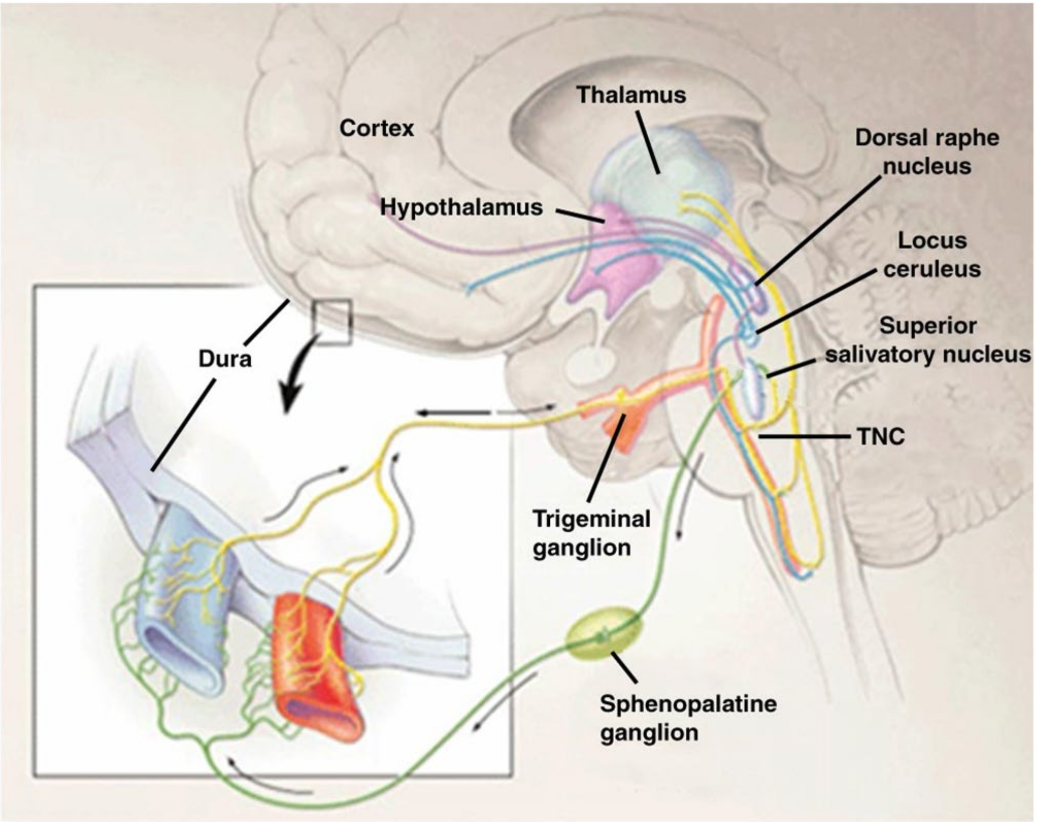


Early theories linked cranial vasodilation to migraine pain

Multiple brain regions generate migraine symptoms and overlapping phases of migraine

- Goadsby PJ et al. *Physiol Rev.* 2017;97:553–622.

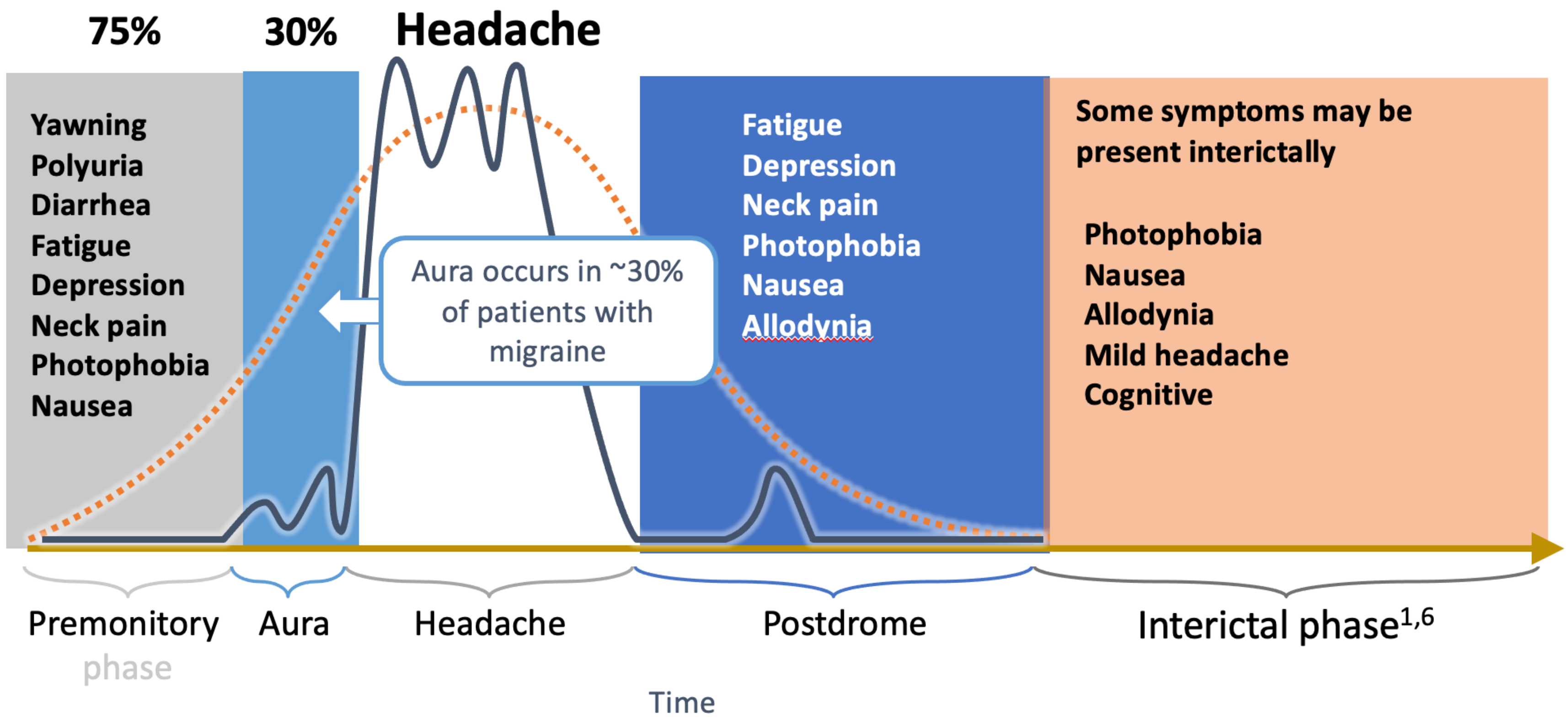
Migraine Overview



- Trigeminal nerve activation leads to vasodilation, and neurogenic inflammation (including CGRP release)
- Parasympathetic activation via sphenopalatine ganglion
- The hypothalamus and changes in functional connectivity play a role in triggering or modulating attacks
- Input synapses on trigeminal nucleus caudalis (TNC)
- Brain stem involvement during attacks before synapses in the thalamus → limbic system, cortex

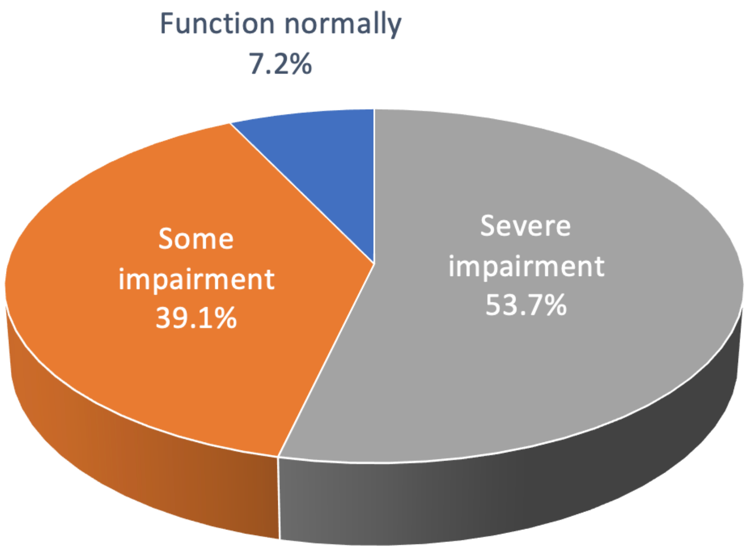
Goadsby PJ, et al. N Engl J Med. 2002;346(4):257-270. Pietrobon D, et al. Nat Rev Neurosci. 2003;4(5):386-398.

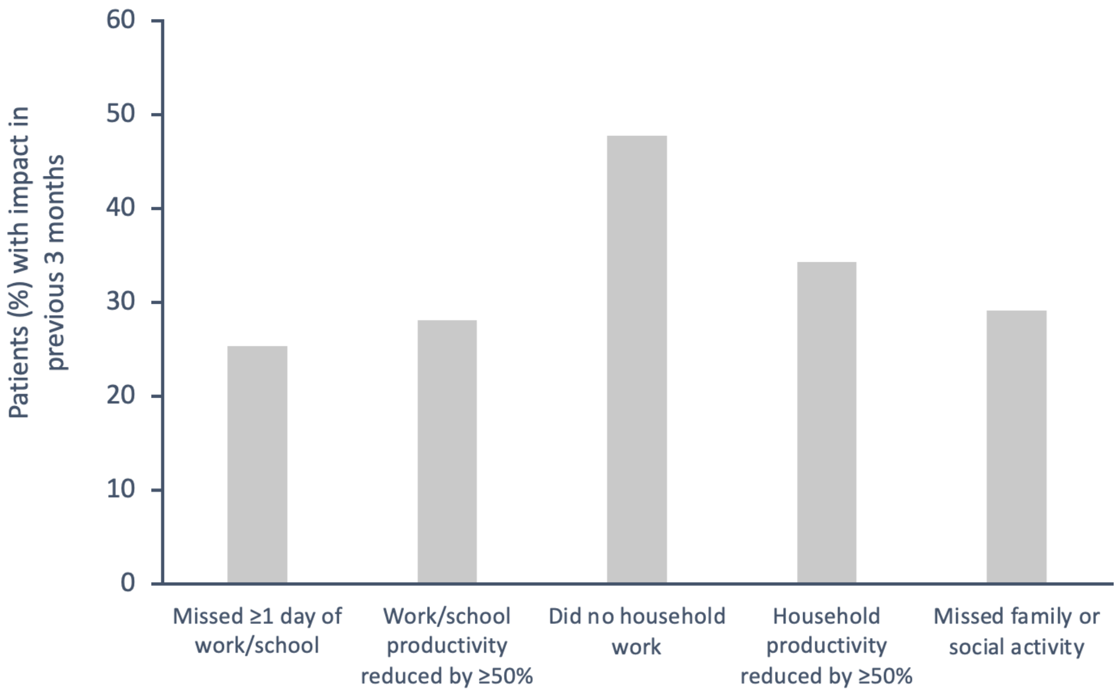
The Phases of Migraine



- Solid line represents pain; dashed line represents other migraine symptoms.
- Adapted from Linde M. *Acta Neurol Scand*. 2006;114(2):71–83.

Migraine Impact on Life Activities





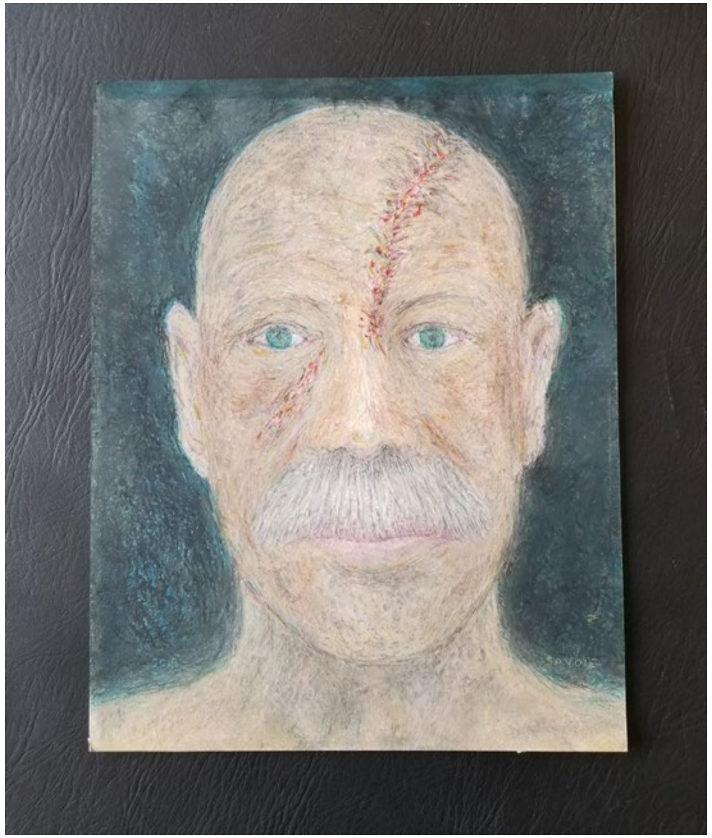
- Patients with migraine (N=18,968) participating in the AMPP survey. Respondents were asked how they are “usually affected by severe headaches”, with the following response options: able to work/function normally; working ability or activity impaired to some degree; working ability or activity severely impaired; and bed rest required.
- Lipton RB et al. *Neurology*. 2007;68:343–349. Buse DC et al. *Headache* 2013;53:1278–1299.

Patient Expectations:

- Take a pill and it goes away right?
- But I have a headache **EVERY DAY!**
- But my headaches are **BAD**! (Migraine not understood as a serious disorder.)
- What about _______________?? (dizziness, confusion, light/sound/odor sensitivity, visual problems) (Migraine is not just a headache.)

Case 1: Migraine Prevention

- Jon is a 47-year-old man who is seeing you for frequent migraine that he’s had since childhood.
- In the past year he has been experiencing an average of 1 migraine per week, but his migraines usually last 1-3 days.
- He runs through his monthly allotment of rizatriptan early every month and has started to use ibuprofen more days than not.
- Previously he used topiramate, which he stopped due to intolerable side effects, and propranolol which did not seem effective.
- How would you approach this patient?



Migraine Preventive Treatment Principles

- Start low, go slow (oral drugs)
- Counsel about side effects and pregnancy plans
- An adequate trial may be 3 months
- Avoid medication overuse (especially triptans, opioids, barbiturates)
- Use a calendar/journal to assess effectiveness

https://headachemigraine.org/migraine/

AHS. Headache. 2019;59:1-18.

Oral Migraine Preventives

Drug Class	Examples
Antiepileptic drugs	Divalproex sodium,* valproate sodium,* topiramate,* gabapentin
Beta-blockers	Propranolol,* timolol,* metoprolol, atenolol, nadolol
Other antihypertensives	Lisinopril, candesartan, verapamil
Antidepressants (other than SSRIs)	Amitriptyline, nortriptyline, venlafaxine, duloxetine
Neurotoxin	OnabotulinumtoxinA* (chronic migraine)
Other/nutraceuticals	Memantine, amantadine, tizanidine

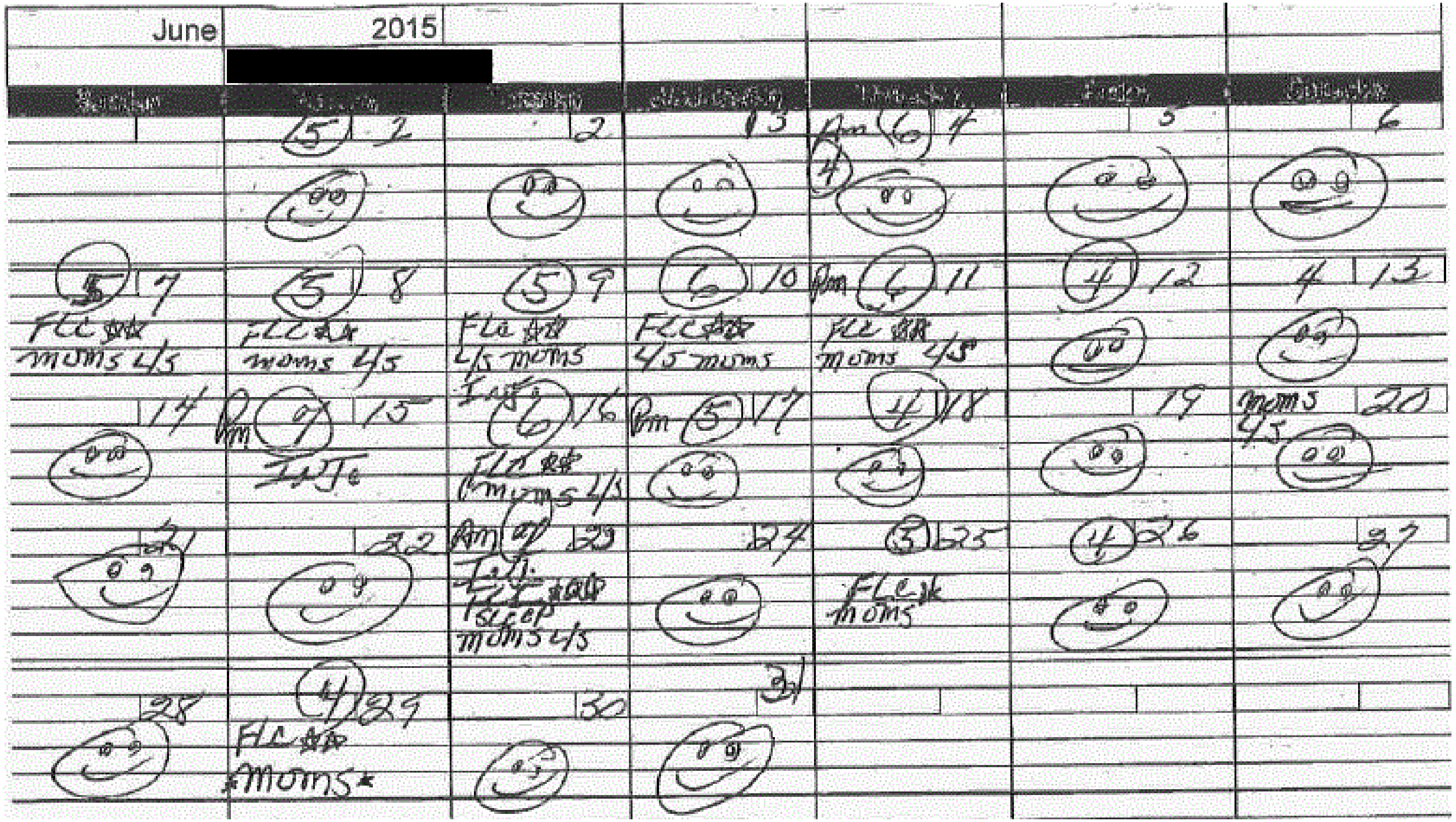
*FDA approved for migraine

Non-prescription Preventive Treatment

Drug Class	Examples
Nutraceuticals	Riboflavin, co-Q10, petasites (butterbur), magnesium
Devices	• External trigeminal nerve stimulation (Cefaly) • Single-pulse transcranial magnetic stimulation (eNeura) • Non-invasive vagus nerve stimulator (gammaCore) • Remote limb stimulation/desending pain modulation (Nerivio)
Lifestyle interventions	Sleep, regular routine, exercise, weight management
Behavioral	Biofeedback, cognitive behavioral therapy
Physical	PT, acupuncture, chiropractic, TMJ evaluation

*FDA approved for migraine

Sample Headache Calendar

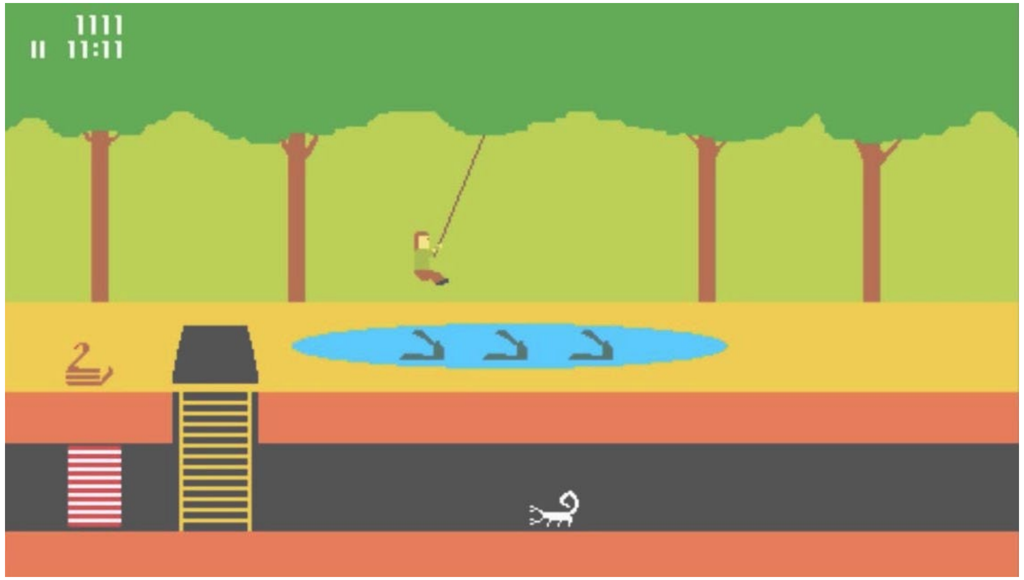


June 2015 [redacted]

	5 1	2	3	Pm 6 4	5	6
5 7 FLC moms 4/5	5 8 FLC moms 4/5	5 9 FLC 4/5 moms	6 10 FLC 4/5 moms	Pm 6 11 FLC moms 4/5	4 12	4 13
14	Pm 7 15	6 16 FLC moms 4/5	Pm 5 17	4 18	19	moms 4/5 20
21	22	Am 23	24	3 25 FLC moms	4 26	27
28	4 29 FLC moms	30	31			

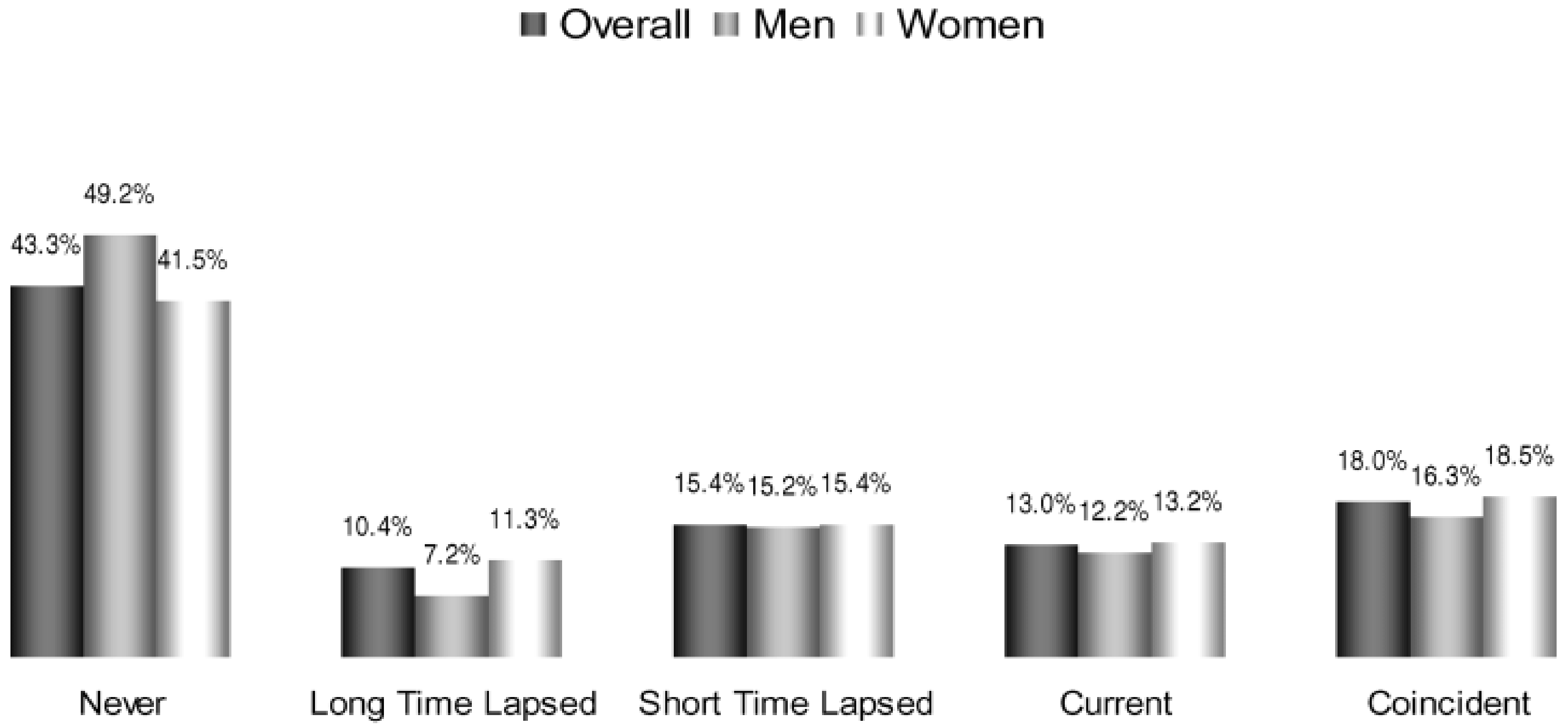
Preventive Treatment Pitfalls

- Preventive treatments rarely prevent all migraine, most acute treatments do not lead to pain freedom
- Need to individualize treatment: need for new therapeutic targets
- Serious adverse events and contraindications
- Little evidence for chronic migraine/daily headache



Scher AI et al. *Cephalalgia*. 2010;30(3):321-328.
Puledda F et al. J Neurol. 2017 Sep;264(9):2031-2039.
Buse et al. J Manag Care Spec Pharm. 2020 Jul 17:1-10

Most People with Migraine Are Not on Preventive Treatments

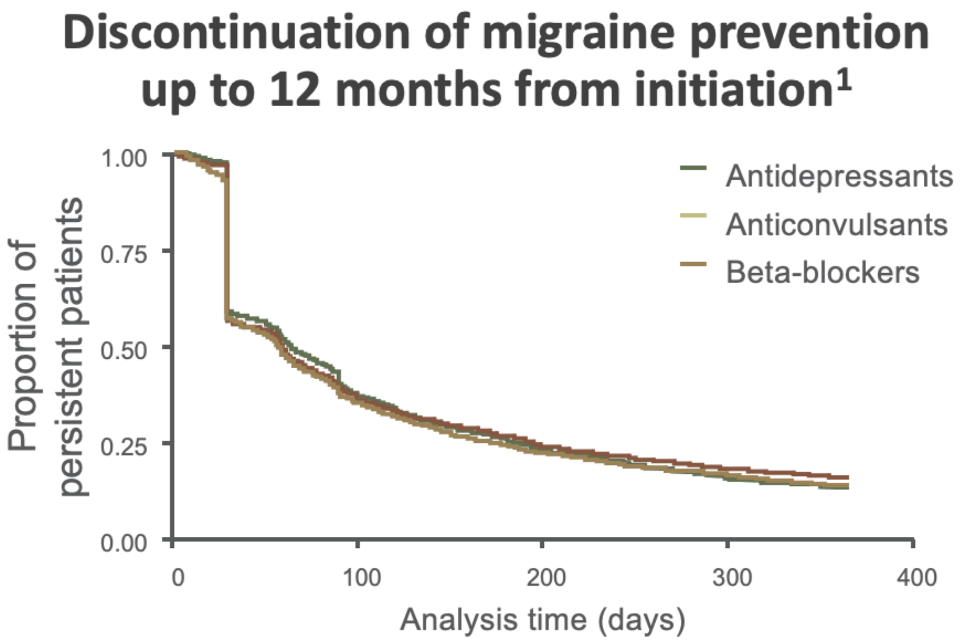


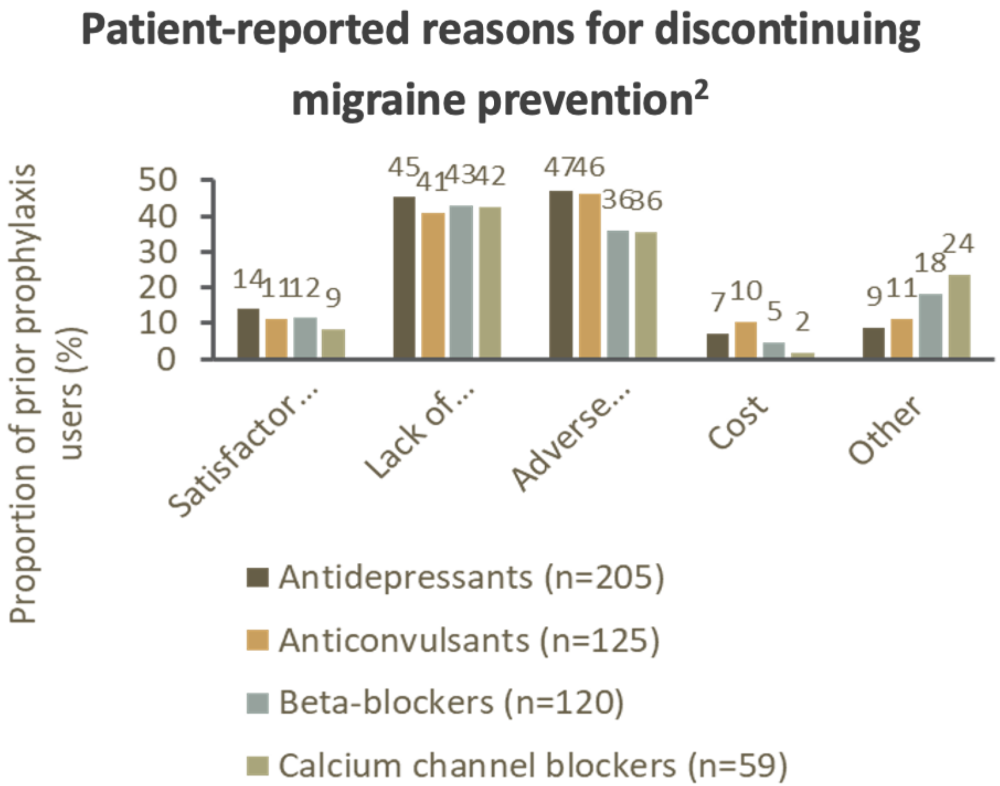
Short-term lapsed: stopped the preventive use less than 1 year before. Long-term lapsed: stopped preventive use 1 year or more before.

Diamond, Bigal, Silberstein et al Headache 2007

BRAINWEEK™

Adherence to Oral Preventives Is Poor

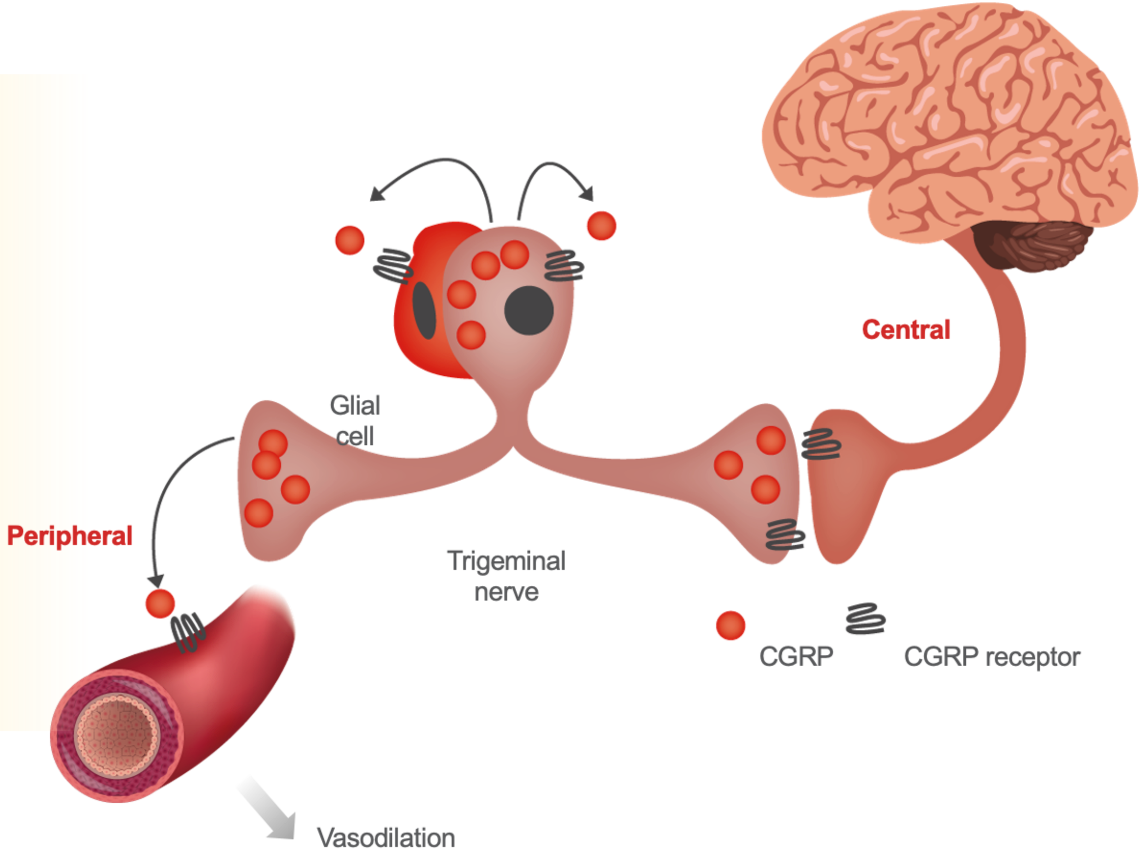




1. Hepp Z, et al. *Cephalalgia.* 2017;37:470–485. 2. Blumenfeld AM, et al. *Headache.* 2013;53:644–655.

Calcitonin Gene-related Peptide

- Widely expressed in the CNS and PNS; expressed in 35–50% of neurons in the trigeminal ganglia
- CGRP plays roles in vasodilation, inflammation, pain, and central activation of the brain
- CGRP antagonism has not been shown to cause vasoconstriction



PNS, peripheral nervous system.

Eftekhari S et al. *J Pain.* 2013;14:1289–1303. Edvinsson L, Ho TW. *Neurotherapeutics*. 2010;7:164–175.

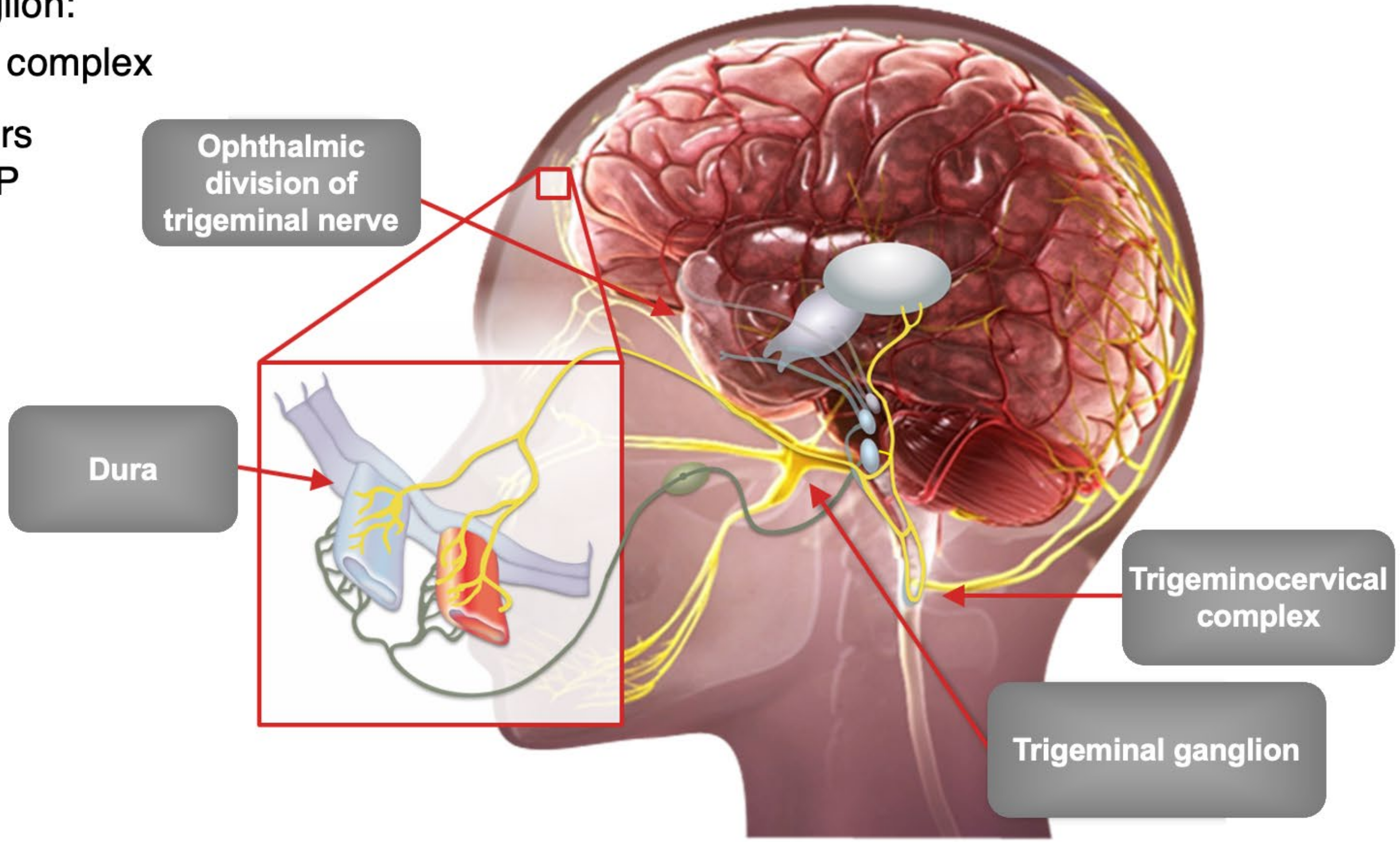
The Role of CGRP in Migraine

1. IV CGRP triggers typical migraine (or cluster headache)
2. CGRP levels increase in the jugular vein during migraine attacks
3. CGRP levels go down after treating migraine with triptans
4. Blocking CGRP treats migraine

Tso AR, et al. Curr Treat Options Neurol. 2017;19(8):27.
Raddant AC, et al. Expert Rev Mol Med. 2011;13:e36.
Tepper SJ. Headache. 2018; 58(suppl 3):238-275.

The Trigeminovascular System in Migraine

- Projections from the trigeminal ganglion:
  - Converge in the trigeminocervical complex
  - Release classical neurotransmitters and neuropeptides, such as CGRP
- The trigeminocervical complex
  - Located in brain stem and upper cervical spinal cord
  - Connected to key brain centers
  - Activation crucial for migraine headache



Goadsby PJ et al. *Physiol Rev.* 2017;97:553–622.

Monoclonal Antibodies vs CGRP for Migraine

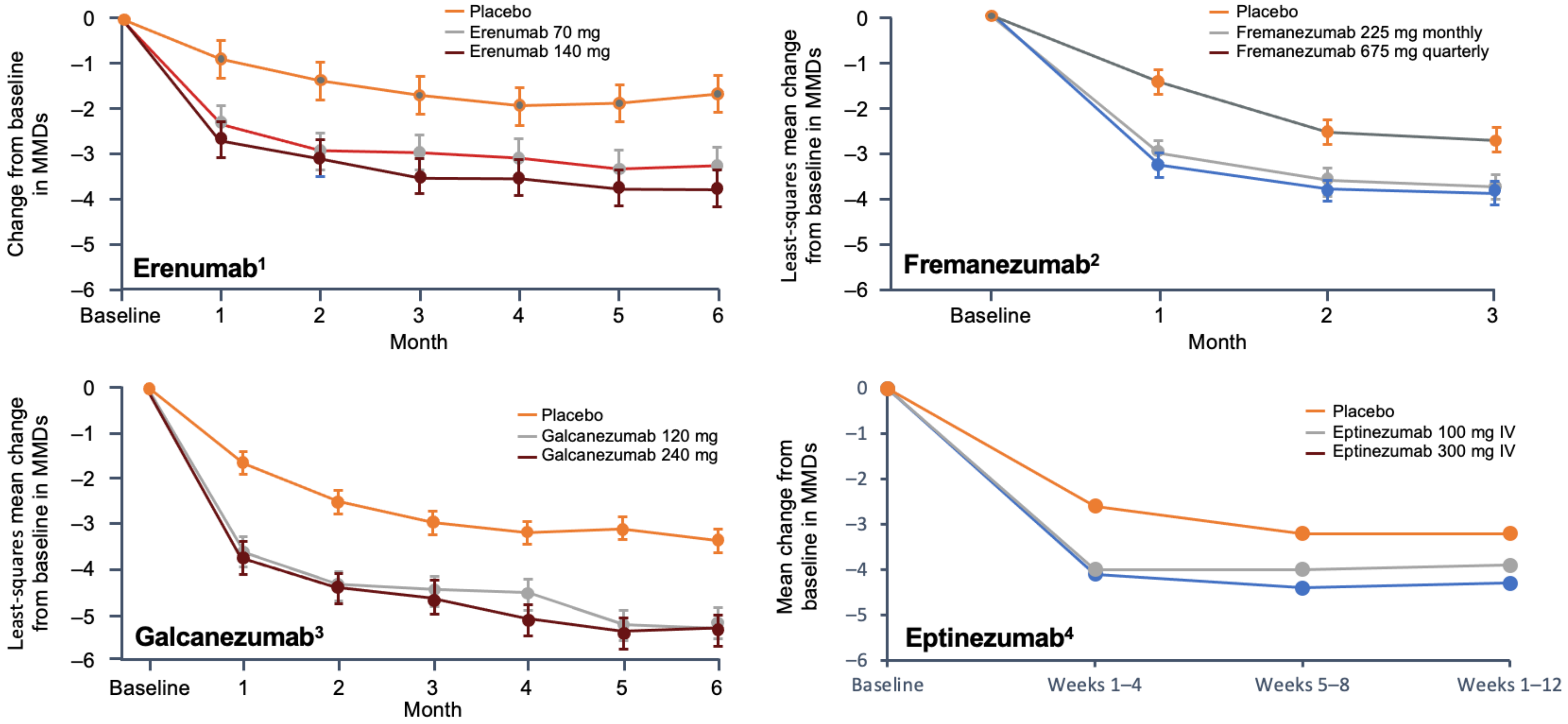
Characteristic	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab
mAb type	Human IgG2	Humanized IgG2a	Humanized IgG4	Humanized IgG1
CGRP target	Receptor	Ligand	Ligand	Ligand
Route of administration	SC	SC	SC	IV infusion
Dose frequency	Monthly	Quarterly/monthly	Monthly	Quarterly
Indication/ development stage	Migraine: approved	▪ Migraine: approved ▪ Posttraumatic headache: phase 2	▪ Migraine: approved ▪ Episodic cluster headache: approved	Migraine: approved
Half-life	28 days	31 days	27 days	27 days
Study design – phase 3, placebo controlled (Rx/analysis wks)	12/12 24/last 12	12/12	24/24	24/12 12/12

- Ig, immunoglobulin; IV, intravenous; SC, subcutaneous

CGRP Questions for Migraine Prevention?

- Do they work?
- Safety
- What’s different about anti-CGRP mAb compared to other preventives?

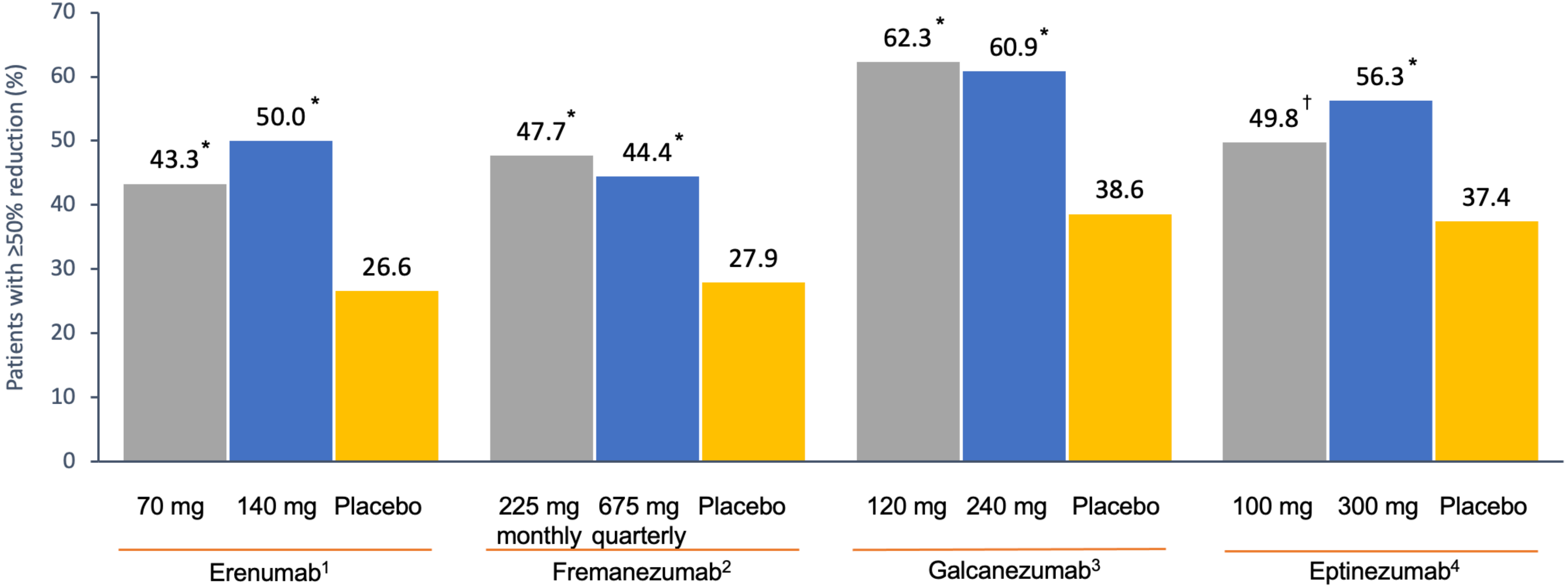
All Reduce Migraine Days in Phase 3 Trials for Episodic Migraine



MMD: monthly migraine day

1. *N Engl J Med*. 2017;377:2123-32; 2. *JAMA*. 2018;319:1999-2008; 3. *JAMA Neurol*. 2018;75:1080-88; 4. *Cephalalgia*. 2017;37(1S):377; 5. *Cephalalgia*. 2019;39:817-26; 6. *Lancet*. 2019;394:1030-40; 7. *Neurology*. 2019;92:e2309-20.

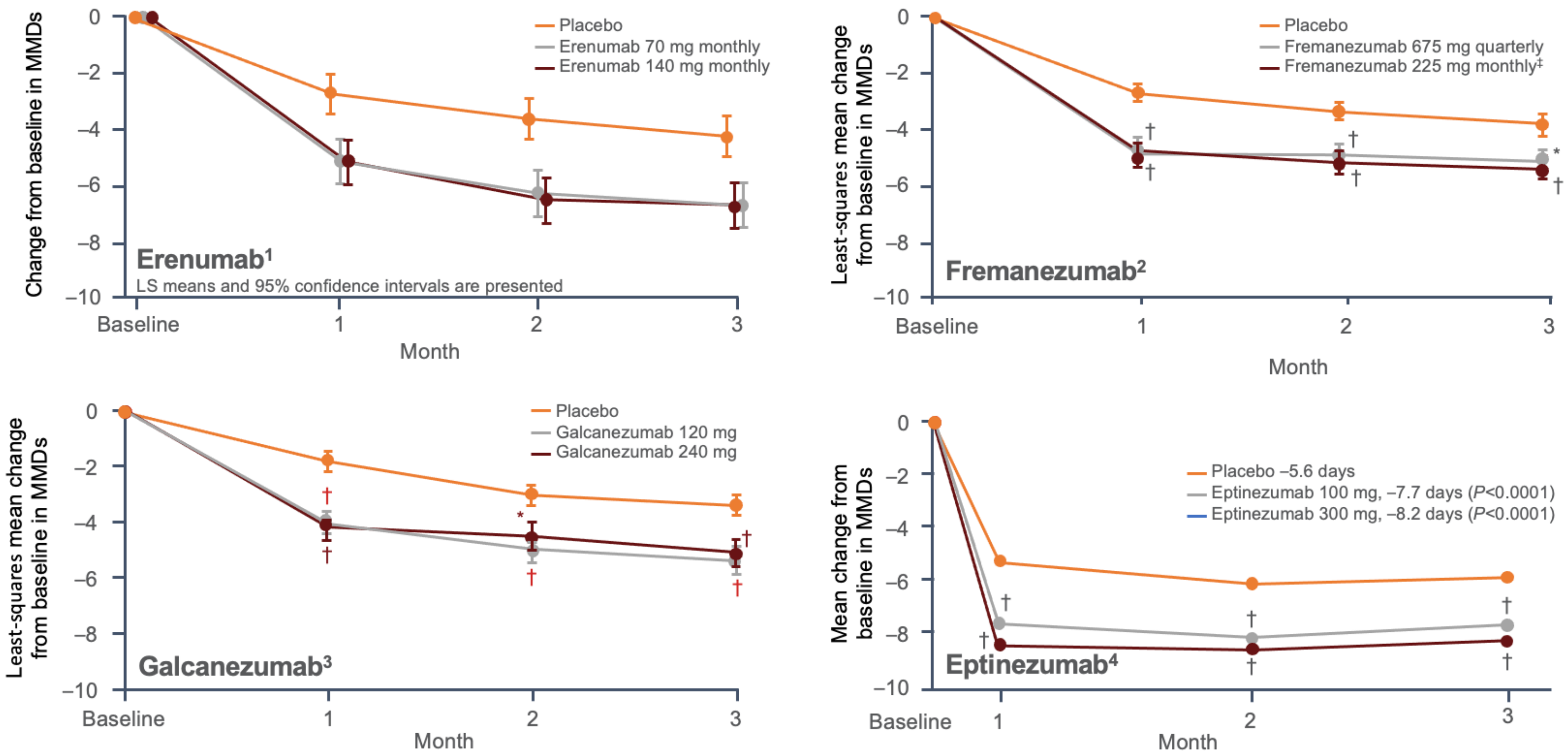
Reduction in Mean MMDs ≥50%



*P<0.001 vs placebo. †P<0.01 vs placebo.

1. Goadsby. *N Engl J Med*. 2017;377:2123-2132; 2. Dodick. *JAMA*. 2018;319:1999-2008; 3. Stauffer . *JAMA Neurol*. 2018;75:1080-1088; 4. Saper. *Neurology*. 2018;90(15 Suppl):S20.001.

Chronic Migraine: Reduction of Mean MMDs



1. *Lancet Neurol*. 2017;16:425-34; 2. *N Engl J Med*. 2017;377:2113-22; 3. *Neurology*. 2018;91:e2211-21; 4. *Headache*. 2017;57(Suppl 3):130; 5. *Cephalalgia*. 2018;38:1611-21; 6. *Lancet*. 2019;394:1030-40; 7. *Headache*. 2019;59(Suppl. 1):23.

Safety of CGRP mAbs: Adverse Events (AEs)

Injection-site reactions most common AEs with SC[1-3]

Nasopharyngitis most common AE

	Erenumab[1]	Fremanezumab[2]	Galcanezumab[3]	Eptinezumab[4]	
Monthly	140 mg, 5%	225 mg, 43%	120 mg, 18%	100 mg, 6%	300 mg, 8%
Quarterly		675 mg, 45%			
Placebo	3%	38%	13%	6%	6%

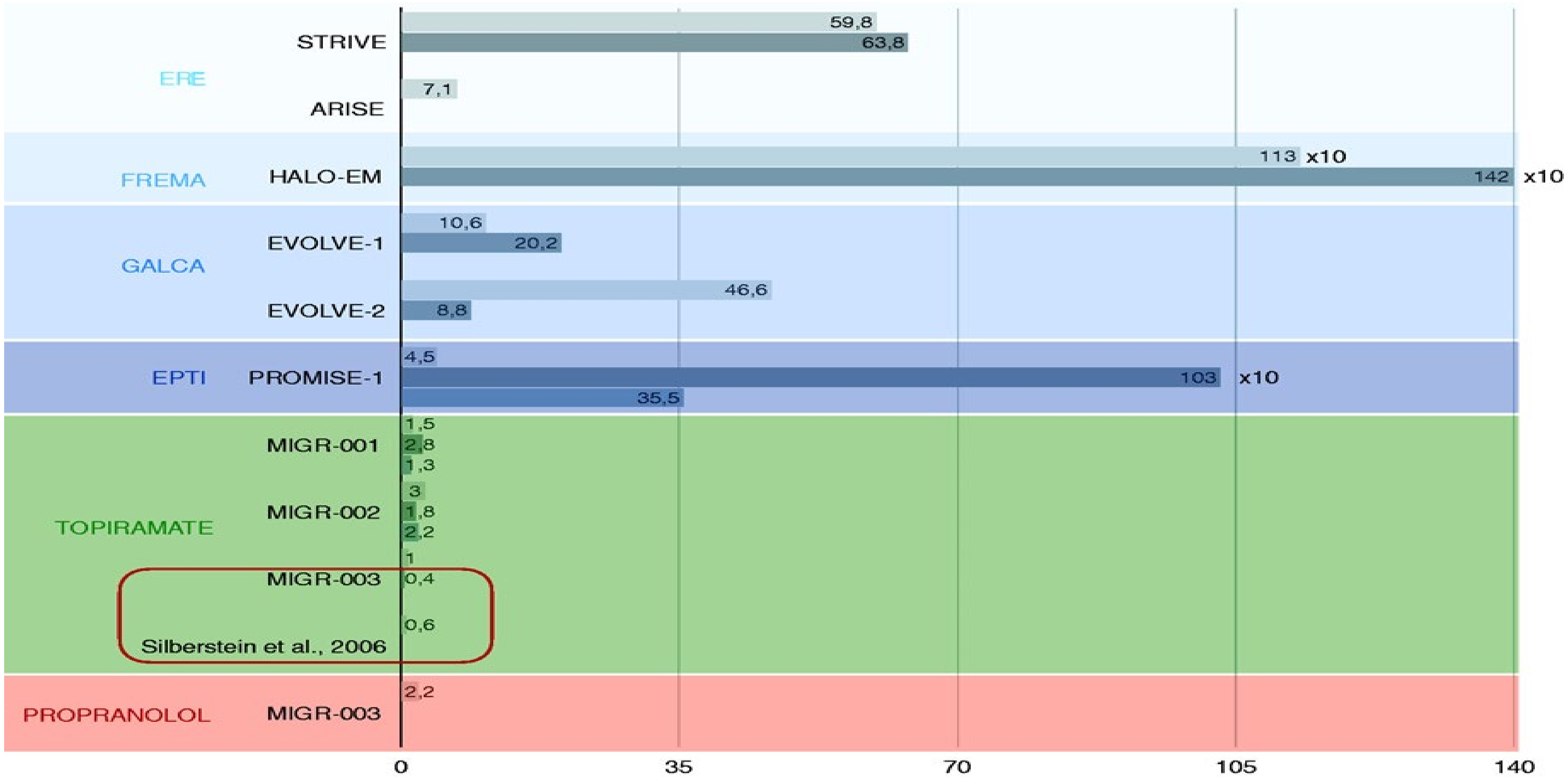
- Label warnings
  - Hypersensitivity reactions reported with erenumab, fremanezumab, galcanezumab, and eptinezumab[1-4]
  - Constipation with serious complications and hypertension reported with erenumab[1]
- No serious CV AEs reported in placebo-controlled clinical trials; however, a recent case report suggested a possible association between CGRP inhibition and ischemic stroke in a patient receiving erenumab[5]

1. Aimovig US prescribing information. 2. Ajovy US prescribing information. 3. Emgality US prescribing information. 4. Vyepti US prescribing information. 5. Aradi S et al. *J Stroke Cerebrovasc Dis*. 2019;28:104286.

Safety (continued)

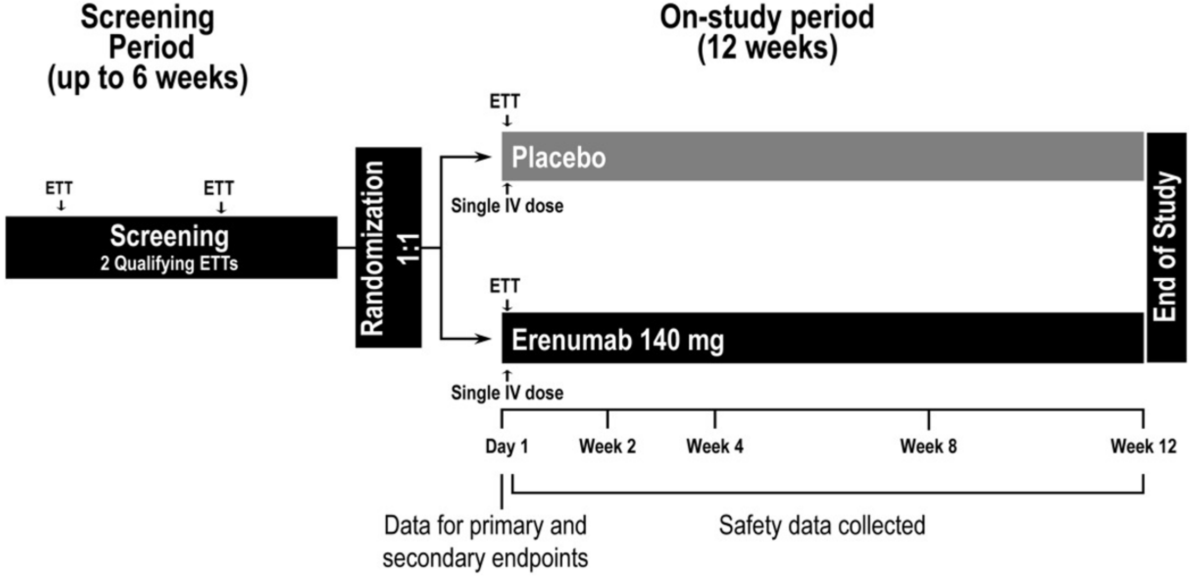
- Unlikely to penetrate CNS: sedation, mood disorders unlikely
- Blocking CGRP does not cause immune suppression
- Studies excluded many with recent/unstable cardiac events or stroke
- No pregnancy data
- Newborns can ingest antibodies orally

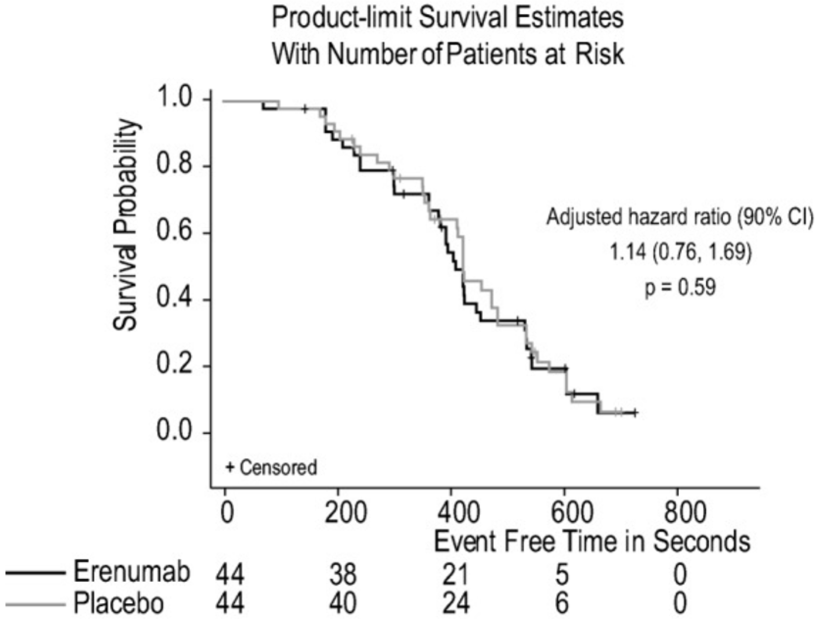
NNT Vs Number Needed to Harm in Migraine Trials:



Drellia K, et al. Cephalalgia. 2021 Feb 10:0333102421989601.

The Effect of IV Erenumab on Exercise Time During a Treadmill Test in Patients With Stable Angina: No Change in Onset of ST Depression





Headache: The Journal of Head and Face Pain, Volume: 58, Issue: 5, Pages: 715-723, First published: 21 May 2018, DOI: (10.1111/head.13316)

mAb vs CGRP Advantages

1. Excellent response in patients who had used >2 previous preventives (low placebo response)
2. Rapid onset of action – as little as <1 week even in chronic migraine
3. Low discontinuation rates in long-term studies
4. Very effective in patients with medication overuse headache
5. Lack of drug interactions, effective in patients with comorbidities
6. Proven to reduce disability
7. Low risk/benefit ratio

Reuter U, et al. *Lancet*. 2018;39210161):2280-2287. Ferrari MD, et al. *Lancet* 2019; 394(10203):1030-1040. Mulleners WM, et al. Lancet Neurol 2020; 19: 814–25. Lipton RB, et al. Neurology. 2019;92(19):e2250-e2260. Cohen JM, et al. J Headache Pain. 2018;19(Suppl 1):80.

Case 2: Unhappy with Acute Options

- Liz is a 29-year-old woman, recently married and working in a hair salon, seeing you for hard-to-treat migraine.
- She recently stopped nortriptyline because she is considering pregnancy in the next year.
- Her migraine frequency is about 1-2 days/week—not especially bad for her—but she's having a tough time getting rid of them before she falls asleep.
- She previously used sumatriptan 100 mg and eletriptan 40 mg but didn't like that they made her feel dizzy.
- Currently she just takes naproxen but it's not very effective.

Acute Headache Treatment: Goals

- Pain relief/pain freedom (pain freedom preferred)
- Consistently effective
- Relief of associated symptoms
- Restore the ability to function (few adverse events)
- Low risk of “rebound” (low recurrence + low risk of worsening over time)
- Match treatment to the attack (stratified care)
- Minimize the use of rescue medications
- Optimize self-care and reduce ED visits

Categories of Acute Treatments

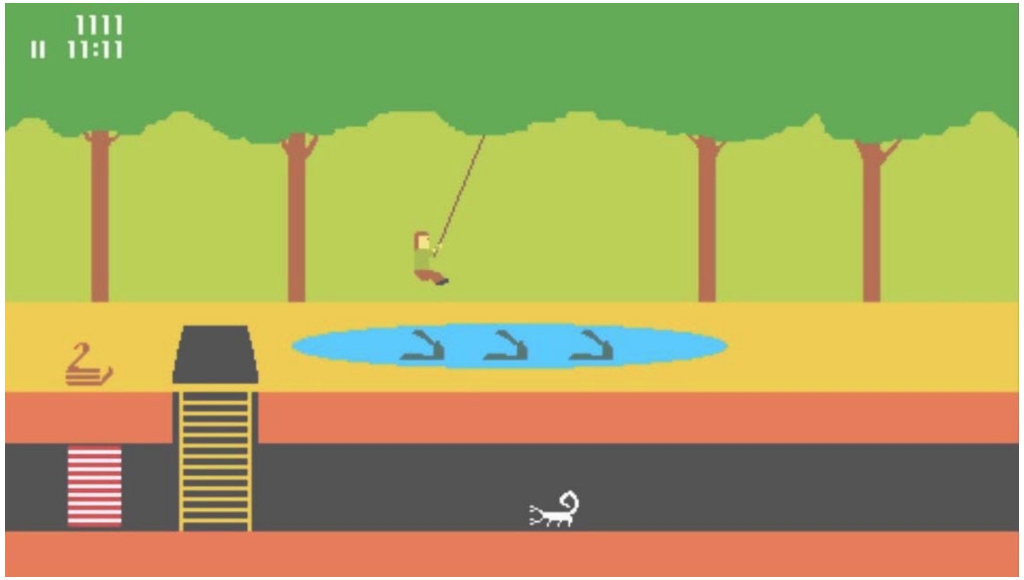
Migraine Specific	Nonspecific
Triptans	Nonsteroidal anti-inflammatories
Dihydroergotamine/ergotamine	Combination analgesics (APAP-ASA-Caffeine)
Lasmiditan	Neuroleptics/antiemetics
Gepants	Opioids ☹️
	Barbiturates ☹️ ☹️
	Corticosteroids, muscle relaxants

Acute Treatment Strategies

- Simple analgesics, combination analgesics often effective for mild-moderate attacks
- Triptans are effective for moderate-severe but may work best early
- Dihydroergomatine, antiemetics can treat severe or long-lasting attacks
- Rescue medication to prevent suffering, ED visits may be worthwhile

Acute Treatment Pitfalls

- No drug > 50% headache freedom
- Rebound, safety issues (depending on class)
- Status migrainosus
- Contraindications to triptans, NSAIDs or tolerability (sedation) complicate treatment



Scher AI et al. *Cephalalgia*. 2010;30(3):321-328.
Puledda F et al. J Neurol. 2017 Sep;264(9):2031-2039.
Buse et al. J Manag Care Spec Pharm. 2020 Jul 17:1-10

Ditans: Lasmiditan

Selective 5-HT_{1F} agonist

No clinically significant activity at 5-HT_{1B} and 5-HT_{1D} receptors

Efficacy comparable to triptans and significantly greater than placebo

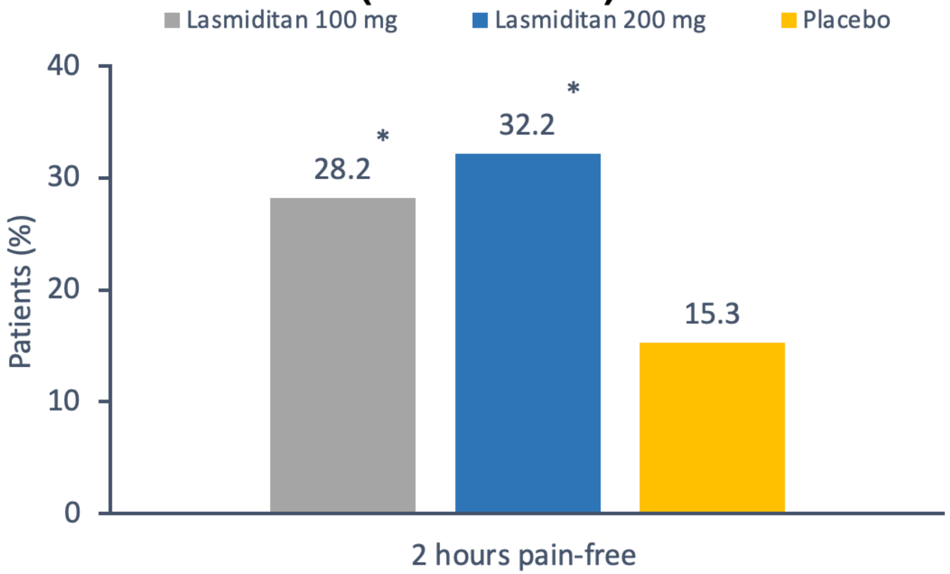
No evidence of vasoconstriction

Recently FDA approved (50, 100 or 200 mg)

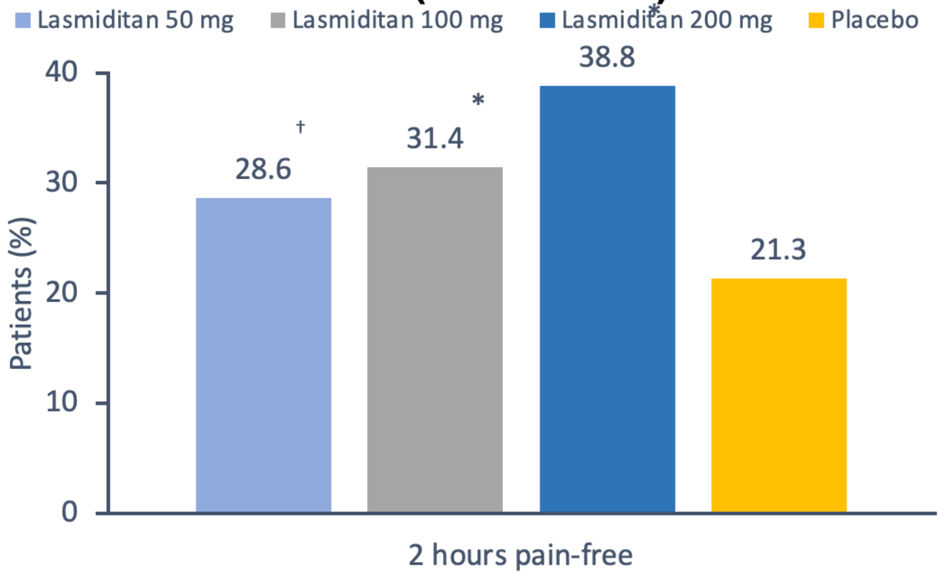
Kuca B et al. *Neurology*. 2018;91:e2222–e2232.

Lasmiditan Phase 3 Studies: Efficacy

- SAMURAI (N=2231)[1]



- SPARTAN (N=3007)[2]

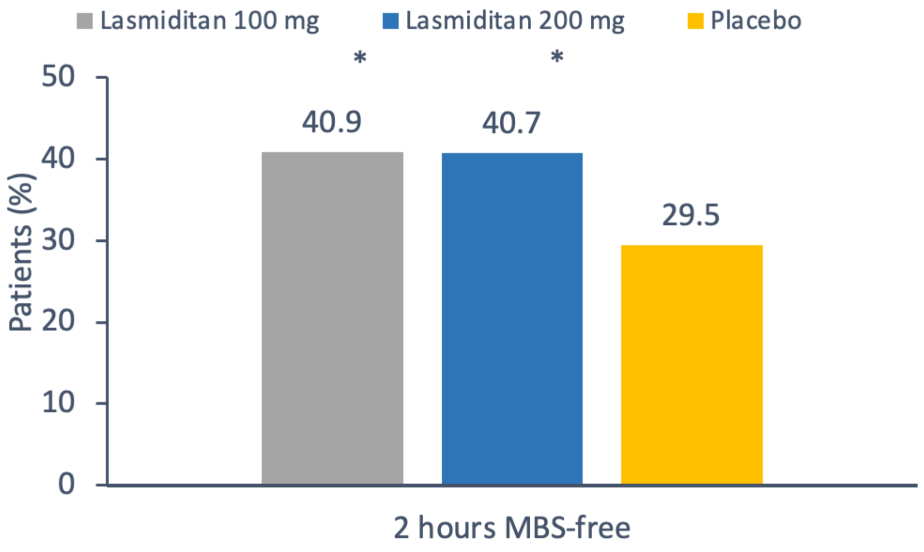


- In SAMURAI, patients (N=2231) with at least moderate disability were randomized to PO lasmiditan (100 or 200 mg) or placebo within 4 hours of onset of migraine attack. In SPARTAN, patients (N=3007) with at least moderate disability were randomized to PO lasmiditan (50, 100, or 200 mg) or placebo. **P*<0.001; †*P*=0.003 vs placebo.
  PO, orally.

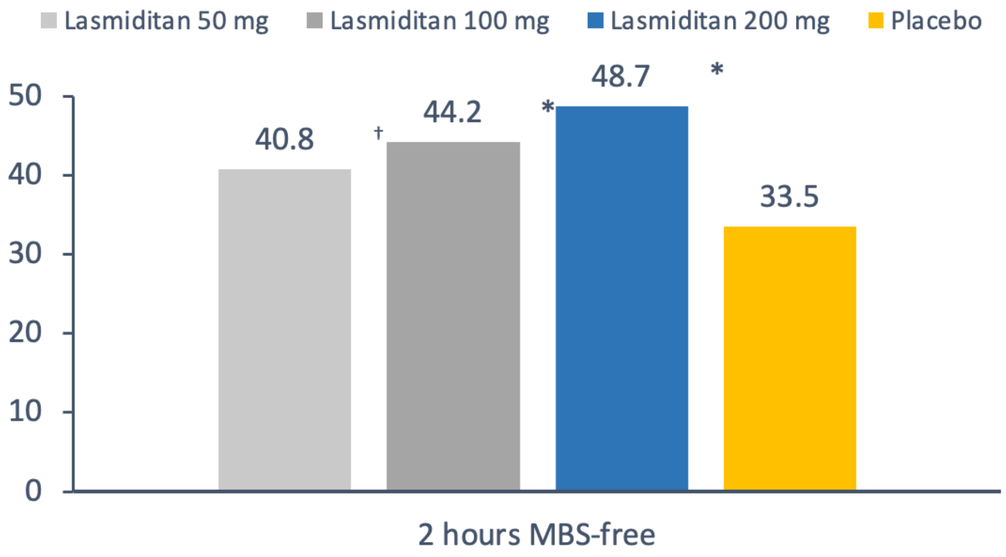
- 1. Kuca B et al. *Neurology*. 2018;91:e2222–e2232. 2. Lilly Announces Positive Results for Second Phase 3 Study of Lasmiditan for the Acute Treatment of Migraine (NYSE:LLY); 2017. Available from: https://investor.lilly.com/static-files/15cf1efc-da8f-485c-9001-6ff3b432b129. Accessed October 23, 2018.

Lasmiditan: Most Bothersome Symptom (MBS) Relief

- SAMURAI[1]



- SPARTAN[2]



Patients chose their MBS from photophobia, nausea, and phonophobia

- In SAMURAI, patients (N=2231) with at least moderate disability were randomized to PO lasmiditan (100 or 200 mg) or placebo within 4 hours of onset of migraine attack. In SPARTAN, patients (N=3007) with at least moderate disability were randomized to PO lasmiditan (50, 100, or 200 mg) or placebo. Among patients who reported an MBS in SAMURAI, 53.8% selected photophobia, 24.2% selected nausea, and 22.0% selected phonophobia as the most common MBS. **P*<0.001; †*P*<0.01 vs placebo.

- 1. Kuca B et al. *Neurology*. 2018;91:e2222–e2232. 2. Lilly Announces Positive Results for Second Phase 3 Study of Lasmiditan for the Acute Treatment of Migraine (NYSE:LLY); 2017. Available from: https://investor.lilly.com/static-files/15cf1efc-da8f-485c-9001-6ff3b432b129. Accessed October 23, 2018.

Lasmiditan SAMURAI phase 3: Safety

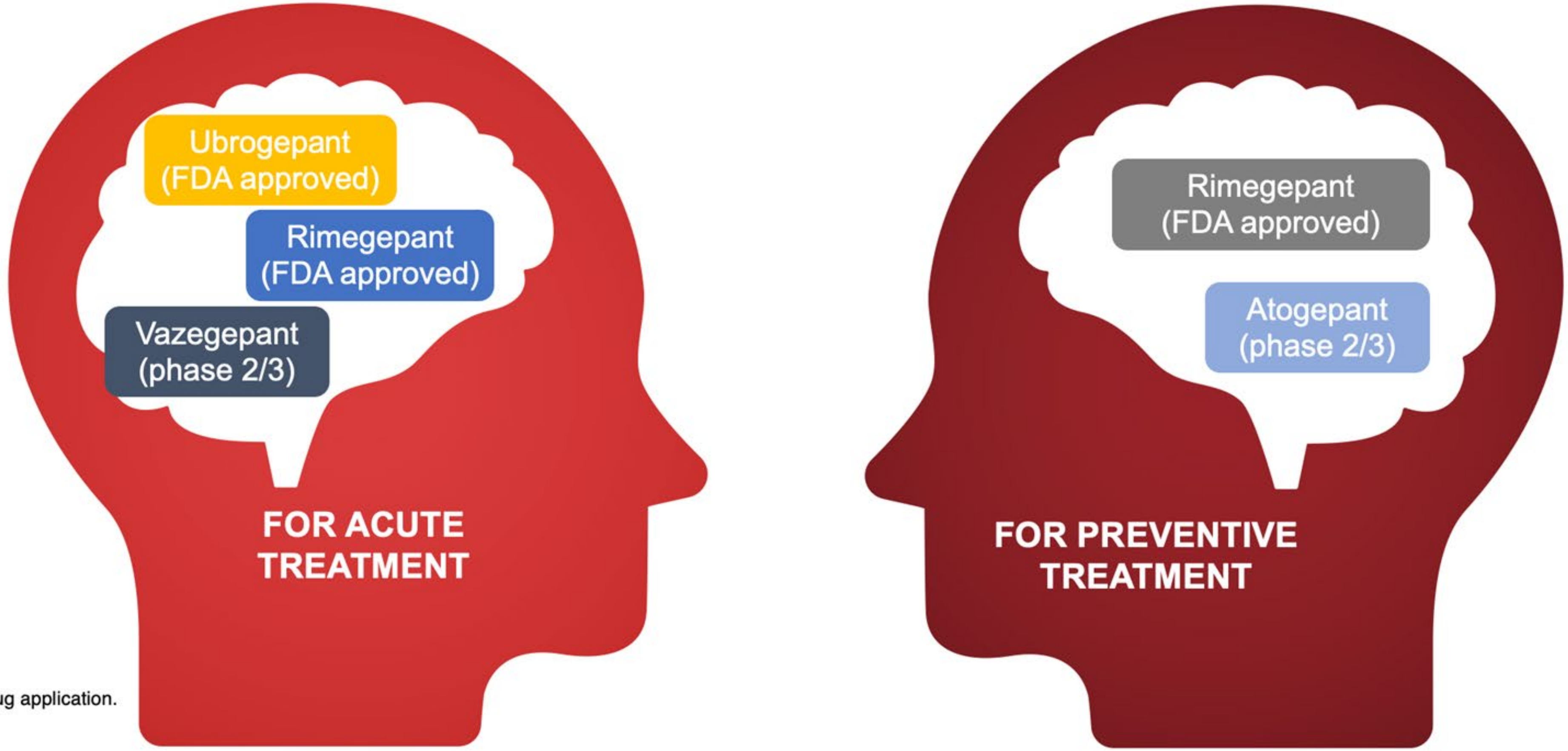
TEAE occurring in ≥2% of patients*	Lasmiditan 100 mg (n=609)	Lasmiditan 200 mg (n=630)	Placebo (n=617)
Dizziness	12.5	16.3	3.4
Fatigue	4.1	3.1	0.3
Nausea	3.0	5.3	1.9
Paresthesia	5.7	7.9	2.1
Somnolence	5.7	5.4	2.3
Lethargy	1.9	2.5	0.3

- The majority of TEAEs in lasmiditan-treated patients were of mild or moderate severity
- There were no AE-related discontinuations or deaths
- Driving restriction < 8 hours

- Patients (N=2231) with at least moderate disability were randomized to PO lasmiditan (100 or 200 mg) or placebo within 4 hours of onset of migraine attack.
  *In any lasmiditan group, and greater than placebo.
  AE, adverse event; TEAE, treatment-emergent adverse event.

Kuca B et al. *Neurology*. 2018;91:e2222–e2232.

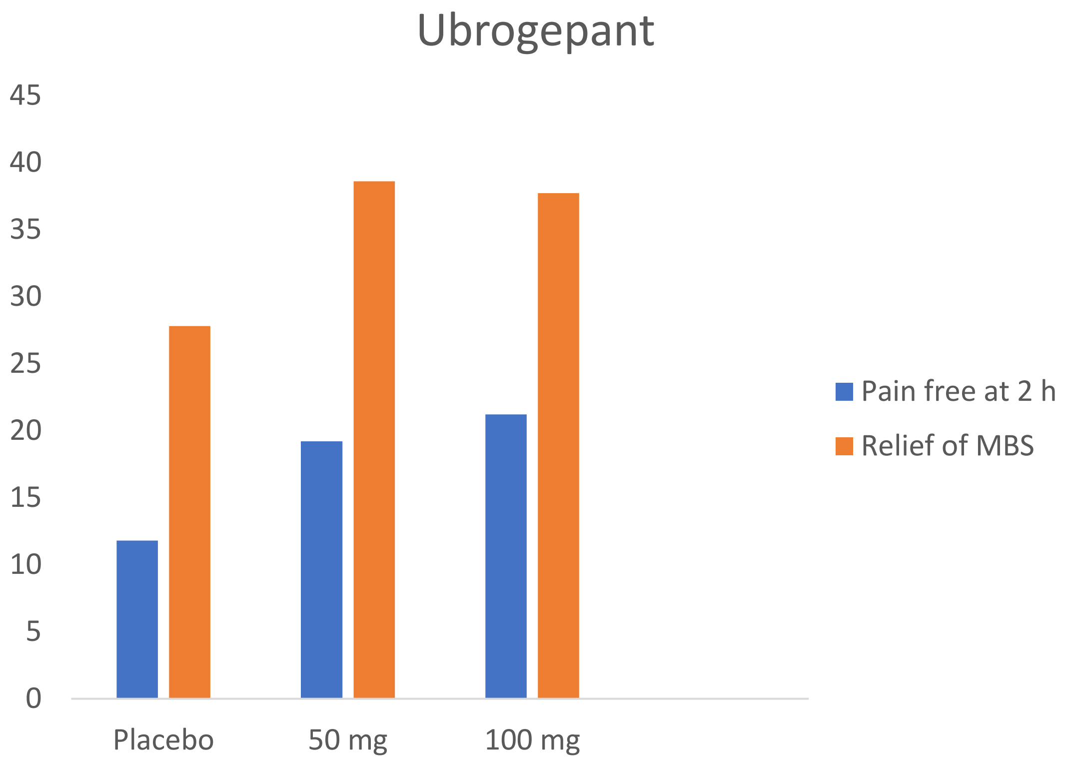
Gepants: Small Molecule CGRP Receptor Antagonists

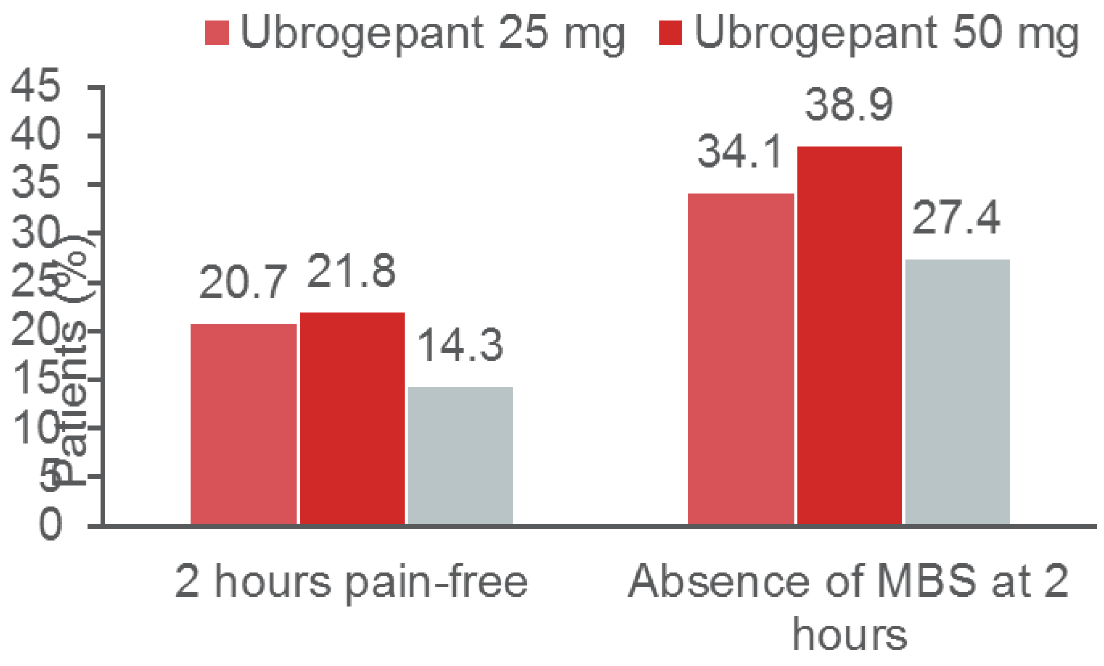


NDA, new drug application.

1. Rubio-Beltran E, et al. *Cephalalgia*. 2020;40:357-366. 2. Conway CM, et al. *Headache*. 2019;59(Suppl. 1):176.

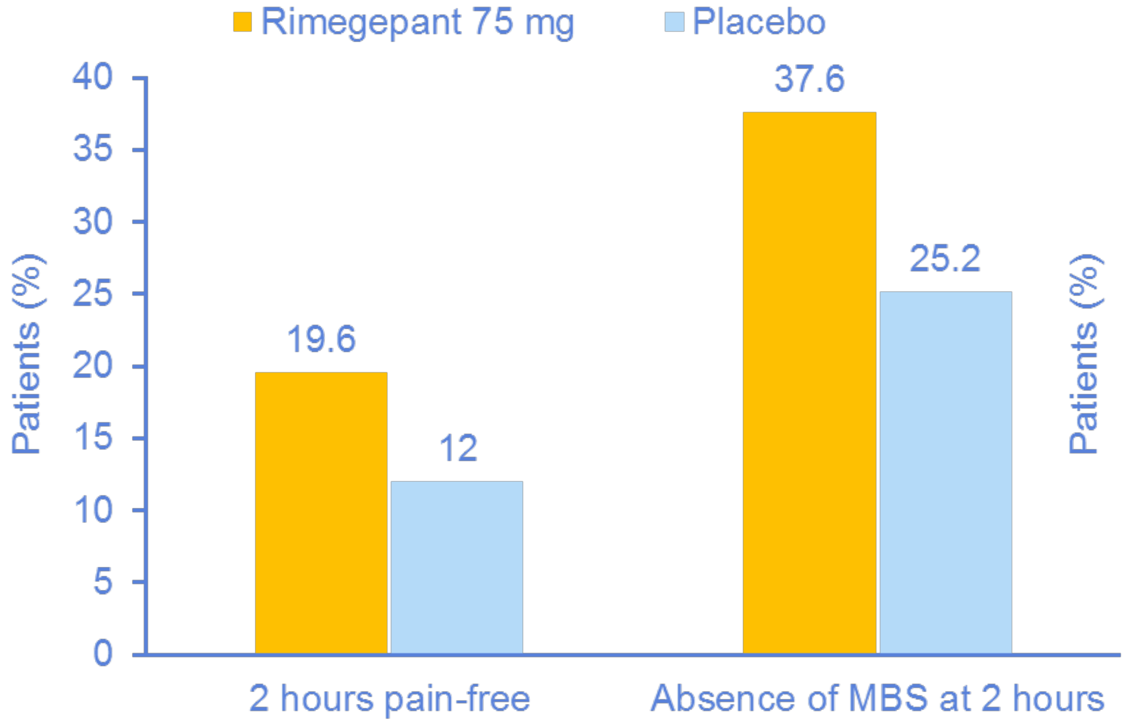
Ubrogepant: Approved 50 mg and 100 mg Tablet

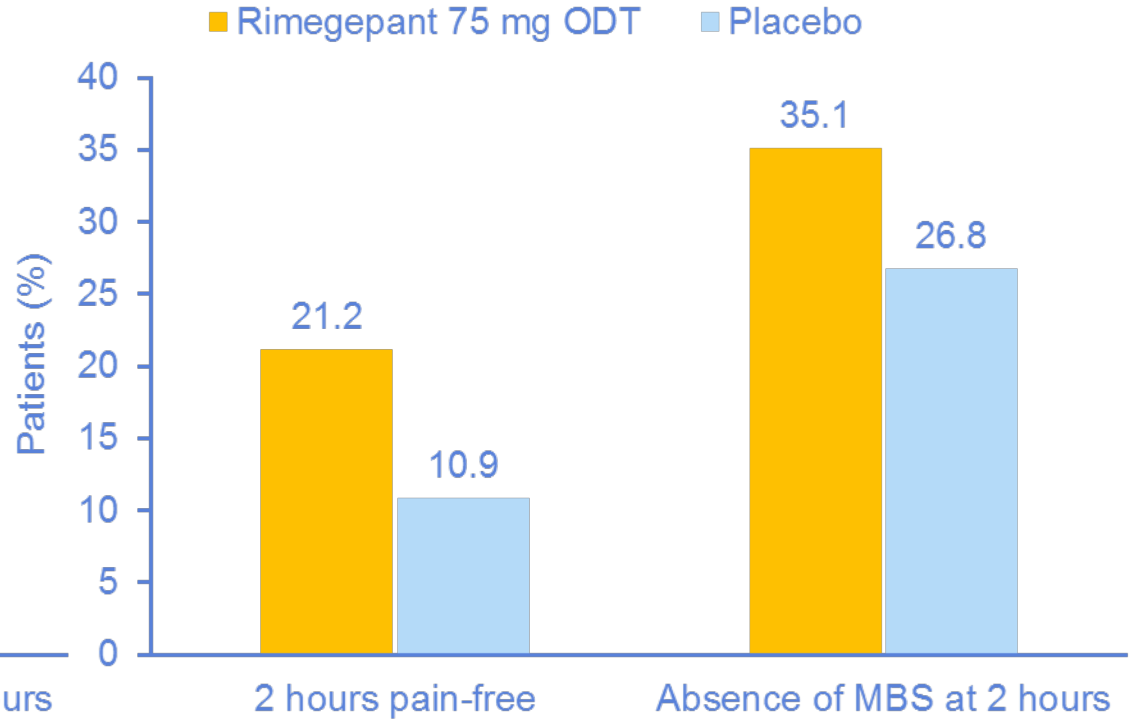




Dodick DW et al. NEJM. 2019;381:2230-2241, Lipton RB, et al. JAMA. 2019;322:1887–1898.

Rimegepant: Approved as 75 mg ODT





1. Lipton RB, et al. N Engl J Med. 2019;381:142–149. 2. Croop R, et al. Lancet. 2019; 394:737–745.

Safety

- Both metabolized by CYP3A4
- Ubrogepant: no liver signal.
  Nausea, somnolence, dizziness, dry mouth < 5%
- Rimegepant: No liver signal.
  Nausea 2%, dizziness similar to placebo

AHS Position on Gepants for Migraine

- Should be available to be prescribed by any healthcare provider to patients who meet the following criteria:
  - Contraindications to triptans or
  - Lack of adequate response to ≥2 oral triptans or
  - Lack of tolerability with ≥2 oral triptans

American Headache Society. Headache. 2019;59(1):1-18.

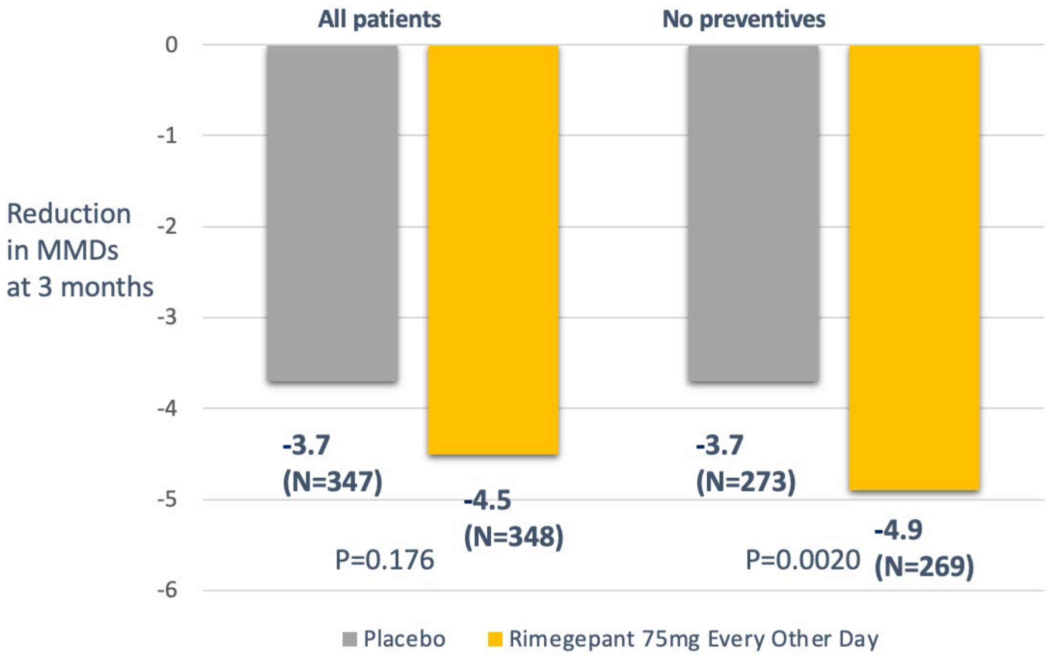
Rimegepant for Migraine Prevention

- Phase III study for prevention of migraine

- Oral rimegepant 75 mg tablet qod for the preventive treatment of both episodic and chronic migraine
- -Met primary endpoint: reduction of MMDs at 3 months
- -T ½ life = 11 hours

- Most common AEs: nausea
- No signal of hepatotoxic effects

- First medication approved for both acute and preventive treatment



Atogepant for Migraine Prevention

- Developed as a potential migraine preventive -T ½ = 10 hours
- Phase IIb/III trial looked at 5 doses ranging from 10 mg to 60 mg taken q daily or twice daily.
  - Primary efficacy endpoint was met for all doses.
- Currently 3 active phase III trials (2 in episodic and 1 in chronic migraine prevention)
- ADVANCE trial (phase III) for episodic migraine has met primary endpoint (reduction in MMD at 12 weeks) and secondary endpoint (50% reduction MMDs at 12 weeks)
  - 4 treatment groups: 10 mg, 30 mg, and 60 mg and placebo
- Most common AEs: constipation, nausea, and upper respiratory tract infection

- 1. P.J. Goadsby, DD, J.M. Trugman, M. Finnegan, H. Lakkis, K. Lu, *et al.*. 92 (15 Supplement) (2019), Article S17.001

Potential Advantages of “Gepants”

- Noninjection anti-CGRP acute therapy
- AEs: nausea (2%-3% for both), somnolence (ubrogepant 2%-3%)
- No sedation (OK to drive)
- No known safety issues with triptans or NSAIDs
- May work late in attack
- Lower rates of recurrence
- Appear effective for prevention

Matching acute treatment to migraine

Fast-acting	• Sumatripan sc >> NS (suma/zolmi), Diclofenac potassium solution
Effectiveness	• SC sumatriptan or nasal device, Rizatriptan, Eletriptan, Lasmiditan
Fewer AEs	• Most NSAIDs. Almotriptan, Sumatriptan 25 mg, Naratriptan. Gepants
Preventative (i.e. menstrual migraine)	• Long-acting NSAIDs (Naproxen, Celecoxib) Frovatriptan > Naratriptan, Eletriptan, DHE, Gepants
Chronic or severe migraine	• DHE, long-acting NSAIDs, neuroleptics, IV/IM ketorolac, ? gepants