The Emerging Role of CGRP Inhibitors in the Prevention and Treatment of Migraine

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painweek

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Presented in Cooperation With

COALITION FOR HEADACHE AND MIGRAINE PATIENTS (CHAMP)

WWW.HEADACHEMIGRAINE.ORG

2

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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

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Learning Objectives

- Review CGRP inhibitors as an emerging treatment option for migraine, as well as their safety and efficacy
- Recognize the varying properties and indications of emerging CGRP inhibitors as they apply to acute and preventive treatment of migraine
- Outline individualized therapy for the prevention and treatment of migraine based on current guidelines and the efficacy and safety of available treatment options

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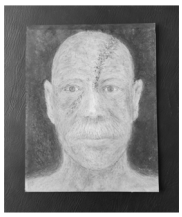
Case 1: Migraine Prevention

- 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?



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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.

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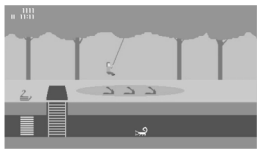
Headache Treatment Pitfalls

- 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

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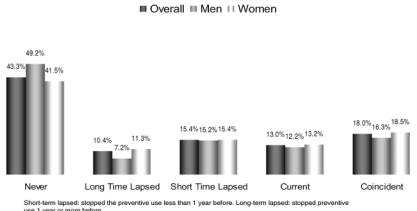
Most People with Migraine Are Not on Preventive Treatments



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

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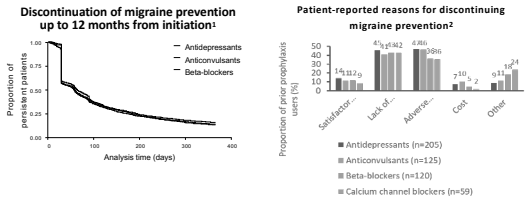
Adherence to Oral Preventives Is Poor



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

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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, riboflavin, co-Q10, petasites, magnesium

*FDA approved for migraine

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Calcitonin gene-related peptide (CGRP) in migraine


theguardian.com/science/2021/mar/04/scientists-discovered-migraine-mechanism-win-brain-prize

Scientists who discovered migraine mechanism win £1.1m Brain prize

World's largest neuroscience prize goes to researchers whose work has paved way for preventive treatments

1,709

▲ Prof Peter Goadsby of King's College London, one of four scientists who received the prize for their work unpicking the neural basis of migraine attacks. Photograph: Ken McKay/ITV/Rex/Shutterstock

Four scientists who discovered a key mechanism that causes migraines, paving the way for new preventive treatments, have won the largest prize for

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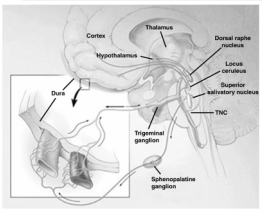
Migraine Overview



- 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.

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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.

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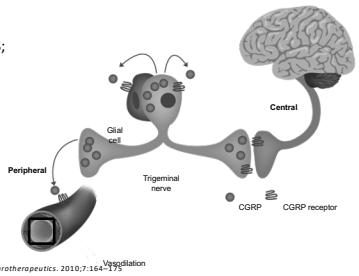
Calcitonin Gene-related Peptide

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.

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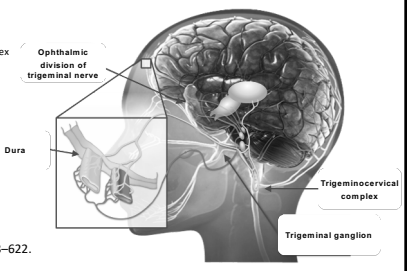
The Trigeminovascular System in Migraine

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.

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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

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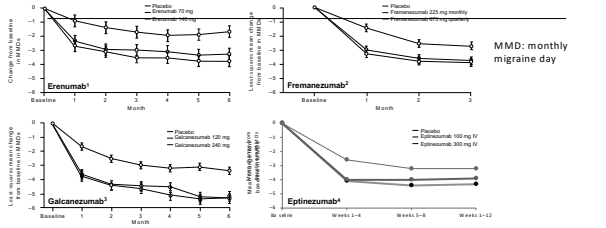
CGRP Questions for Migraine Prevention?

- 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.

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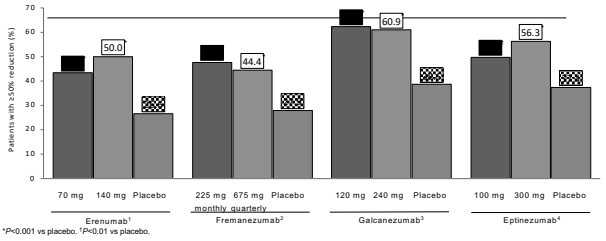
Reduction in mean MMDs ≥50%



**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.

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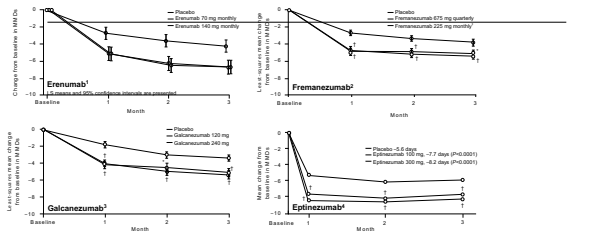
Chronic Migraine: Reduction of Mean MMDs



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.

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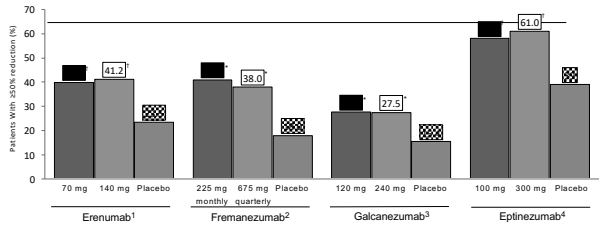
Chronic Migraine: ≥50% Reduction in Mean MMDs



*P<0.001 vs placebo. †P<0.0001 vs placebo.

1. Tepper S et al. *Lancet Neurol.* 2017;16:425-434. 2. Silberstein SD et al. *N Engl J Med.* 2017;377:2113-2122. 3. Detke HC et al. *Neurology.* 2018;91:e2211-2221. 4. Smith J et al. *Headache.* 2017;57(Suppl. 3):130.

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Safety of CGRP mAbs: Adverse Events (AEs)

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

Nasopharyngitis most common AE with IV administration[4]

	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.

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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

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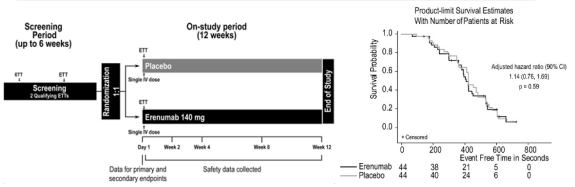
The Effect of IV Erenumab on Exercise Time During a Treadmill Test in Patients With Stable Angina: No Change in Onset of ST Depression



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)

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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.

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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.

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Acute Headache Treatment: Goals

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

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Categories of Acute Treatments

Migraine Specific	**Nonspecific**
Triptans	Nonsteroidal anti-inflammatories
Dihydroergotamine/ergotamine	Combination analgesics
Lasmiditan	Neuroleptics/antiemetics
Migraine devices	Opioids
Gepants	

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Gepants: Small Molecule CGRP Receptor Antagonists

- First anti-CGRP drugs: initial compounds effective but caused liver toxicity (Telcagepant)
- A total of 7 have effectively treated acute migraine (no failures for efficacy)
- Do not cause vasoconstriction in cranial or coronary arteries or issues in clinical trials
- No need to stop months before pregnancy

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

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Gepants Recently Approved or in Development

Ubrogepant (FDA approved)

Rimegepant (FDA approved)

Vazegepant (phase 2/3)

Rimegepant (phase 3)

Atogepant (phase 2/3)

FOR ACUTE TREATMENT

FOR PREVENTIVE TREATMENT

NDA, new drug application.

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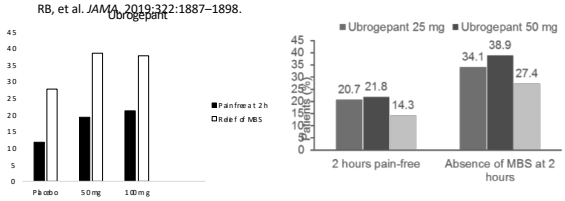
Ubrogepant: Approved 50 mg and 100 mg Tablet

RB, et al. *JAMA*. 2019;322:1887–1898.



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

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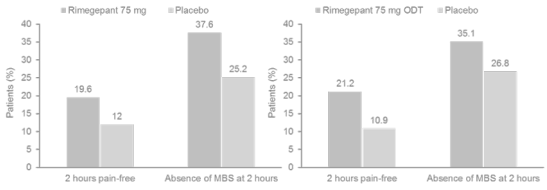
Rimegepant: Approved as 75 mg ODT



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

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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

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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.

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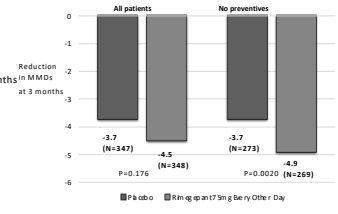
Rimegepant for Migraine Prevention

Undergoing phase III study for prevention of migraine-positive results announced March 2020

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

Would be the first medication approved for both acute and



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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

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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
- Under investigation for prevention

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