# What's New in Migraine?

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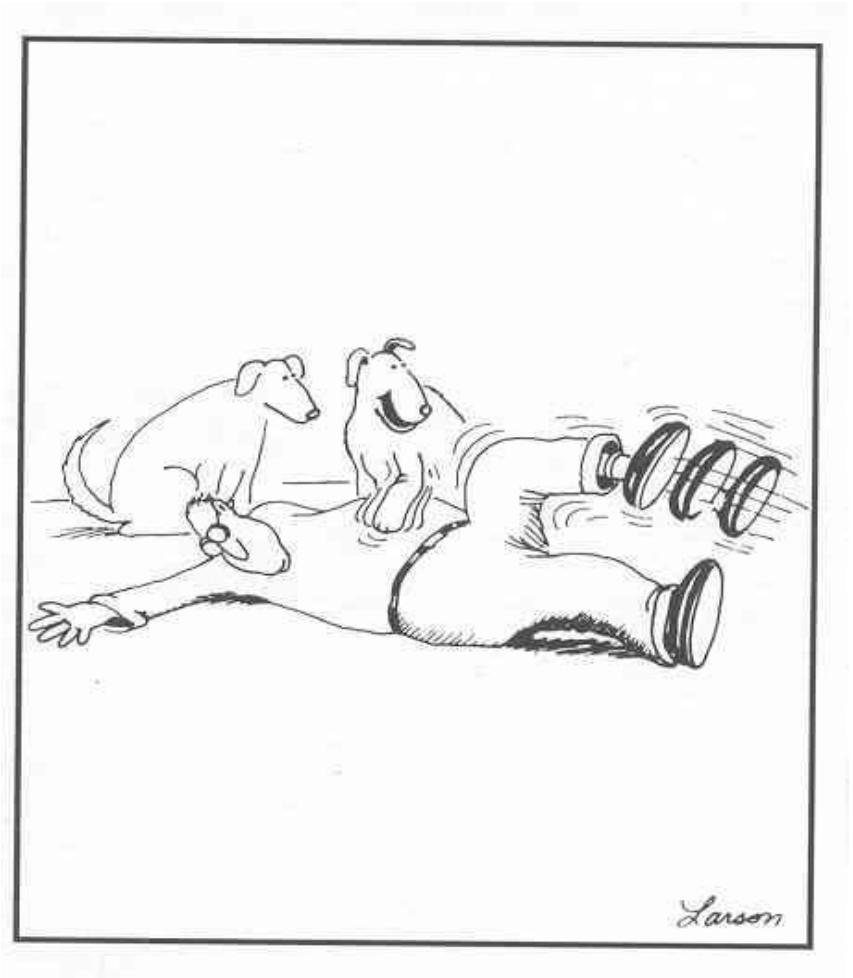
# Disclosures

- No pharmaceutical company grants, honoraria, or advisory boards
- Work to support my dogs – Buck and Satchel



# Diagnostic Criteria for Migraine

**Table 1. Diagnostic Criteria for Migraine.***

**Disease Classification**

**Migraine without aura (ICHD-3)**

At least five attacks fulfilling the following criteria:

- Headache attacks lasting 4–72 hr (untreated or unsuccessfully treated)
- Headache has at least two of the following four characteristics:
  - Unilateral location
  - Pulsating quality
  - Moderate or severe pain intensity
  - Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- During headache, at least one of the following:
  - Nausea and vomiting
  - Photophobia and phonophobia

Headache is not better accounted for by another ICHD-3 diagnosis

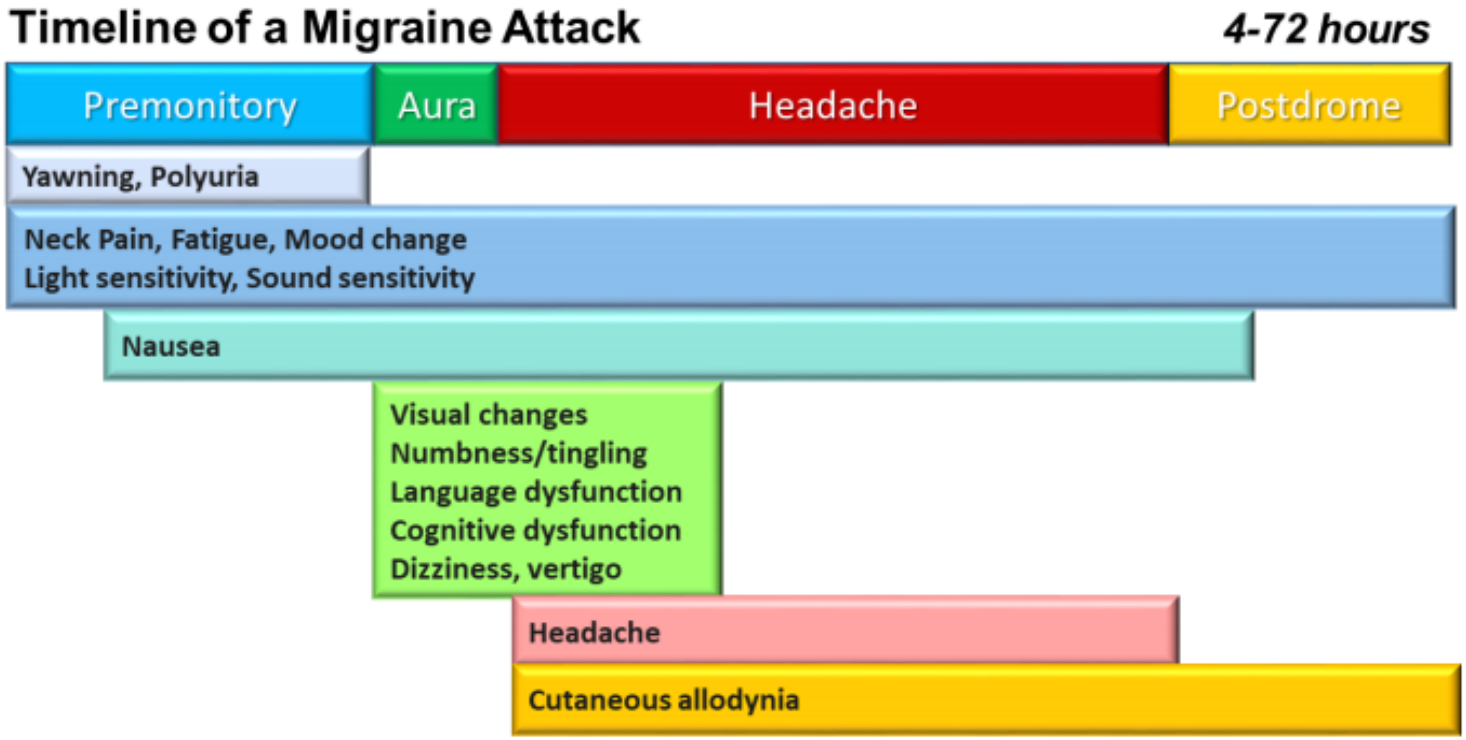
**Migraine (ID Migraine validation study)**

During the past 3 mo, at least two of the following with headaches:

- Nausea or sickness to stomach
- Sensitivity to light (a lot more than when one did not have headaches)
- Limited ability to work, study, or do what one needed to do for at least 1 day

* The diagnostic criteria for migraine without aura are from the *International Classification of Headache Disorders*, third edition (ICHD-3).[16] The simplified criteria for diagnosis of migraine were shown in the ID Migraine validation study to have a high positive predictive value (93% in a primary care setting).[17]

# Timeline of a Migraine Attack



# Migraine versus Secondary Headache

**Table 2. Typical Features of Migraine versus "Red Flags" That Warrant Further Diagnostic Evaluation.**

| Feature |
|---|
| **Typical features of migraine** |
| History of multiple stereotypical attacks lasting 4–72 hr |
| No symptoms between attacks |
| Gradual onset of headache, neck pain |
| Vision, sensory, and language symptoms begin and progress gradually and last ≤1 hr (typical aura) |
| Yawning, neck pain, sensory sensitivity, fatigue, and mood change before and after headache |
| Family history of headache |
| **Features suggestive of secondary headache** |
| New onset of headache (particularly in persons older than 50 yr of age) |
| Headache lasting >72 hr |
| Vision, sensory, and language symptoms lasting >1 hr |
| Very sudden onset of headache or neurologic symptoms |
| Abnormal neurologic examination |
| Associated fever, systemic illness |

# Abortive Treatment of Migraine

Table 3. Selected Therapies for Acute Migraine.*

| Class | Specific Treatments | Reported Mean Therapeutic Effects† | Common or Serious Adverse Effects | Comments |
|---|---|---|---|---|
| Triptans[26] | Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan | Pain relief by 2 hr, 16–51%; pain-free by 2 hr, 9–32%; free of headache for 24 hr, 9–27% | Chest or facial muscle tightness, lightheadedness; contraindicated in patients with coronary artery disease | Response to and side-effect profile of different triptans varies in individual patients; nasal or subcutaneous delivery may be more effective than oral delivery in patients with nausea or vomiting |
| Ergots[27,28] | DHE nasal spray, DHE injection | Pain relief by 2 hr, 20–40% (for DHE nasal spray; limited evidence) | Nausea, dizziness; contraindicated in patients with peripheral vascular disease or coronary artery disease | Intravenous DHE is commonly used for refractory migraine |
| Acetaminophen[29] | | Pain relief by 2 hr, 19%; pain-free by 2 hr, 9% | Minimal with intermittent use | May be more effective in combination with antiemetic agent |
| NSAIDs[30] | Aspirin, diclofenac, ibuprofen, ketorolac, naproxen | Pain relief by 2 hr, 17–29%; pain-free by 2 hr, 7–20% | Gastric irritation, excessive bleeding | May be effective individually or have additive benefit when taken with triptan; different oral preparations (effervescent or powder) may have improved efficacy |
| Combinations[31,32] | Acetaminophen–aspirin–caffeine, sumatriptan–naproxen | Pain relief by 2 hr, 10–17% (limited evidence); pain-free by 2 hr, 20–30% | Same as with NSAIDs and triptans | Caffeine-containing preparations may have increased potential for overuse; combination therapy is more effective than individual agents in some patients |
| Antiemetic agents[23,29,30] | Chlorpromazine, metoclopramide, prochlorperazine | Pain relief by 2 hr with oral metoclopramide (plus aspirin or acetaminophen), 23%; pain relief by 1–2 hr with intravenous delivery in emergency department, 24–67% | Sedation, restlessness (akathisia), dystonic reactions | Phenothiazines plus metoclopramide have benefit for headache as well as nausea; ondansetron is commonly used for nausea, but evidence is lacking |
| Single-pulse TMS[33] | SpringTMS | Pain-free by 2 hr, 17% | No clinically significant adverse effects | Handheld device for patient-delivered therapy; currently FDA-approved for treatment of acute migraine with aura |
| CGRP receptor antagonists[34,35] (under investigation) | Rimegepant, ubrogepant | Pain-free by 2 hr, 14–18% | None reported; safety studies are ongoing | Phase 2 studies have been completed |

* Shown are therapies that have high-quality supporting evidence or are highly recommended in guidelines from the American Headache Society,[22,23] the Canadian Headache Society,[24] and the European Federation of Neurological Societies[25] as well as other Food and Drug Administration (FDA)–approved or emerging therapies. Citations are for primary trial data within guidelines except as noted; trials were of variable quality. All approaches are FDA-approved for the treatment of acute migraine except antiemetics and calcitonin gene–related peptide (CGRP) receptor antagonists. DHE denotes dihydroergotamine, NSAIDs nonsteroidal antiinflammatory drugs, and TMS transcranial magnetic stimulation.

† Values are the percentage of patients with pain relief or freedom from pain after a single dose of the treatment minus the percentage with pain relief or freedom from pain after placebo administration. In most cases, therapy was administered when pain was already moderate or severe.

# Preventive Treatment of Migraine

**Table 4. Selected Preventive Therapies for Migraine.***

| Class | Specific Treatments | Reported Mean Monthly Therapeutic Effects† | Common or Serious Adverse Effects | Comments |
|---|---|---|---|---|
| Tricyclic antidepressants[41] | Amitriptyline, nortriptyline | Data not available | Dry mouth, sedation, weight gain, urinary retention | Low doses are typically used (10 to 50 mg); may be useful in patients with insomnia |
| Beta-blockers[42,43] | Metoprolol, nadolol, propranolol,‡ timolol‡ | Headache days, −0.4 (meta-analysis for propranolol) | Hypotension, exercise intolerance, sexual dysfunction | May be useful in patients with hypertension, tachycardia, or anxiety |
| Anticonvulsant agent[44] | Topiramate‡ | Episodic migraine days, −1.1 to −1.3; chronic migraine days, −1.5 to −3.3 | Paresthesias, weight loss, cognitive dysfunction, depression | Also used for weight loss; preparations with various half-lives are available |
| Anticonvulsant agent[45] | Divalproex sodium‡ | Migraine days, −2.6; migraine attacks, −0.6 to −3.4 | Tremor, weight gain, hair loss, fetal neural-tube defects | May be efficacious, but adverse effects limit its use |
| Candesartan[43] | | Headache days, −0.7 to −1.7; migraine days, −0.6 to −1.1 | Dizziness | Side effects are generally acceptable |
| Flunarizine[41] | | Migraine attacks, −1.2 to −1.8 | Sedation, weight gain, depression | Not available in the United States |
| Nonprescription therapies[46] | Coenzyme Q10, magnesium, melatonin, petasites, riboflavin | Migraine attacks: −1.1 with coenzyme Q10, −0.5 to −0.9 with magnesium, −0.8 with petasites or riboflavin | Diarrhea with magnesium | Side effects are generally acceptable, but current evidence of efficacy is poor |
| Botulinum toxins[47] | OnabotulinumtoxinA‡ | Chronic migraine headache days, −1.4 to −2.3; migraine days, −1.5 to −2.4 | Muscle weakness, headache | Delivered by subcutaneous injection at multiple sites; approved for chronic migraine only |
| Supraorbital nerve stimulation[48] | Cefaly device‡ | Migraine days, −2.1 | Local discomfort, skin irritation | Headband with forehead stimulation; applied for 20 min daily |
| Monoclonal antibodies targeting CGRP or its receptor[49,50] (under investigation) | Eptinezumab, erenumab, fremanezumab, galcanezumab | Episodic migraine headache days, −1.0 to −1.2; high-frequency episodic migraine days, −2.8; days with chronic migraine headache, −2.5; hr with chronic migraine headache, −30.4 | Injection-site reactions; safety studies are ongoing | Multiple phase 3 trials have been completed; administered subcutaneously or intravenously every 1 to 3 mo; rapid onset of efficacy; rates of response of 75% and in some cases 100% have been reported |

* Shown are therapies that have high-quality supporting evidence or are highly recommended in guidelines are from American Academy of Neurology and the American Headache Society,[39,40] the Canadian Headache Society,[41] and the European Federation of Neurological Societies[25] as well as other FDA-approved or emerging therapies. Citations for primary clinical-trial data are included in these guidelines except where noted. All studies were of episodic migraine unless otherwise specified. Episodic migraine is defined as less than 15 headache days per month; chronic migraine is defined as 15 or more headache days per month, with migraine features on at least 8 of those days.

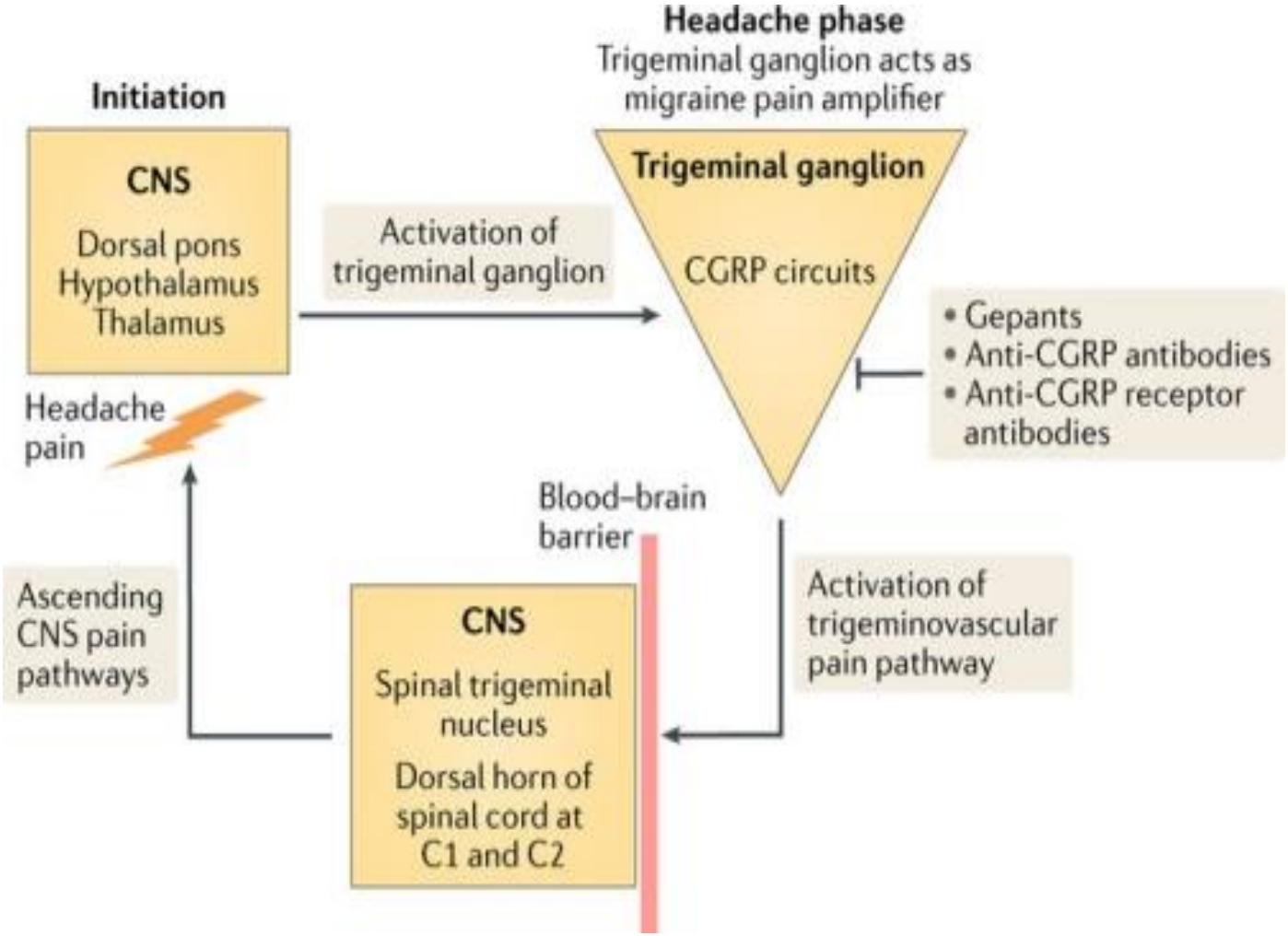
† Values are the number of migraine attacks, or number of days or hours with symptoms, per month with the treatment minus the number with placebo; negative values indicate a benefit with the treatment. The mean monthly effect (typically after 3 months of treatment) is summarized.

‡ These therapies have been approved by the FDA as preventive therapies for migraine.

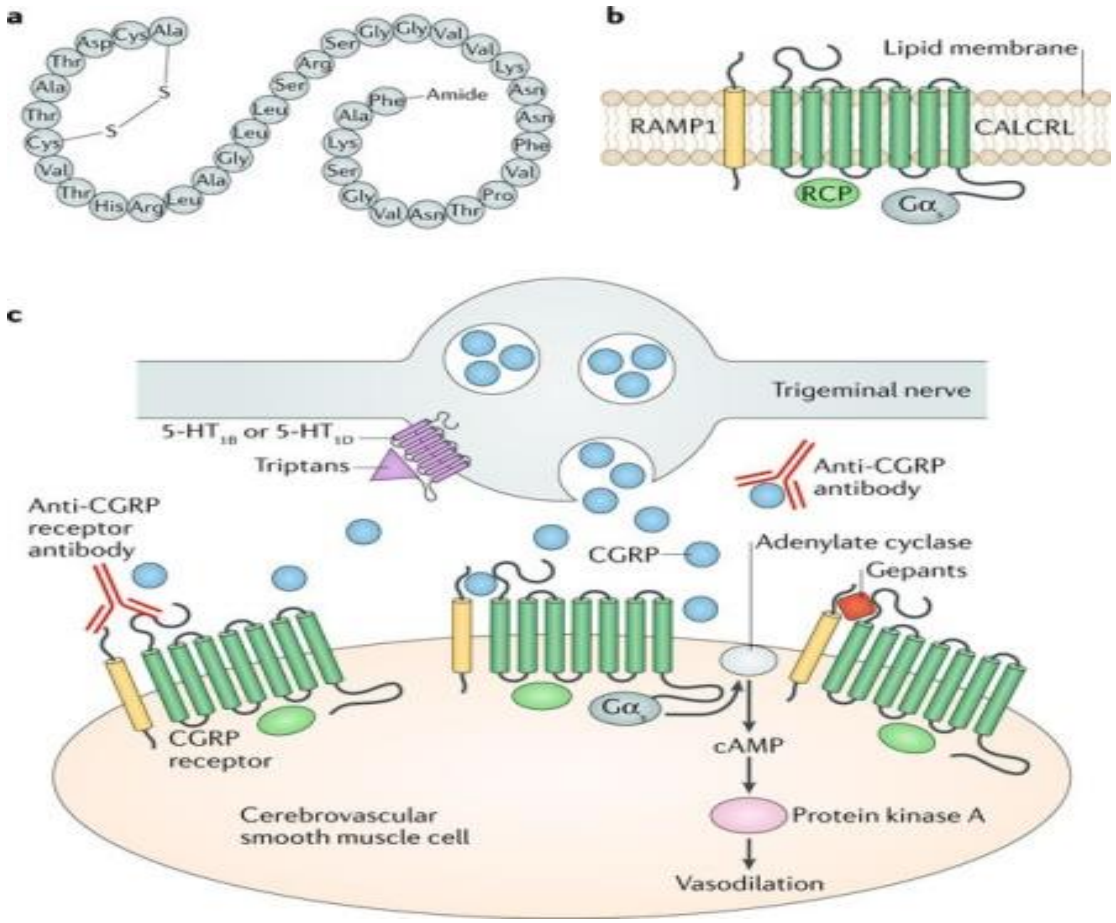
# Calcitonin-Gene Related Peptide

- Calcitonin-gene related peptide (CGRP) is a 37 amino acid neuropeptide
- Potent vasodilator
- Maintenance of vascular homeostasis
- CNS: pain modulation, perception, and central sensitization
- Periphery: vasodilation and mast cell degranulation

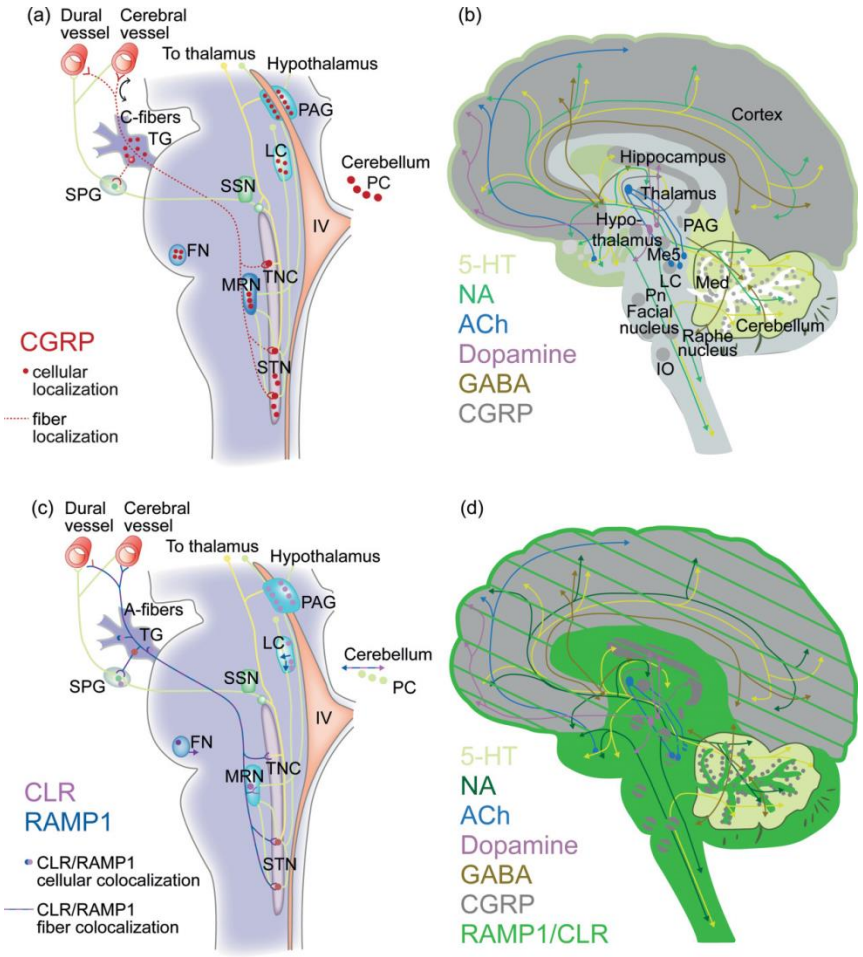
# Proposed involvement of the trigeminal ganglion in migraine headache and mode of action of CGRP-targeted therapies



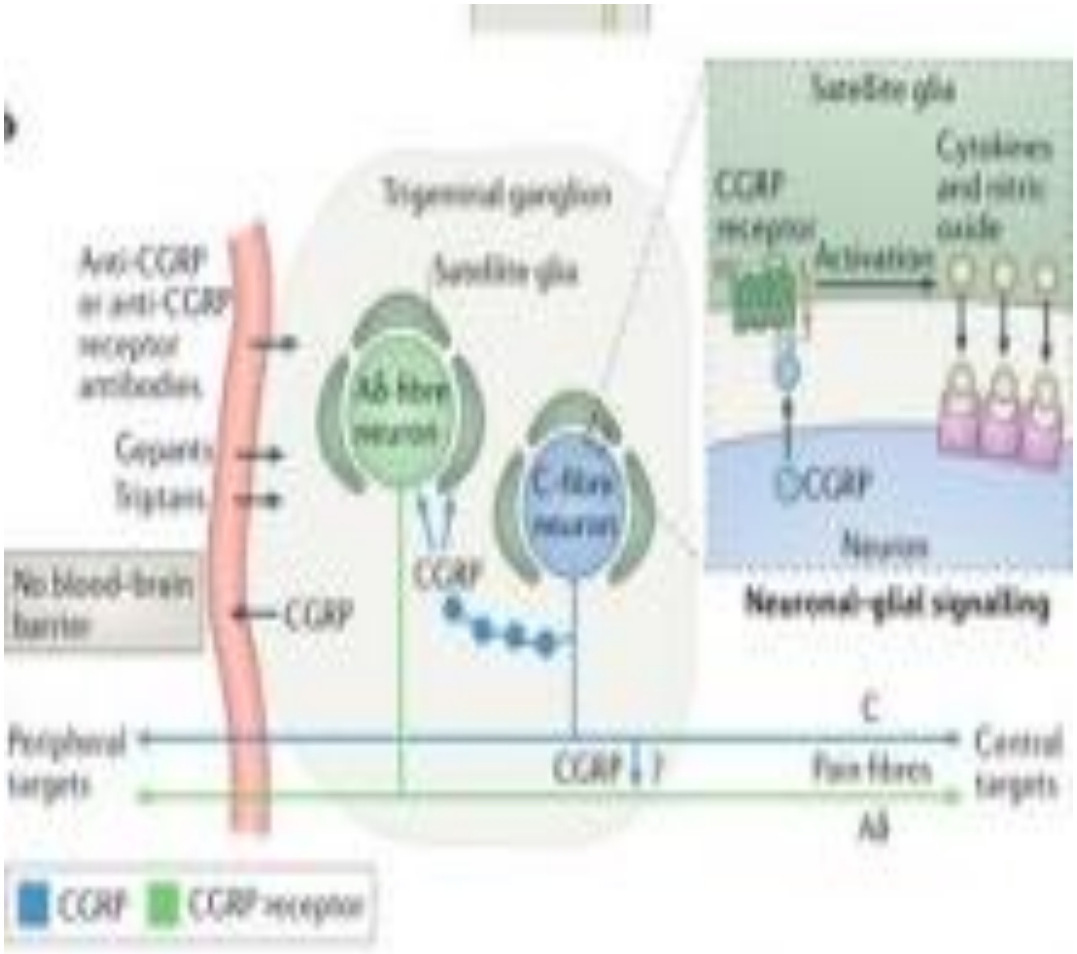
# Components of CGRP transmission and sites of action for CGRP-related migraine therapies



# CGRP and RAMP 1 Receptor Sites



# CGRP and CGRP Receptors in the Trigeminovascular System



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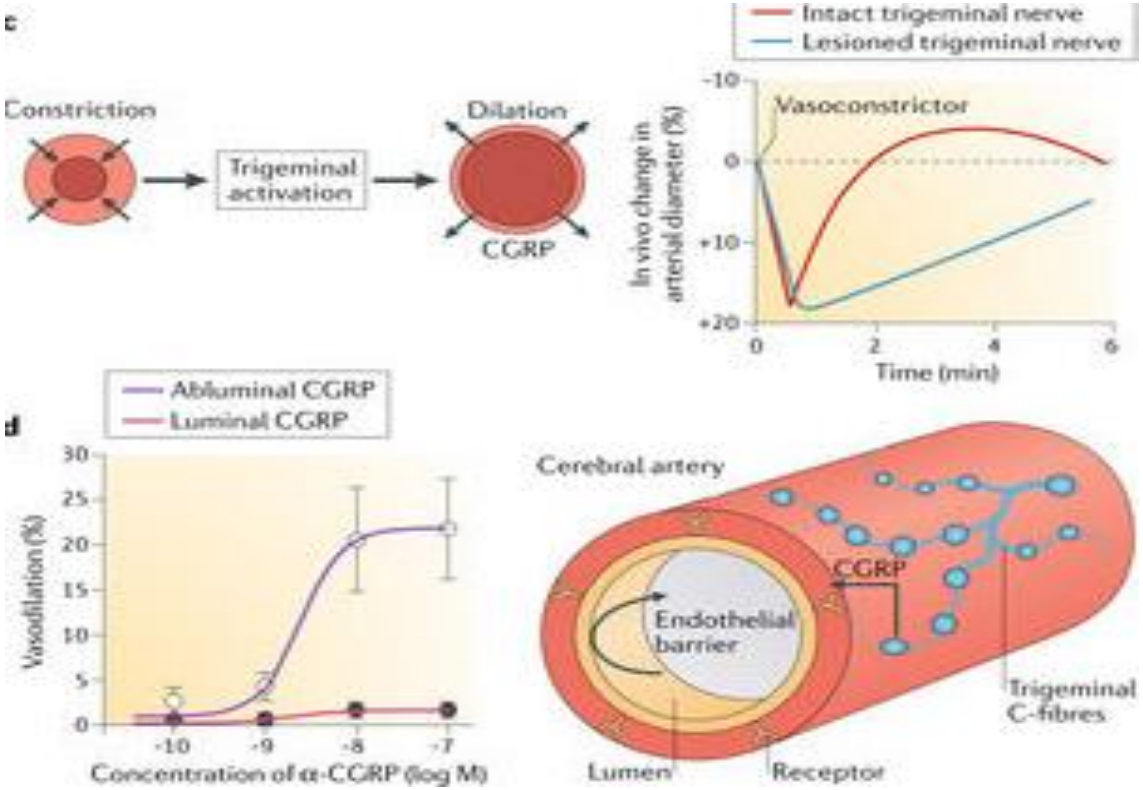
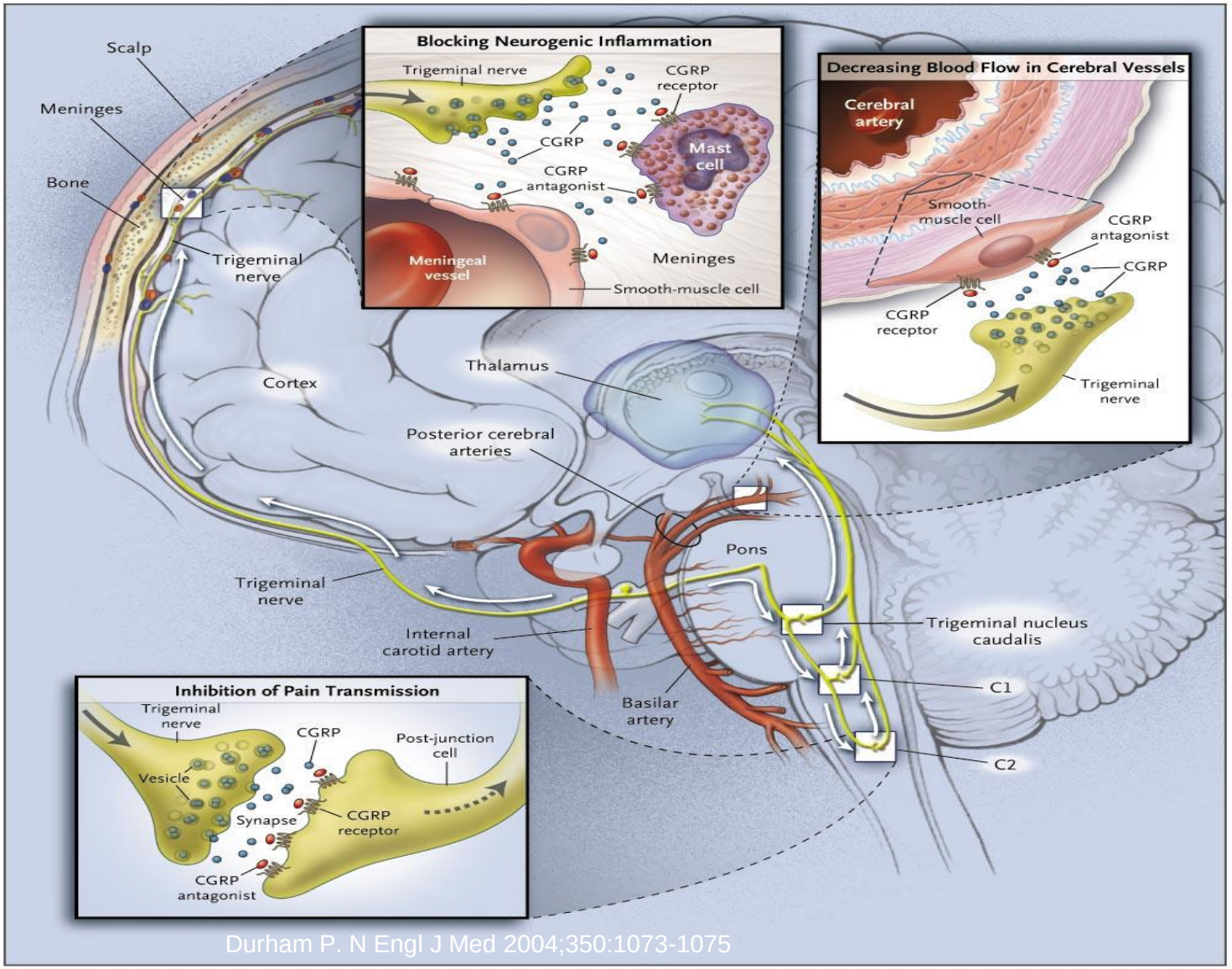


# Possible Sites of Action of the Nonpeptide CGRP-Receptor Antagonist




Durham P. N Engl J Med 2004;350:1073-1075

ORIGINAL ARTICLE

# Calcitonin Gene–Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine

Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Husstedt, M.D., Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, Ph.D., Stephane Pollentier, M.D., and Lynna M. Lesko, M.D., for the BIBN 4096 BS Clinical Proof of Concept Study Group

## ABSTRACT

### BACKGROUND

Calcitonin gene–related peptide (CGRP) may have a causative role in migraine. We therefore hypothesized that a CGRP-receptor antagonist might be effective in the treatment of migraine attacks.

### METHODS

In an international, multicenter, double-blind, randomized clinical trial of BIBN 4096 BS, a highly specific and potent nonpeptide CGRP-receptor antagonist, 126 patients with migraine received one of the following: placebo or 0.25, 0.5, 1, 2.5, 5, or 10 mg of BIBN 4096 BS intravenously over a period of 10 minutes. A group-sequential adaptive treatment-assignment design was used to minimize the number of patients exposed.

### RESULTS

The 2.5-mg dose was selected, with a response rate of 66 percent, as compared with 27 percent for placebo (P=0.001). The BIBN 4096 BS group as a whole had a response rate of 60 percent. Significant superiority over placebo was also observed with respect to most secondary end points: the pain-free rate at 2 hours; the rate of sustained response over a period of 24 hours; the rate of recurrence of headache; improvement in nausea, photophobia, phonophobia, and functional capacity; and the time to meaningful relief. An effect was apparent after 30 minutes and increased over the next few hours. The overall rate of adverse events was 25 percent after the 2.5-mg dose of the drug and 20 percent for the BIBN 4096 BS group as a whole, as compared with 12 percent for placebo. The most frequent side effect was paresthesia. There were no serious adverse events.

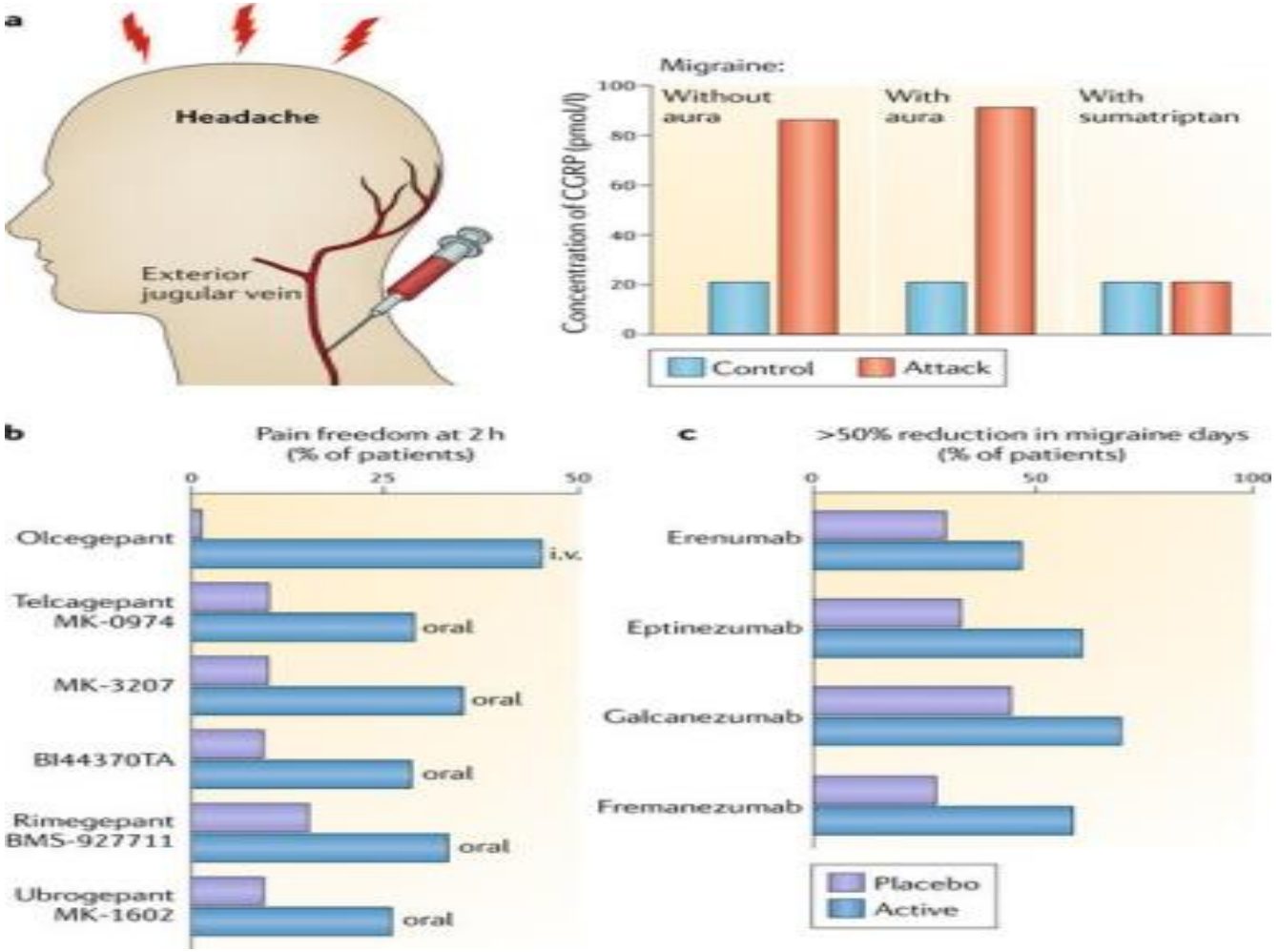
### CONCLUSIONS

The CGRP antagonist BIBN 4096 BS was effective in treating acute attacks of migraine.

From the Department of Neurology, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark (J.O.); the Department of Neurology, University of Essen, Essen, Germany (H.-C.D.); the Department of Neurology, University Hospital, Münster, Germany (I.W.H.); the Institute of Neurology, London (P.J.G.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, Conn. (D.H., L.M.L.); and Boehringer Ingelheim Pharma, Ingelheim, Germany (U.M., S.P.). Address reprint requests to Dr. Olsen at the University of Copenhagen, Department of Neurology, Glostrup Hospital, 2600 Glostrup, Copenhagen, Denmark, or at jeol@glostruphosp.kbhamt.dk.

N Engl J Med 2004;350:1104-10.

# Clinical data that demonstrate that CGRP has an important role in migraine headache and its treatment



# CGRP Receptor Antagonists

Oral agents for acute therapy

- Olcegepant
- Telcagepant
- Rimegepant
- Ubrogepant

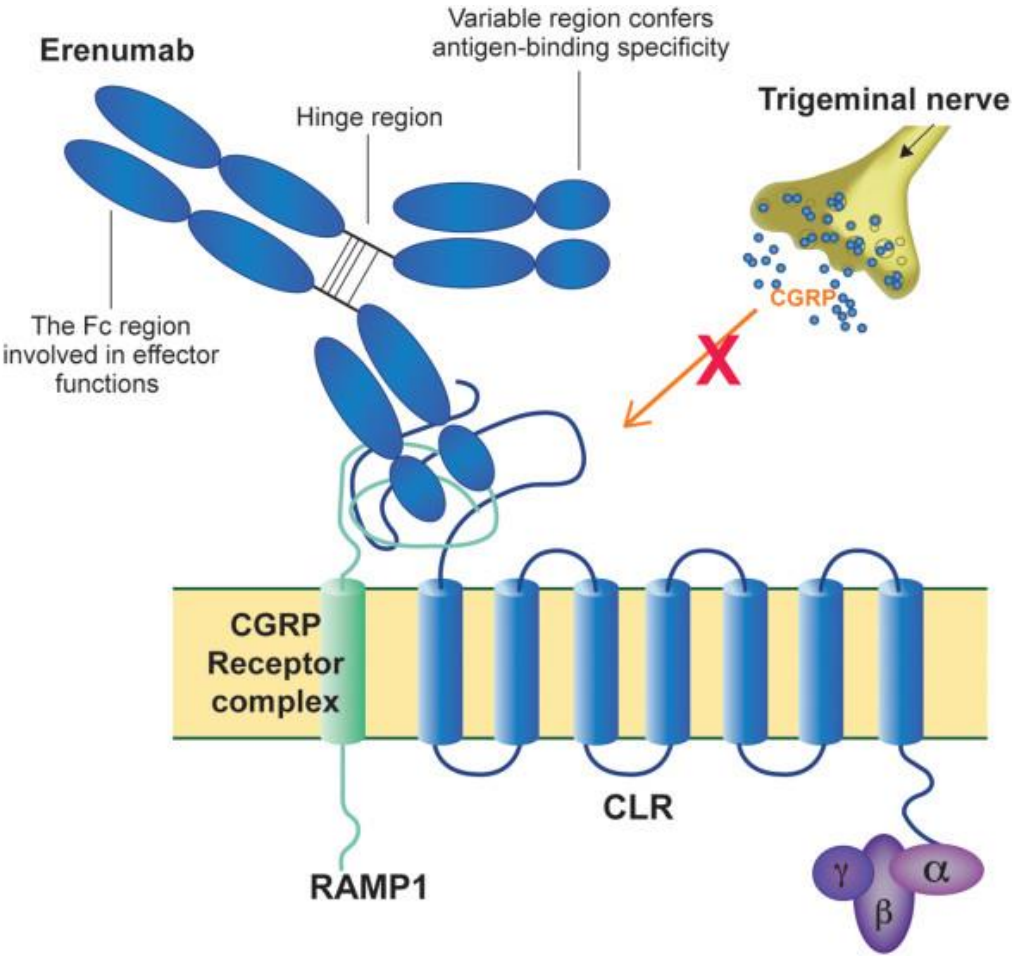
# CGRP Monoclonal Antibodies

- Long half-life injectable medications (IV or SQ)
- Developed for migraine prevention
- 4 in development
  - 3 target the CGRP ligand
    - Galcanezumab (Eli Lilly and Co.)
    - Eptinezumab (Alder Biopharmaceuticals)
    - Fremanezumab (Teva Pharmaceuticals)
  - 1 targets the CGRP receptor
    - Erenumab (Amgen)

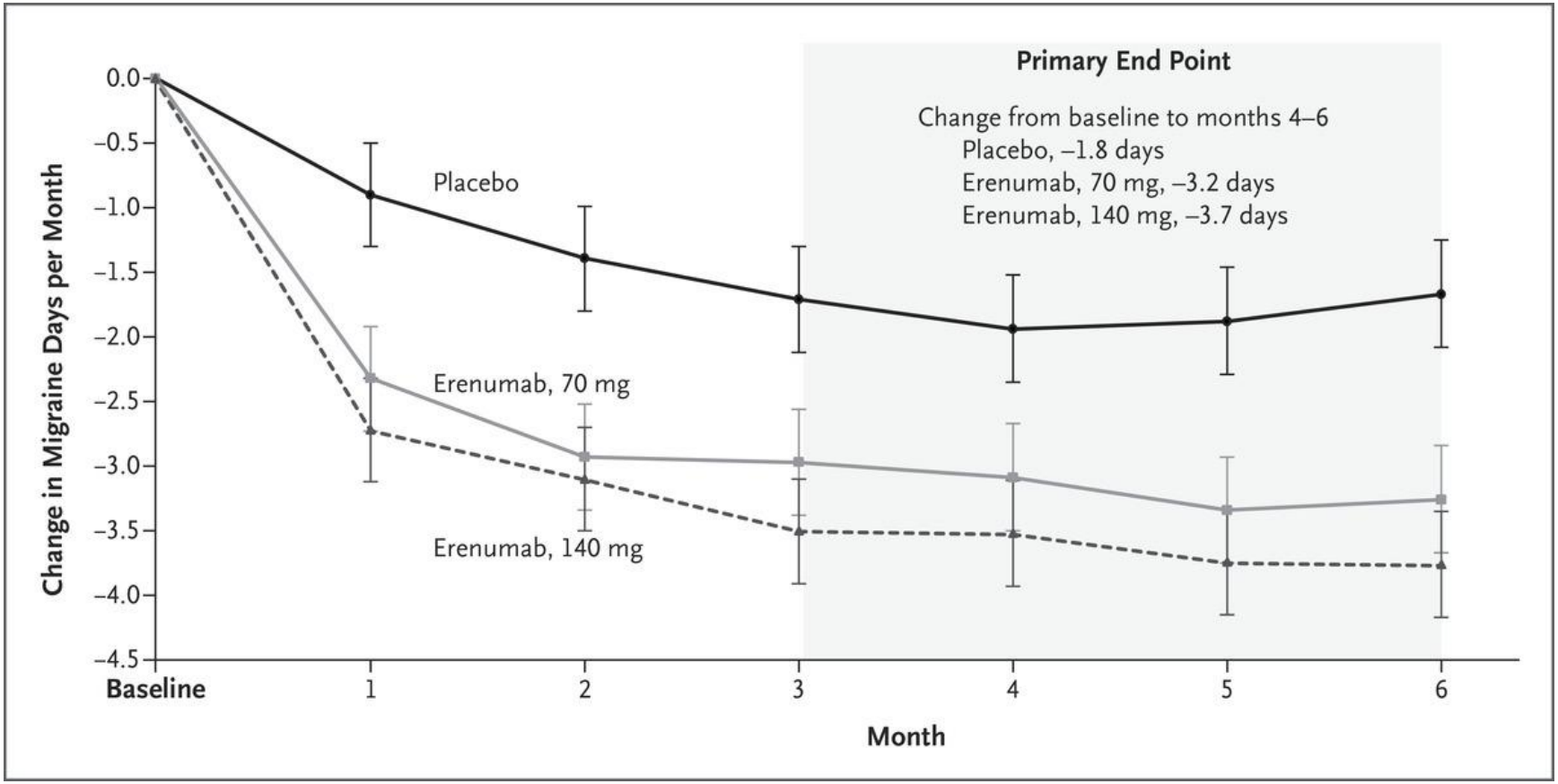
# Concerns About CGRP Blockade

- CGRP is a vasodilator peptide
  - ? Medication-induced hypertension
  - ? Inhibition of cardio-protective mechanisms during ischemia
- Cochlear function
- Reduced expression of CGRP – cisplatin-induced renal injury
- Bone differentiation
- Pregnancy

# Erenumab Binding



# Erenumab (Aimovig) in Episodic Migraine



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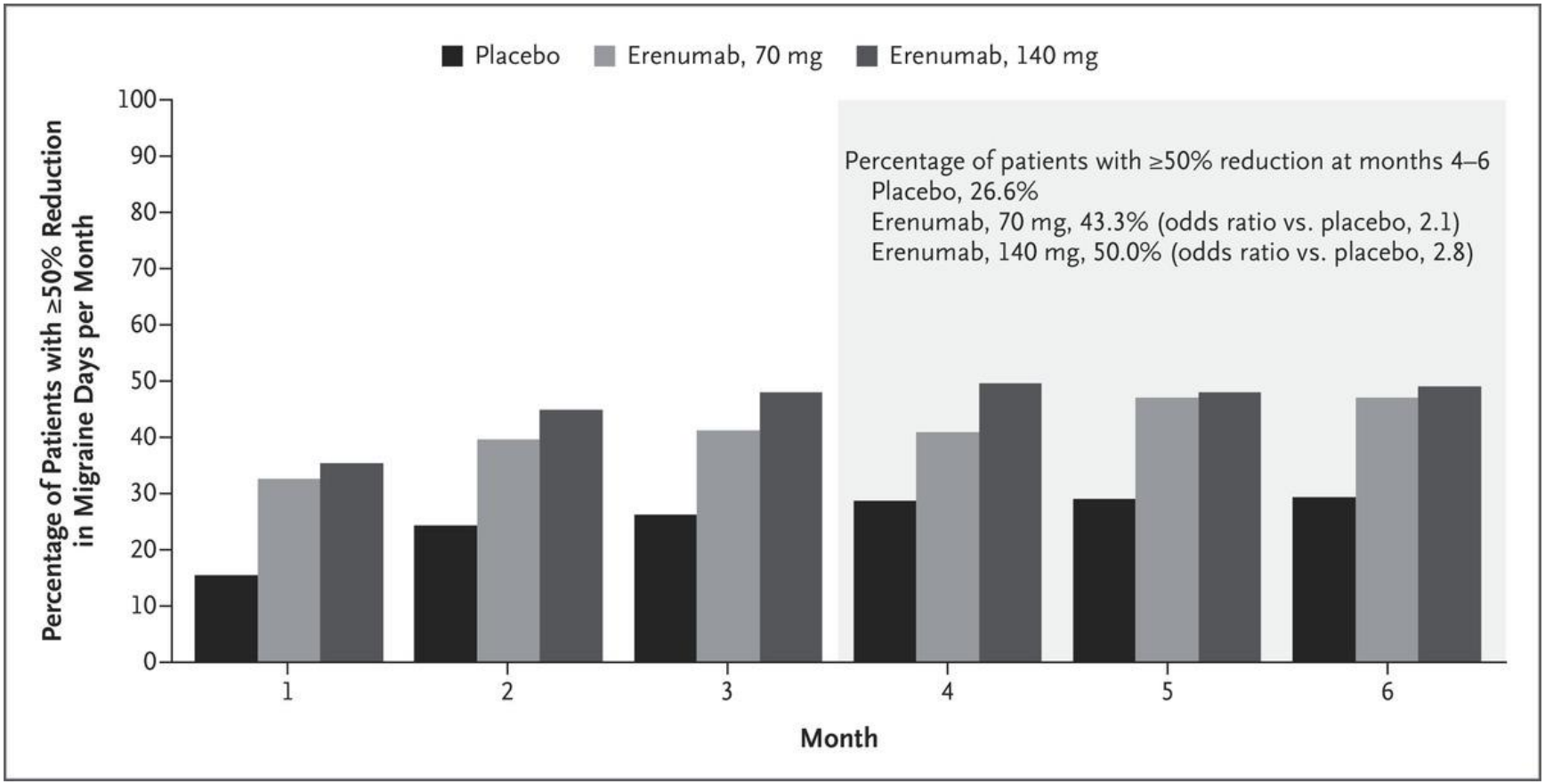
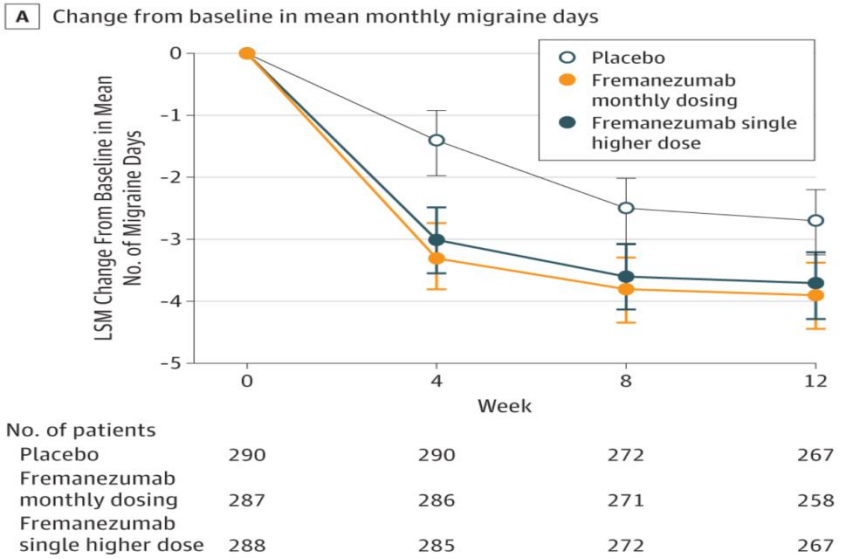
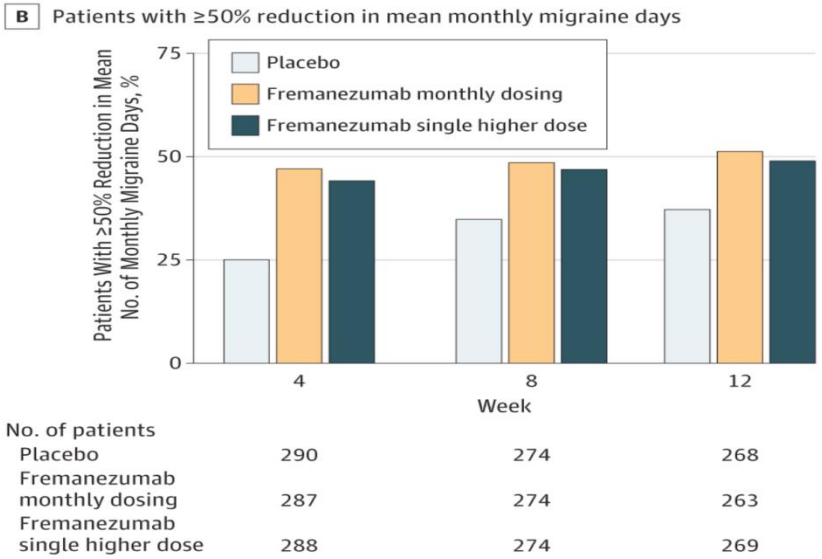


From: **Effect of Fremanezumab Compared With Placebo for Prevention of Episodic MigraineA Randomized Clinical Trial**

JAMA. 2018;319(19):1999-2008. doi:10.1001/jama.2018.4853




Panel A For the primary analysis (analysis of covariance) of mean migraine days per month from baseline to week 12, the difference vs placebo for the fremanezumab monthly dosing group was –1.5 days (95% CI, –2.01 to –0.93 days; P<.001) and for the fremanezumab single-higher-dose group was –1.3 days (95% CI, –1.79 to –0.72 days; P<.001).

Panel B shows the percentage of patients with at least a 50% reduction in mean number of monthly migraine days during the 12 weeks following the first administration of the study drug. The overall difference vs placebo for the fremanezumab monthly dosing group was 19.8% (95% CI, 12.0%-27.6%; P<.001) and for the fremanezumab single-higher-dose group was 16.5% (95% CI, 8.9%-24.1%; P<.001).

From: **Effect of Different Doses of Galcanezumab vs Placebo for Episodic Migraine PreventionA Randomized Clinical Trial**

JAMA Neurol. 2018;75(2):187-193. doi:10.1001/jamaneurol.2017.3859

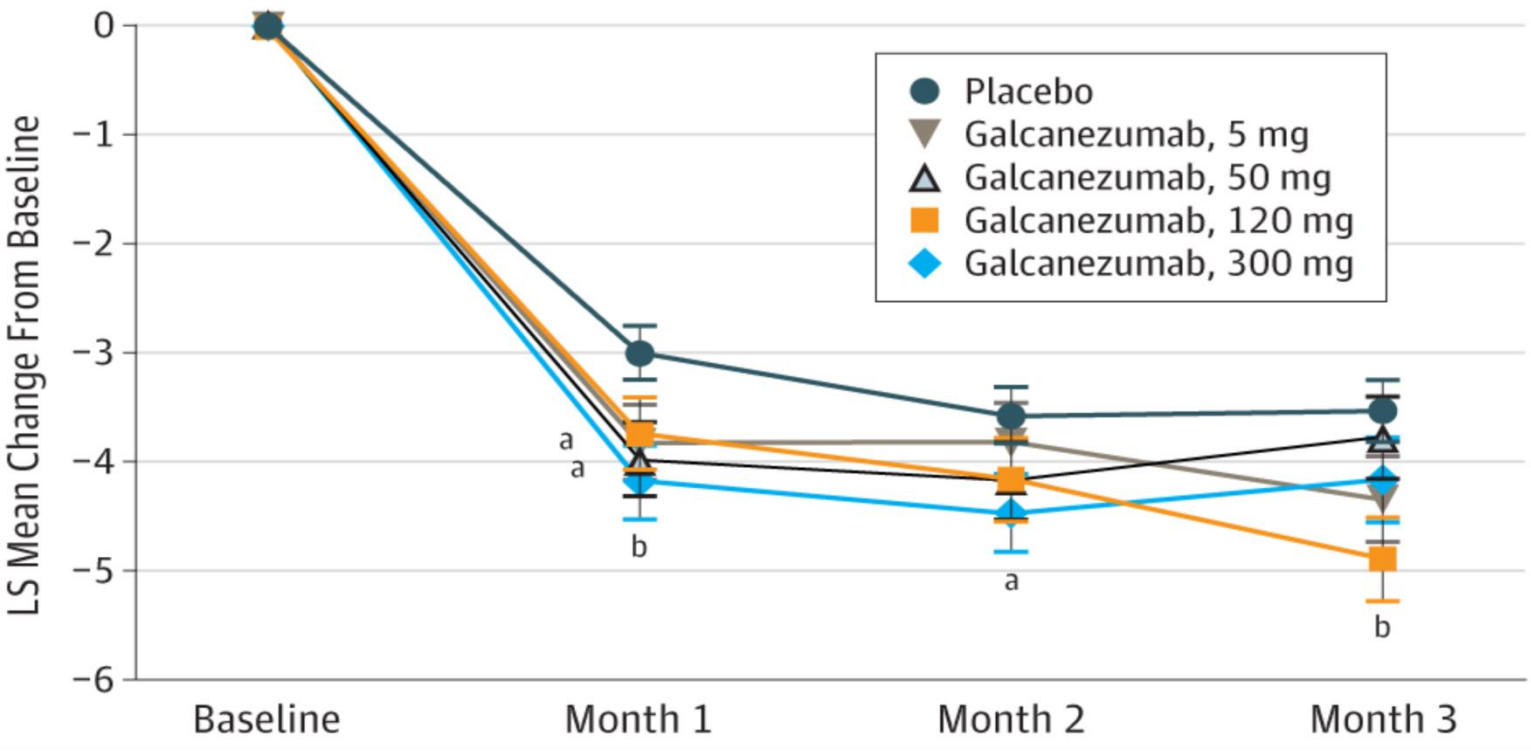



Figure Legend:

Change in the Number of Migraine Headache Days During Study Period 3 From Baseline to End Point (Month 3 of Study Period 3) Among Patients Who Received Placebo or GalcanezumabLS indicates least square; error bars, SE.

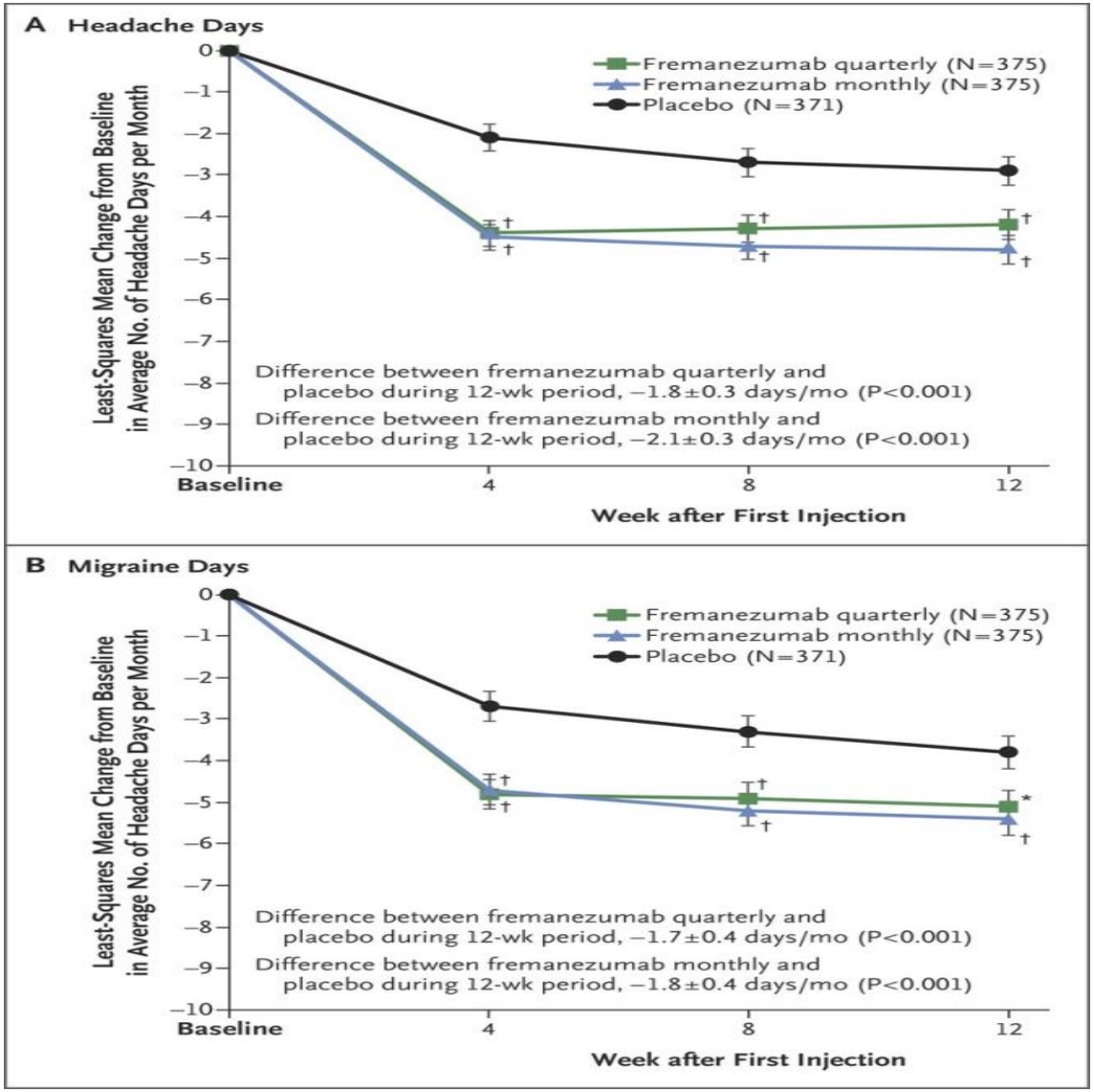
[a]P ≤ .05.

[b]P < .01.

# Galcanezumab in Episodic Cluster

- Galcanezumab met its primary endpoint in a Phase 3 study of patients with episodic cluster headache, demonstrating statistically significant differences in the reduction of weekly cluster headache attacks compared to placebo across weeks one to three of the two-month, double-blind treatment period.
- A statistically significantly greater percentage of patients treated with galcanezumab also achieved at least a 50 percent reduction in weekly cluster headache attacks compared to placebo at Week 3, the gated secondary endpoint.

# Fremanezumab in Chronic Migraine



# Primary endpoint results and 50% responder rates in phase II EM migraine prevention trials with CGRP mAbs

| | Dose | Baseline migraine days/4 weeks (active/placebo) | Mean reduction of migraine days (weeks 8–12) active/placebo | 50% responder rate (weeks 8–12) active/placebo |
|---|---|---|---|---|
| Galcanezumab | 150 mg s.c.; every 14 days | 6.7/7.0 | −4.2/−3.0* | 70/45 |
| Eptinezumab | Single 1000 mg I.V. | 8.8/8.4 | −5.6/−4.6* (week 5–8) | 77/67 |
| Fremanezumab | 625/225 mg s.c.; monthly | 11.5/11.5/11.3 | −6.09/−6.27/−3.46* | 59/53/28 (week 1–12) |
| Erenumab | 70 mg s.c.; monthly | 8.6/8.8 | −3.4/−2.3* | 46/30 |

From: **The Changing Landscape of Pediatric Migraine TherapyA Review**

JAMA Neurol. Published online March 12, 2018. doi:10.1001/jamaneurol.2018.0046

**Table. Data on Nutraceuticals**

| Name | Proposed Mechanism of Action | Adverse Effects | Evidence in Children |
|---|---|---|---|
| Riboflavin | Action in mitochondrial energy production[55] | Yellow-orange coloration of urine[56]; gastrointestinal adverse effects (nausea, vomiting, diarrhea, and increased appetite)[56-58] | A small retrospective open-label trial showed significant reduction in headache at 3-4 mo, but not at 6 mo.[56] Study was limited by the wide variation in diagnoses, including multiple periodic syndromes.[59] Two RCTs did not achieve statistical significance in reduction of migraine frequency, but were limited by high placebo effect, and medium dosing of riboflavin, respectively.[57,58] |
| Magnesium | Role in ATP production and membrane stabilization,[60] deficient in some pediatric patients with migraine[61] | Gastrointestinal adverse effects including diarrhea[62] | Small, prospective open-label study including other periodic syndromes showed reduction in the frequency of periodic syndromes where migraine was included[63]; RCT including other periodic syndromes showed a downward trend of frequency.[64] |
| Coenzyme Q10 | Action in mitochondrial energy production[55] | Tolerability excellent, 1 participant developed a cutaneous rash[65] | Open-label study[66] that was converted to a crossover RCT[67] showed reduction in frequency of migraines compared with placebo in the initial treatment period, but this was not sustained, limited by high dropout rate. |
| Butterbur[a] | Anti-inflammatory properties[59] | Contains pyrrolizidine alkaloids that are hepatotoxic, carcinogenic, and veno-occlusive[68] | Prospective open-label trial showed reduction in frequency of migraine headaches.[69] |
| Melatonin | Anti-inflammatory and analgesic effects[70] | Sleepiness, vomiting, and mild hypotension[71] | Three-month small open-label trial, included children with migraine and tension-type headache showed reduction in frequency of headaches[72] |

# Cost of Drugs for Migraine Prevention

| Drug | Some Available Formulations | Usual Adult Dosage[1] | Cost[2] |
|---|---|---|---|
| **Beta Blockers** | | | |
| Metoprolol[3] – generic | 25, 50, 100 mg tabs | 50-100 mg bid | $1.80 |
| *Lopressor* (Validus) | 50, 100 mg tabs | | 57.60 |
| extended-release – generic | 25, 50, 100, 200 mg ER tabs | 100-200 mg once/d | 36.30 |
| *Toprol-XL* (AstraZeneca) | | | 53.90 |
| Propranolol – generic | 10, 20, 40, 60, 80 mg tabs | 40-160 mg divided bid | 20.40 |
| extended-release – generic | 60, 80, 120, 160 mg ER caps | 60-160 mg once/d | 50.10 |
| *Inderal LA* (Akrimax) | | | 530.40 |
| Timolol – generic | 5, 10, 20 mg tabs | 10-15 mg bid or 20 mg once/d | 75.30 |
| **Antiepileptic Drugs** | | | |
| Valproate[4] – generic | 125, 250, 500 mg delayed-release tabs; | 250-500 mg bid | 17.80 |
| *Depakote* (Abbvie) | 125 mg sprinkle caps | | 195.80 |
| extended-release – generic | 250, 500 mg ER tabs | 500-1000 mg once/d | 87.60 |
| *Depakote ER* | | | 156.60 |
| Topiramate[5] – generic | 25, 50, 100, 200 mg tabs; | 50 mg bid[6] | 13.50 |
| *Topamax* (Janssen) | 15, 25 mg sprinkle caps | | 574.60 |
| **Tricyclic Antidepressants[3]** | | | |
| Amitriptyline – generic | 10, 25, 50, 75, 100, 150 mg tabs | 25-150 mg once/d | 9.50 |
| Nortriptyline – generic | 10, 25, 50, 75 mg caps | 25-150 mg once/d | 8.00 |
| **SNRI[3]** | | | |
| Venlafaxine – generic | 25, 37.5, 50, 75, 100 mg tabs | 25-50 mg tid | 47.70 |
| extended-release – generic | 37.5, 75, 150 mg caps; | 75-150 mg once/d | 11.70 |
| | 37.5, 75, 150, 225 mg tabs | | |
| *Effexor XR* (Pfizer) | 37.5, 75, 150 mg caps | | 352.50 |
| **Botulinum Toxin Type A** | | | |
| OnabotulinumtoxinA – *Botox* (Allergan)[7] | 100, 200 unit vials | 155 units IM every 12 weeks[8] | 1158.00[9] |
| **Calcitonin Gene-Related Peptide Receptor Antagonist** | | | |
| Erenumab-aooe – *Aimovig* (Amgen/Novartis) | 70 mg/mL prefilled syringe or *Sure Click* autoinjector | | 575.00[10] |

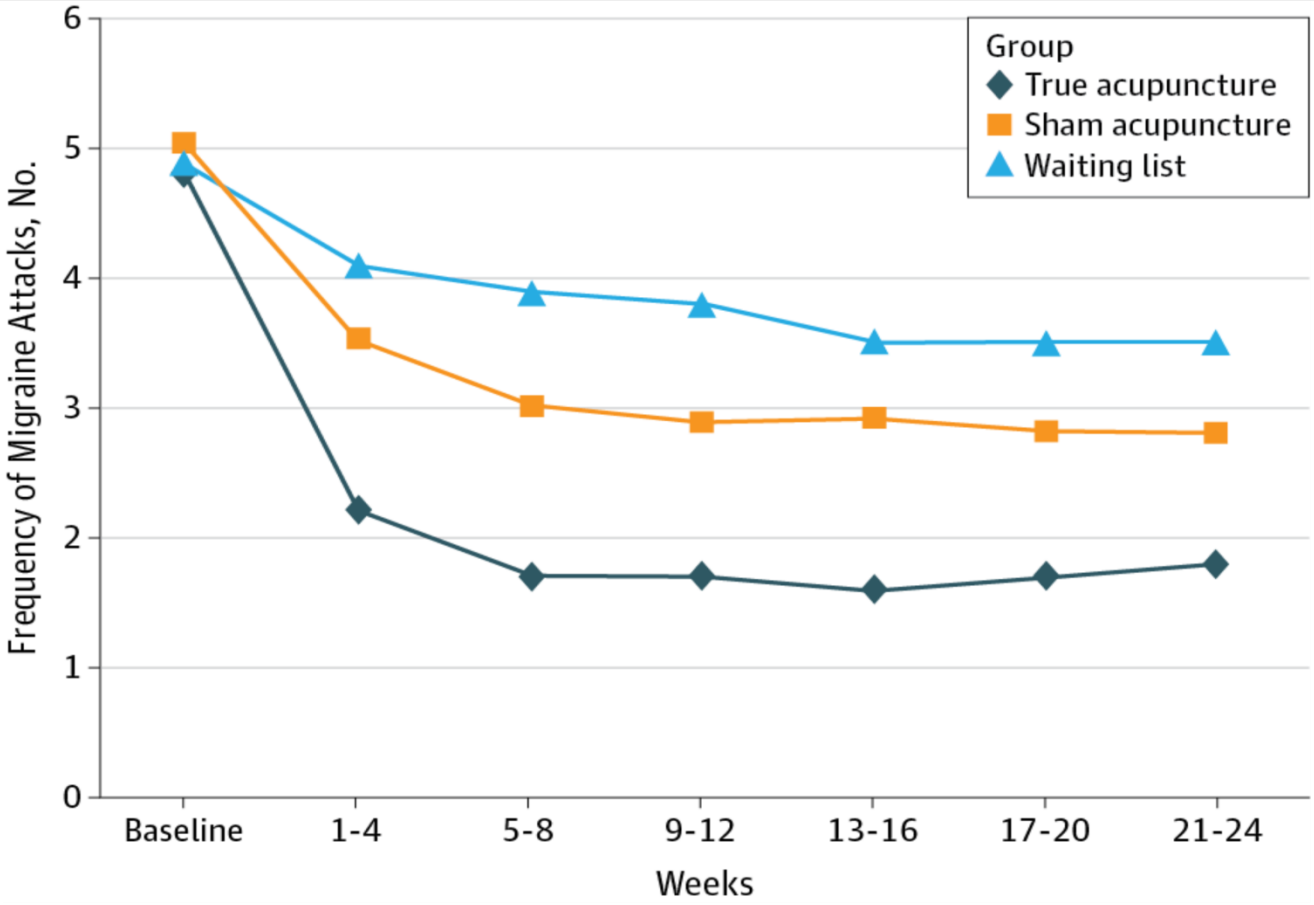
# What is the long-term efficacy of acupuncture for prophylaxis of migraine?

- **Findings** In this 24-week, randomized clinical trial that included 249 patients with migraine without aura, true acupuncture significantly reduced the frequency of migraine attacks, compared with sham acupuncture and being placed on a waiting list for treatment.
- **Meaning** Among patients with migraine without aura, true acupuncture may be associated with long-term reduction in migraine recurrence compared with sham acupuncture or waiting list.

*JAMA Intern Med.* 2017;177(4):508-515. doi:10.1001/jamainternmed.2016.9378

From: **The Long-term Effect of Acupuncture for Migraine ProphylaxisA Randomized Clinical Trial**

JAMA Intern Med. 2017;177(4):508-515. doi:10.1001/jamainternmed.2016.9378




Frequency of Migraine Attacks Throughout the Study

# Hazard Ratios for Cardiovascular Disease in Migraine

**Nurses' Health Study II (n=115 541)**

- Major cardiovascular disease event (n=1329):
  - 1.84 (1.64 to 2.06) <0.01
- Myocardial infarction (n=678):
  - 1.79 (1.52 to 2.10) <0.01
- Stroke (n=651):
  - 1.89 (1.60 to 2.22) <0.01
- Angina/coronary revascularization (n=203):
  - 2.35 (1.77 to 3.12) <0.01
- Cardiovascular mortality (n=223):
  - 1.66 (1.25 to 2.21) <0.01

Kurth et al. BMJ 2016:353:i2610

# Serotonin Receptors

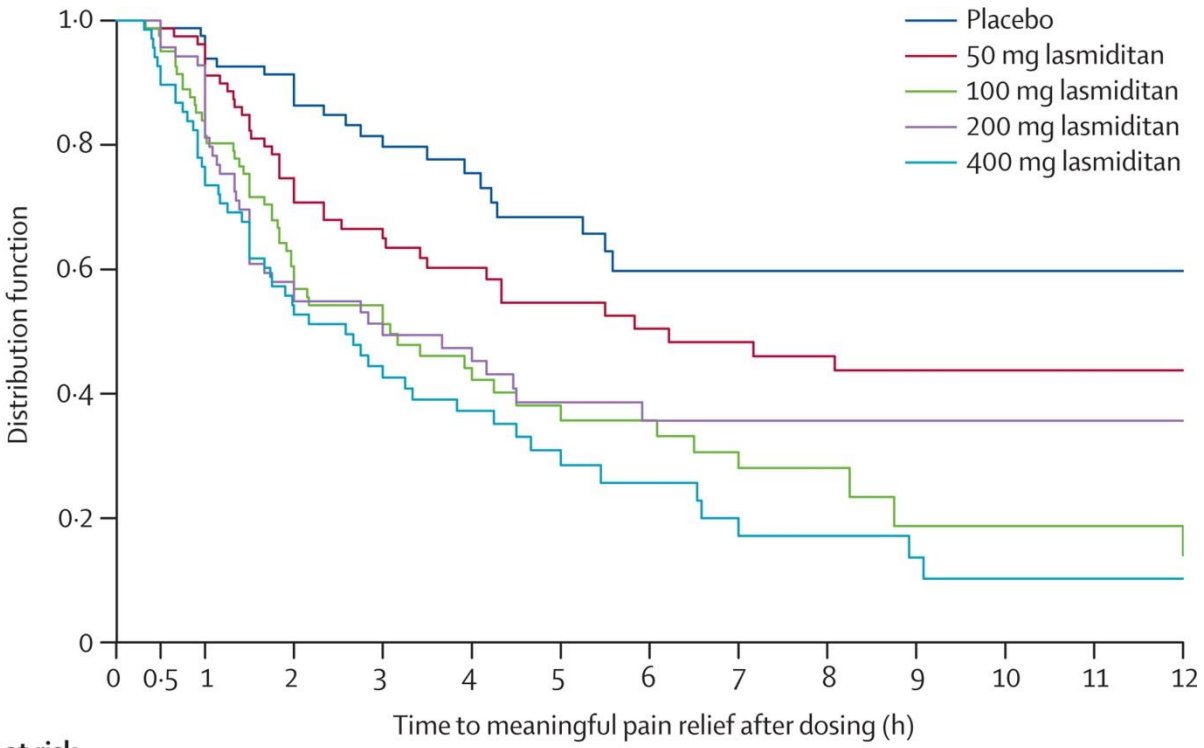
**Table 1** Summary of the main characteristics of 5-$HT_1$ receptors

| Receptor subtype | Distribution | Effector mechanism | Physiological action | Agonists used as antimigraine therapy |
|---|---|---|---|---|
| 5-$HT_{1A}$ | CNS<br>Raphe nuclei, hippocampus, amygdala, septum, entorhinal cortex, hypothalamus<br>PNS<br>Cholinergic heteroceptor in myenteric plexus | - Inhibition of adenylyl cyclase<br>- Opening of $K^+$ channels<br>- Inhibition of voltage gated $Ca^{2+}$ channels | - Serotonergic auto receptor<br>- Neuronal inhibition<br>- Facilitate ACh and NA release<br>- Cholinergic nerve terminal in myenteric plexus<br>- Hyperphagia | None |
| 5-$HT_{1B}$ | CNS<br>Subiculum, substantia nigra<br>PNS<br>Vascular smooth muscle | Inhibition of adenylyl cyclase | - Serotonergic auto receptor<br>- Control release of ACh and NA<br>- Contraction of vascular smooth muscle | Ergot alkaloids<br>Triptans |
| 5-$HT_{1D}$ | CNS<br>Cranial blood vessel<br>PNS<br>Vascular smooth muscle | Inhibition of adenylyl cyclase | - Serotonergic auto receptor<br>- GABAergic and cholinergic heteroreceptor<br>- Vasoconstriction of intracranial blood vessel | Ergot alkaloids<br>Triptans |
| 5-$HT_{1e}$ | CNS<br>Cortex striatum<br>PNS<br>mRNA in vascular tissue | Inhibition of adenylyl cyclase | Unknown | None |
| 5-$HT_{1F}$ | CNS<br>Cortex, spinal cord, hippocampus, locus coeruleus, hypothalamus, amygdala, cerebellum, dorsal raphe nucleus, pineal gland<br>PNS<br>Uterus, mesentery, vascular smooth muscle | Inhibition of adenylyl cyclase | Trigeminal neuroinhibition in guinea pig and rat | Lasmiditan |

# Lasmiditan

- Lasmiditan is a novel selective 5-HT(1F) receptor agonist.
- In the intravenous placebo-controlled RCT, lasmiditan doses of 2.5-45 mg were used, and there was a linear association between headache relief (HR) rates and dose levels ($P < 0.02$). For lasmiditan 20 mg, HR was 64 % and for placebo it was 45 % (NS).
- In the oral placebo-controlled RCT, lasmiditan doses of 50, 100, 200 and 400 mg were used. For HR, all doses of lasmiditan were superior to placebo ($P < 0.05$). For lasmiditan 400 mg, HR was 64 % and it was 25 % for placebo.

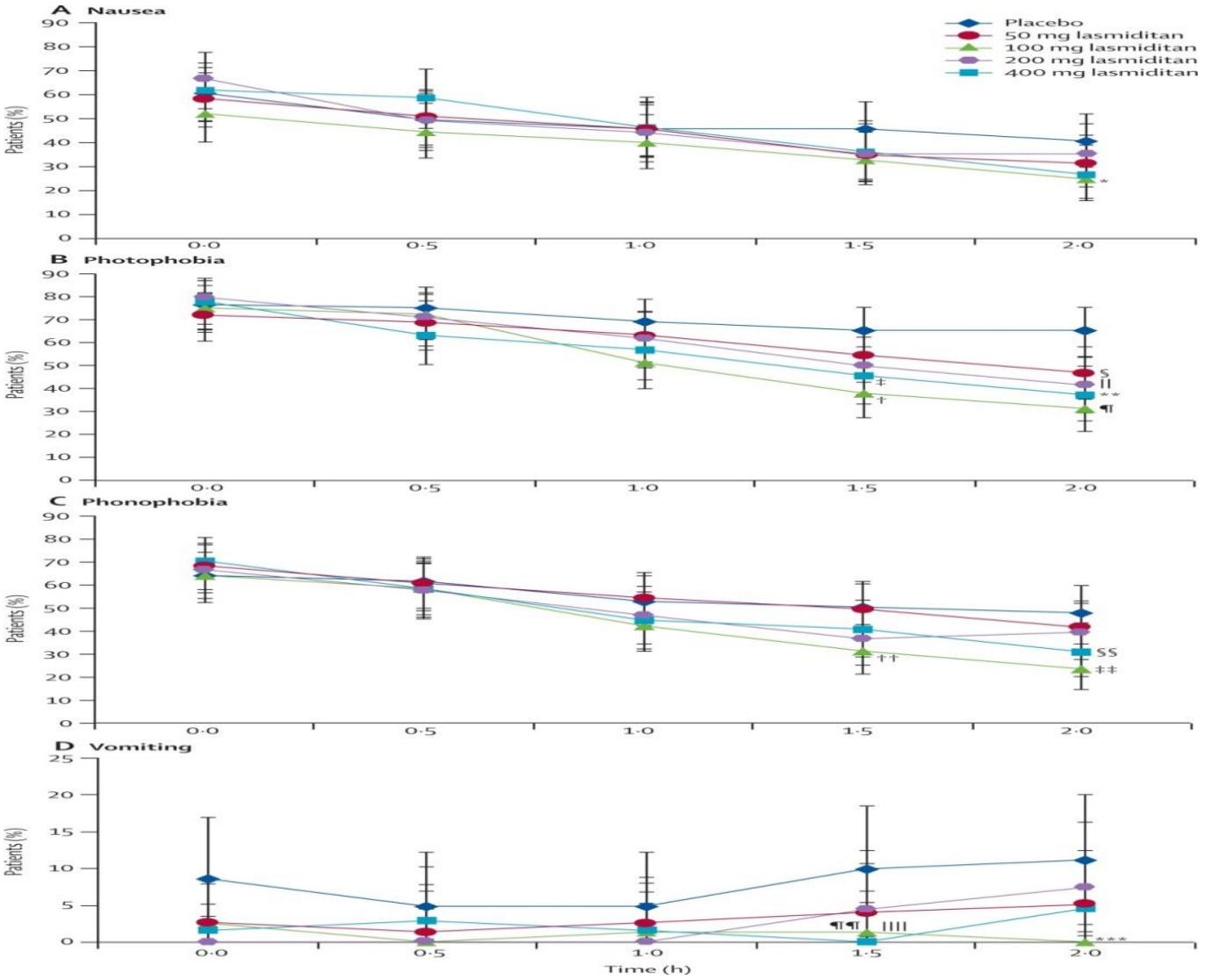
# Lasmiditan Efficacy




**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 81 | 80 | 76 | 67 | 32 | 19 | 15 | 11 | 11 |
| 50 mg lasmiditan | 79 | 78 | 72 | 53 | 33 | 24 | 20 | 15 | 13 |
| 100 mg lasmiditan | 81 | 77 | 66 | 45 | 22 | 14 | 6 | 4 | 3 |
| 200 mg lasmiditan | 69 | 66 | 56 | 36 | 22 | 12 | 10 | 8 | 8 |
| 400 mg lasmiditan | 68 | 61 | 50 | 35 | 20 | 9 | 6 | 3 | 3 |

# Migraine Associated Symptoms



# Lasmiditan

- Adverse events (AEs) emerging from the treatment were reported by 22 % of the patients receiving placebo and by 65, 73, 87 and 87 % of patients receiving 50, 100, 200 and 400 mg, respectively. The majority of AEs after lasmiditan 100 and 400 mg were moderate or severe.
- For the understanding of migraine pathophysiology, it is very important to note that a selective 5-HT(1F) receptor agonist like lasmiditan is effective in the acute treatment of migraine. Thus, migraine can be treated with a drug that has no vasoconstrictor ability.
- While lasmiditan most likely is effective in the treatment of migraine attacks it had, unfortunately, a high incidence of CNS related AEs in the oral RCT.

From: **Timolol Eyedrops in the Treatment of Acute Migraine AttacksA Randomized Crossover Study**

JAMA Neurol. Published online May 14, 2018. doi:10.1001/jamaneurol.2018.0970

**Table. Summary and Participants' Survey Responses While Using Placebo and Timolol[a]**

| Clinical Question | Mean (SD), % | Participant 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Migraine Attacks With a Severity of None or Mild At 2 h, %** | | | | | | | | | | | |
| Placebo | 67 (30) | 44 | 54 | 0 | 91 | 71 | 80 | 63 | 100 | 67 | 0 |
| Timolol | 78 (31) | 80 | 18 | 100 | 72 | 100 | 92 | 89 | 100 | 100 | 25 |
| **Total No. of Migraine Attacks** | | | | | | | | | | | |
| Placebo | 8 (6.7) | 9 | 24 | 11 | 11 | 7 | 5 | 8 | 1 | 3 | 1 |
| Timolol | 11.8 (11) | 20 | 38 | 5 | 11 | 4 | 12 | 9 | 8 | 7 | 4 |
| **Exit Survey Results While Participant Was Still Masked** | | | | | | | | | | | |
| Overall effectiveness (1 to 4) | | | | | | | | | | | |
| Placebo | 1.4 (0.9) | 1 | 1 | 1 | 4 | 1 | 1 | 1 | 1 | 1 | 1.5 |
| Timolol | 2.4 (1.4) | 4 | 1 | 2 | 1 | 2 | 4 | 4 | 1 | 4 | 1 |
| Desire to use compared with current treatment | | | | | | | | | | | |
| Would use in place of an abortive treatment? | Yes for 2.5 of 10 (25%) | No | No | No | Yes for placebo | No | Maybe | Yes | No | Yes | No |
| Would use in addition to abortive treatment? | Yes for 5.5 of 10 (55%) | Yes | No | No | Yes for placebo | Yes | Yes | Yes | Maybe | Yes | No |

[a] The mean value for percentage of migraine attacks with none or mild severity.

Table Title:

Summary and Participants' Survey Responses While Using Placebo and Timolol[a]

Neurology®

October 18, 2017 ARTICLE

# Randomized study of IV prochlorperazine plus diphenhydramine vs IV hydromorphone for migraine

Benjamin W. Friedman, Eddie Irizarry, Clemencia Solorzano, Alexander Latev, Karolyn Rosa, Eleftheria Zias, David R. Vinson, Polly E. Bijur and E. John Gallagher

First published October 18, 2017, DOI: https://doi.org/10.1212/WNL.0000000000004642

- Participants received hydromorphone 1 mg or prochlorperazine 10 mg + diphenhydramine 25 mg. Diphenhydramine was administered to prevent akathisia, a common side effect of IV prochlorperazine.
- The primary outcome was sustained headache relief, defined as a headache level of mild or none within 2 hours and maintaining that level for 48 hours without rescue medication.
- The primary outcome was achieved in the prochlorperazine arm by 37 of 62 (60%) participants and in the hydromorphone arm by 20 of 64 (31%) participants (difference 28%, 95% confidence interval 12–45, number needed to treat 4, 95% confidence interval 2–9).
- IV hydromorphone is substantially less effective than IV prochlorperazine for the treatment of acute migraine in the ED and should not be used as first-line therapy.

# Is there a link between migraine and cervical artery dissection?

- **Findings** In a cohort study of 2485 patients aged 18 to 45 years with first-ever acute ischemic stroke, a history of migraine, especially the subtype without aura, was independently associated with cervical artery dissection. The strength of this association was higher in men and in younger individuals.
- **Meaning** In young patients with ischemic stroke, migraine is consistently associated with cervical artery dissection. This finding implicates possible common biologic mechanisms underlying the 2 disorders.

*JAMA Neurol.* 2017;74(5):512-518. doi:10.1001/jamaneurol.2016.5704