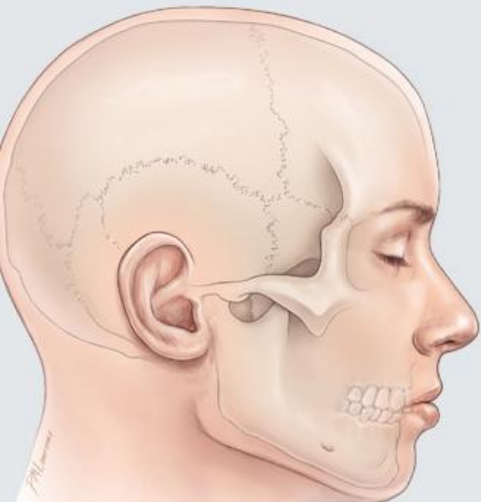


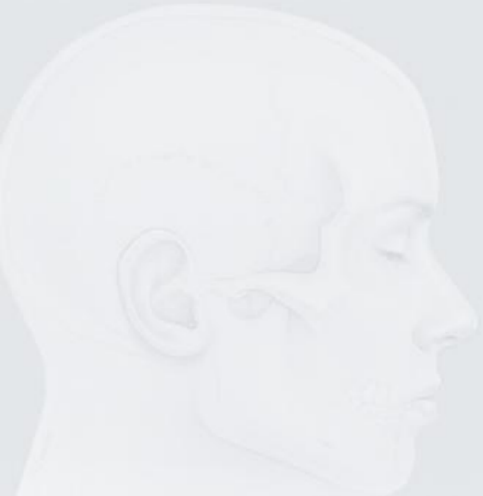
# **10 Things You Didn't Know About Migraine**

Karissa Secora, PA-C, AQH  
Lewis Headache Center  
Barrow Neurological Institute  
Phoenix, AZ



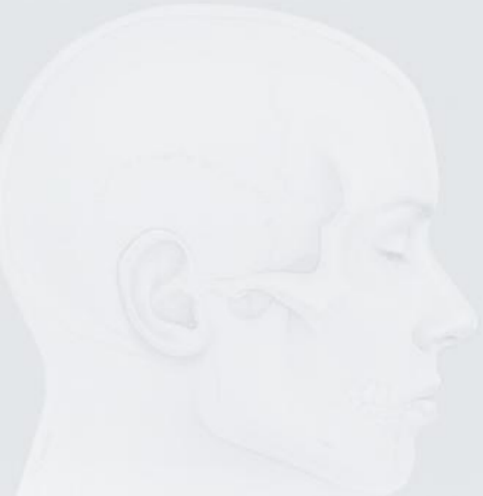
# Disclosures

- I have relevant relationships with ineligible companies to disclose within the past 24 months.
- Speaker: AbbVie and Medical Logix, LLC



# Objectives

- Recognize **key molecules** that play a role in the etiology of migraine.
- Label the **4 phases** of a migraine.
- Differentiate when neuroimaging is **necessary**.

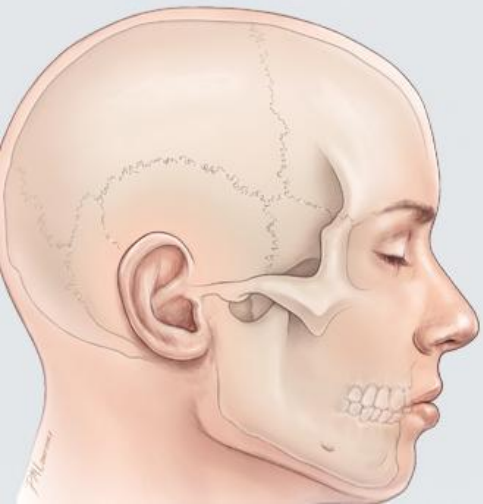


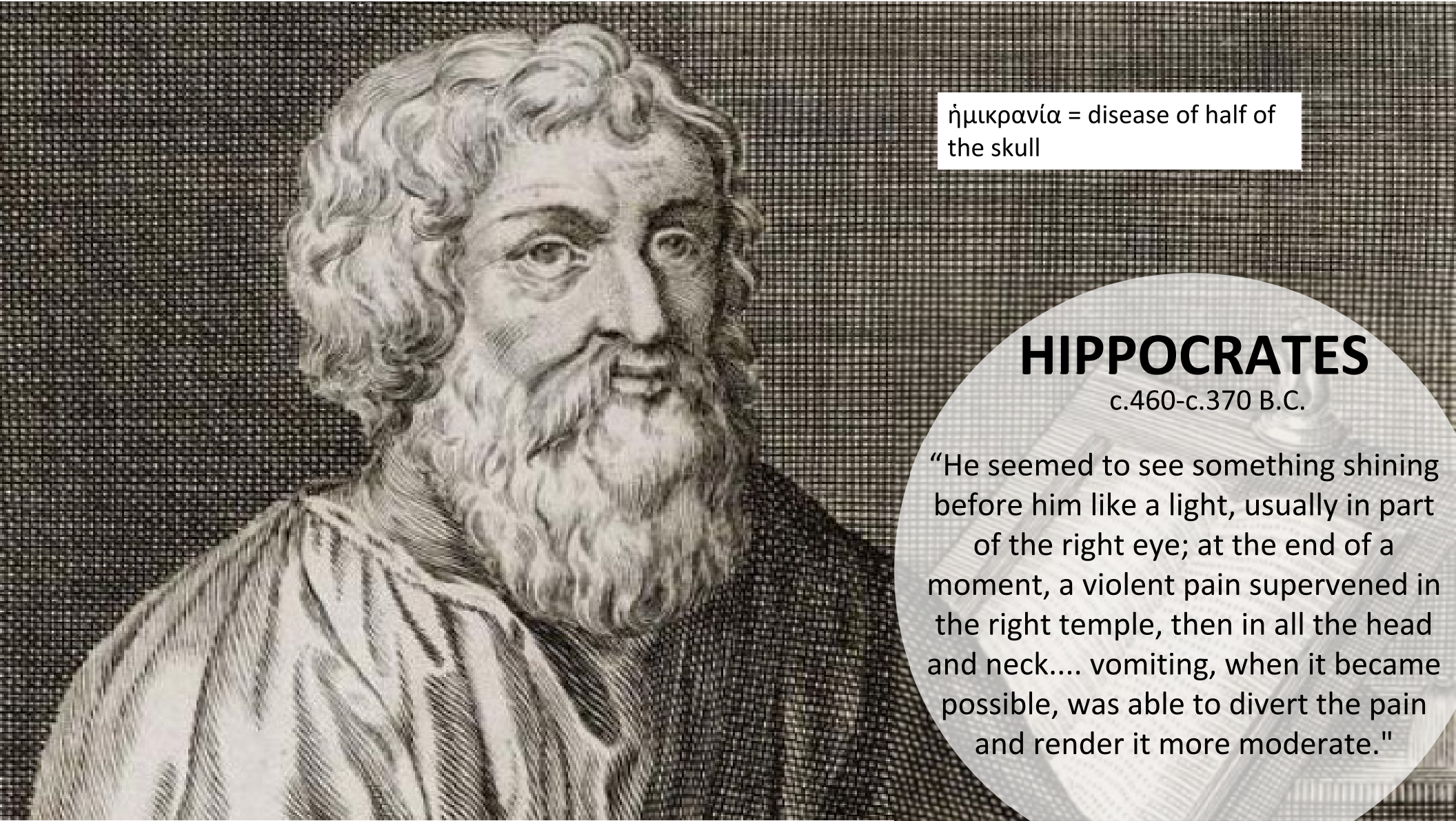
## Game Plan

1. History
2. Prevalence
3. Causes
4. Symptoms before the pain
5. Imaging – Is it needed?
6. “Complex migraine”
7. Babies might get “migraine”
8. New acute treatment options
9. New prevention treatment options
10. MORE treatments coming



**MIGRAINE STARTED  
A LONG TIME AGO**



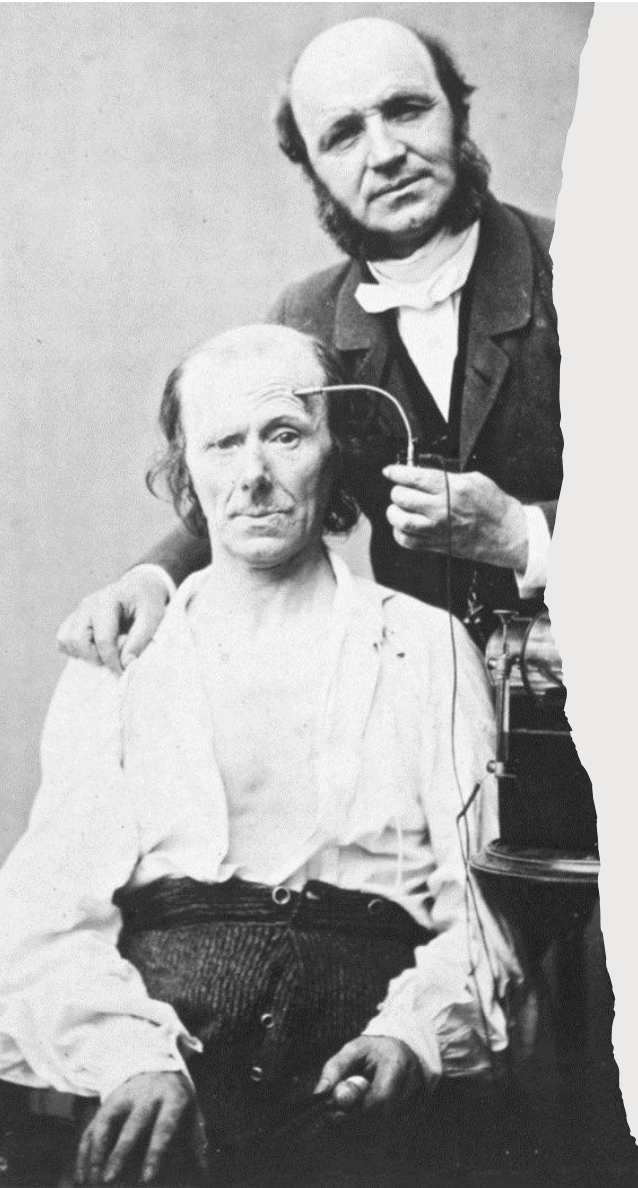


ἡμικρανία = disease of half of the skull

## HIPPOCRATES

c.460-c.370 B.C.

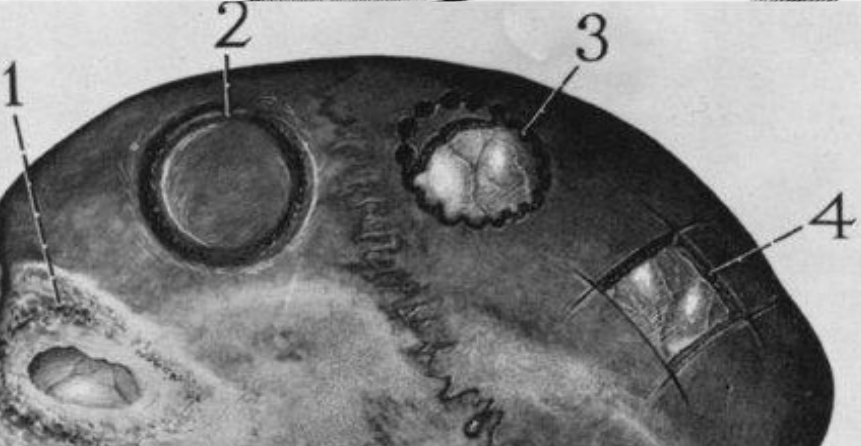
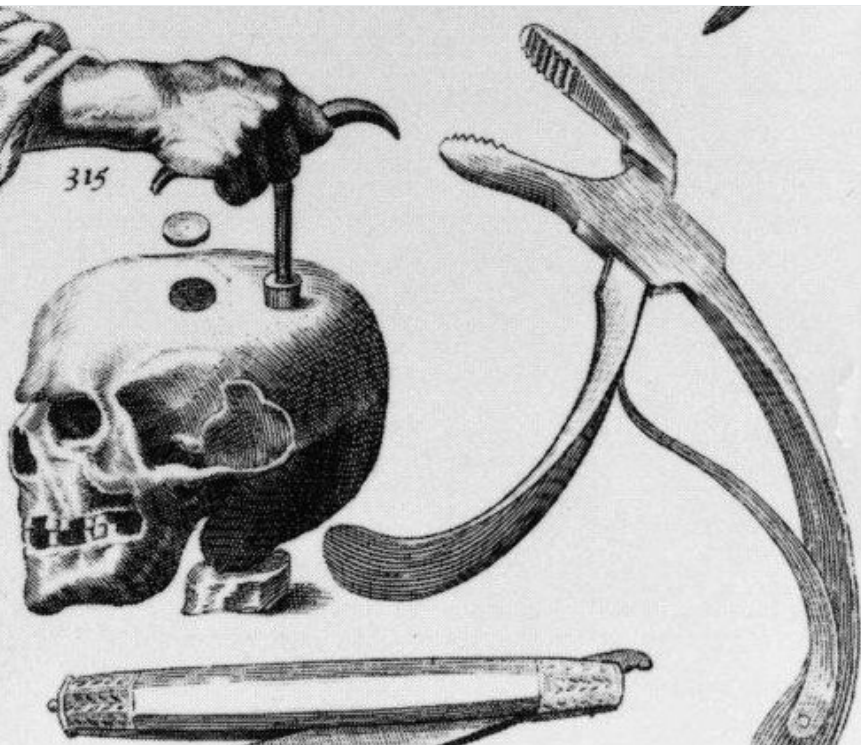
“He seemed to see something shining before him like a light, usually in part of the right eye; at the end of a moment, a violent pain supervened in the right temple, then in all the head and neck.... vomiting, when it became possible, was able to divert the pain and render it more moderate.”



## Ancient Treatment Options

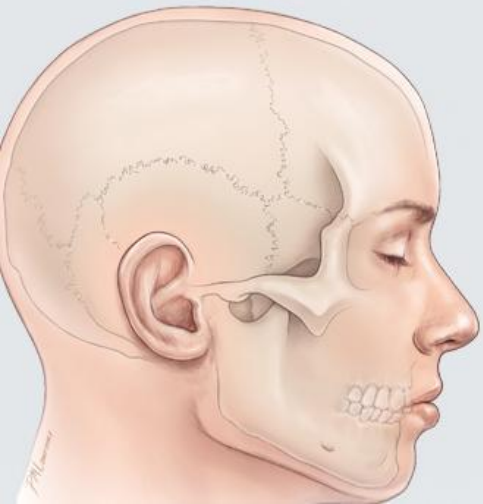
- Frankincense, cumin, ulan berry, and goose grease mixture
- Coriander, wormwood, juniper, honey, and opium
- Extract of willow bark
- Creation of blisters to the contralateral scalp
- Hot iron
- Garlic applied to incision in the temple
- Electrotherapy
- Crocodile with herbs in its mouth bound to their head







## 2. PREVALENCE AND BURDEN



## Key Facts

Globally, headache disorders including migraine are the **#1 reason for disability** in those under the age of 50<sup>1</sup>

Migraine impacts over **37 million** men, women, and children<sup>2</sup>

Direct costs associated with migraine are over **\$11 billion** each year in the US<sup>3</sup>

1. GBD (2019) Diseases and injuries collaborators (2020) global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet* 396:1204–1222

2. American Migraine Foundation

3. Wu J, Davis-Ajami ML, Lu ZK. Impact of migraine on health care utilization and expenses in obese adults: a US population-based study. *Clinicoecon Outcomes Res.* 2018;11:51-59. Published 2018 Dec 31. doi:10.2147/CEOR.S189699

Research/Disease Areas (Dollars in millions and rounded)	2013	2014	2015	2016	2017	2018	2019	2020	2021 Estimated	2022 Estimated
Allergic Rhinitis (Hay Fever)	\$9	\$6	\$5	\$7	\$6	\$5	\$7	\$7	\$7	\$8
ALS	\$39	\$48	\$49	\$52	\$78	\$83	\$105	\$107	\$110	\$115
Alzheimer's Disease	\$504	\$562	\$589	\$929	\$1,361	\$1,789	\$2,240	\$2,683	\$2,994	\$3,079
Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD) <sup>2</sup>	+	+	\$631	\$986	\$1,423	\$1,911	\$2,398	\$2,869	\$3,194	\$3,287

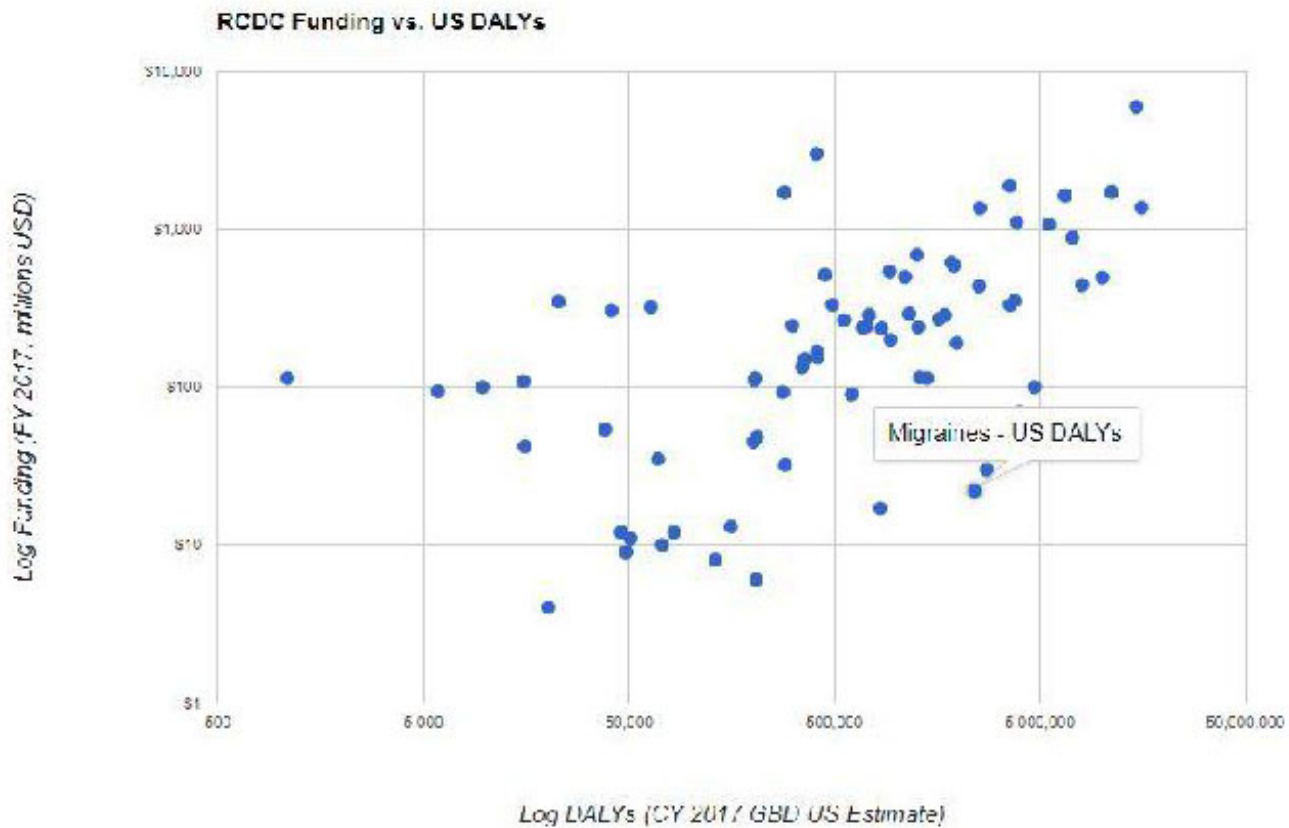
= \$3.3 billion

Asthma	\$207	\$241	\$281	\$266	\$285	\$304	\$313	\$338	\$350	\$338
--------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------

= \$338 million

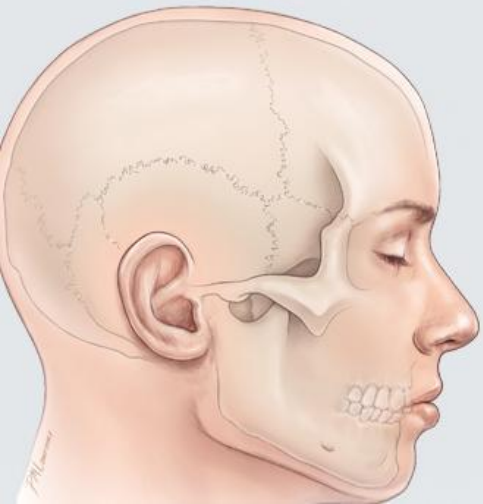
Migraines	\$19	\$20	\$20	\$18	\$22	\$21	\$28	\$28	\$29	\$30
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= \$30 million



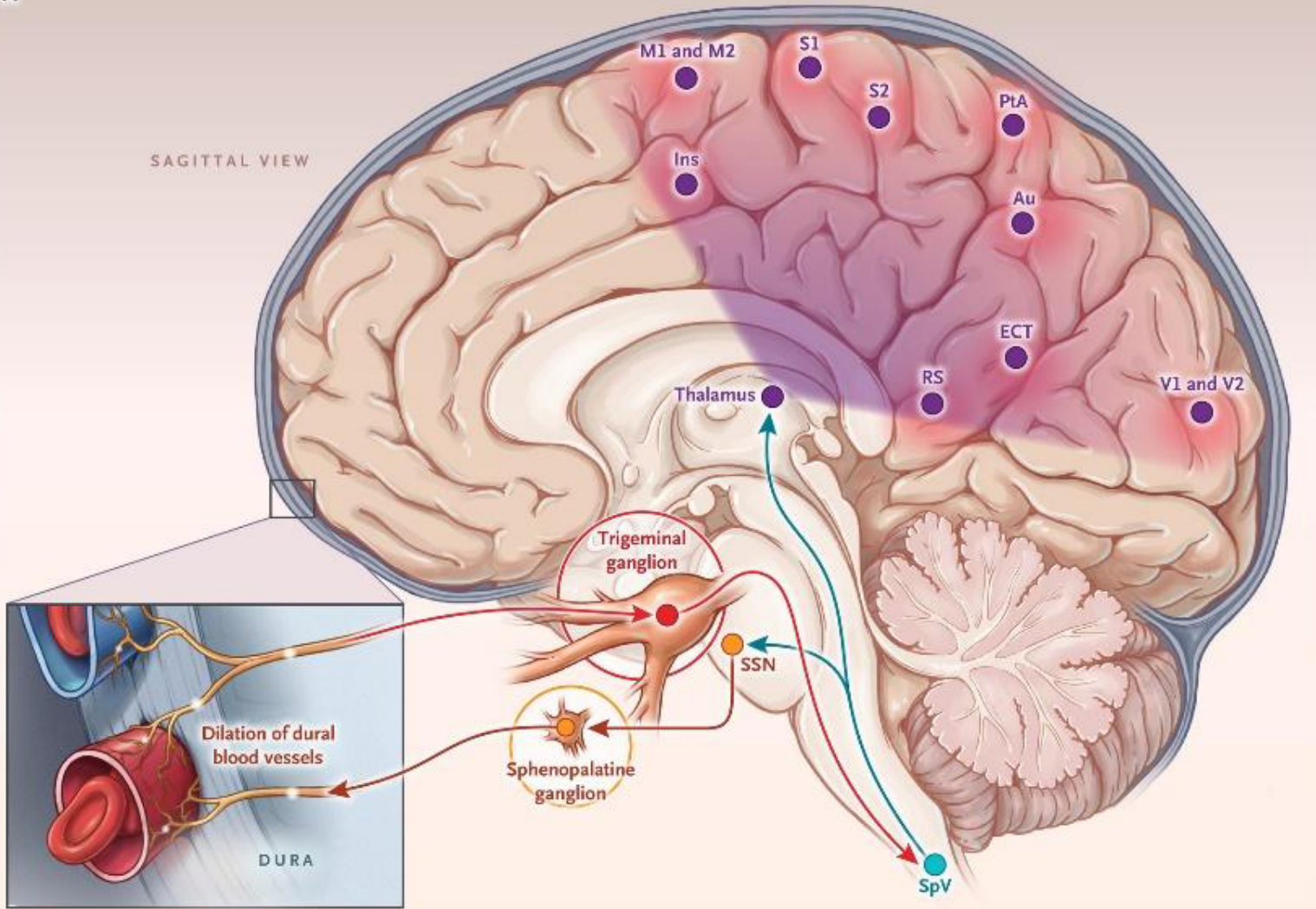
**Report on NIH Funding vs. Global Burden of Disease**

### 3. WHAT CAUSES A MIGRAINE?

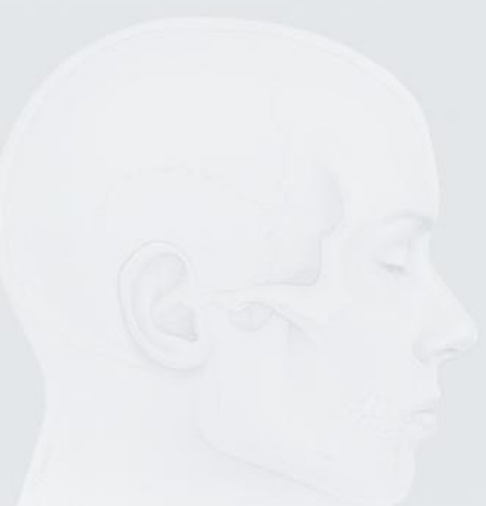


A

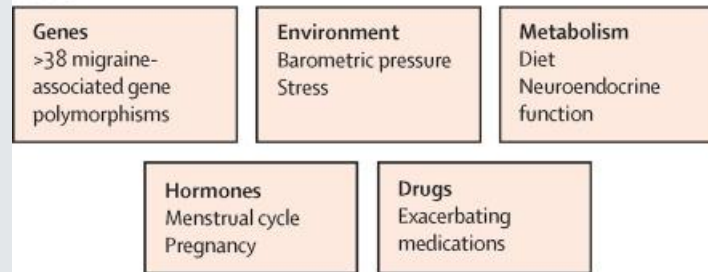
SAGITTAL VIEW



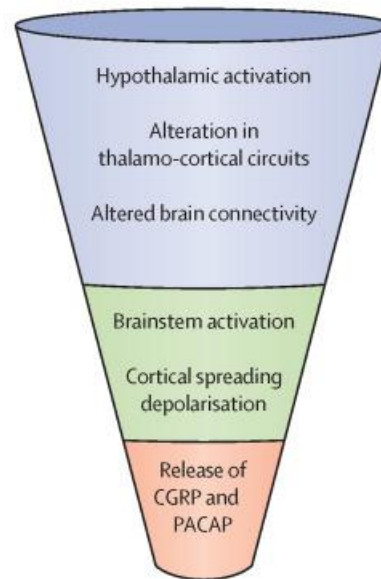
Ashina M. Migraine. N Engl J Med. 2020  
Nov 5;383(19):1866-1876. doi:  
10.1056/NEJMra1915327. PMID:  
33211930



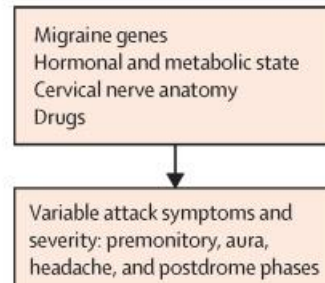
**Factors**



**Mechanisms**



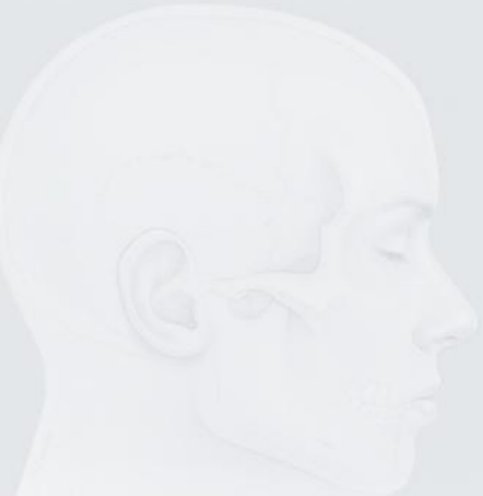
**Migraine attack**



Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol.* 2018 Feb;17(2):174-182. doi: 10.1016/S1474-4422(17)30435-0. Epub 2017 Dec 8.

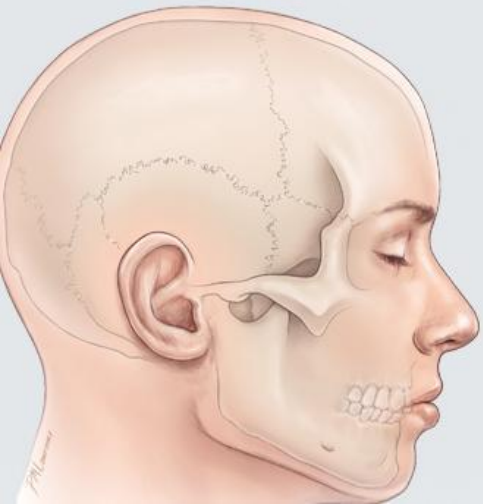
# Key Molecules in Migraine Pathophysiology

- Substance P
- PACAP – pituitary adenylase cyclase-activating polypeptide
- VIP – vasoactive intestinal peptide
- **CGRP** – calcitonin gene-related peptide

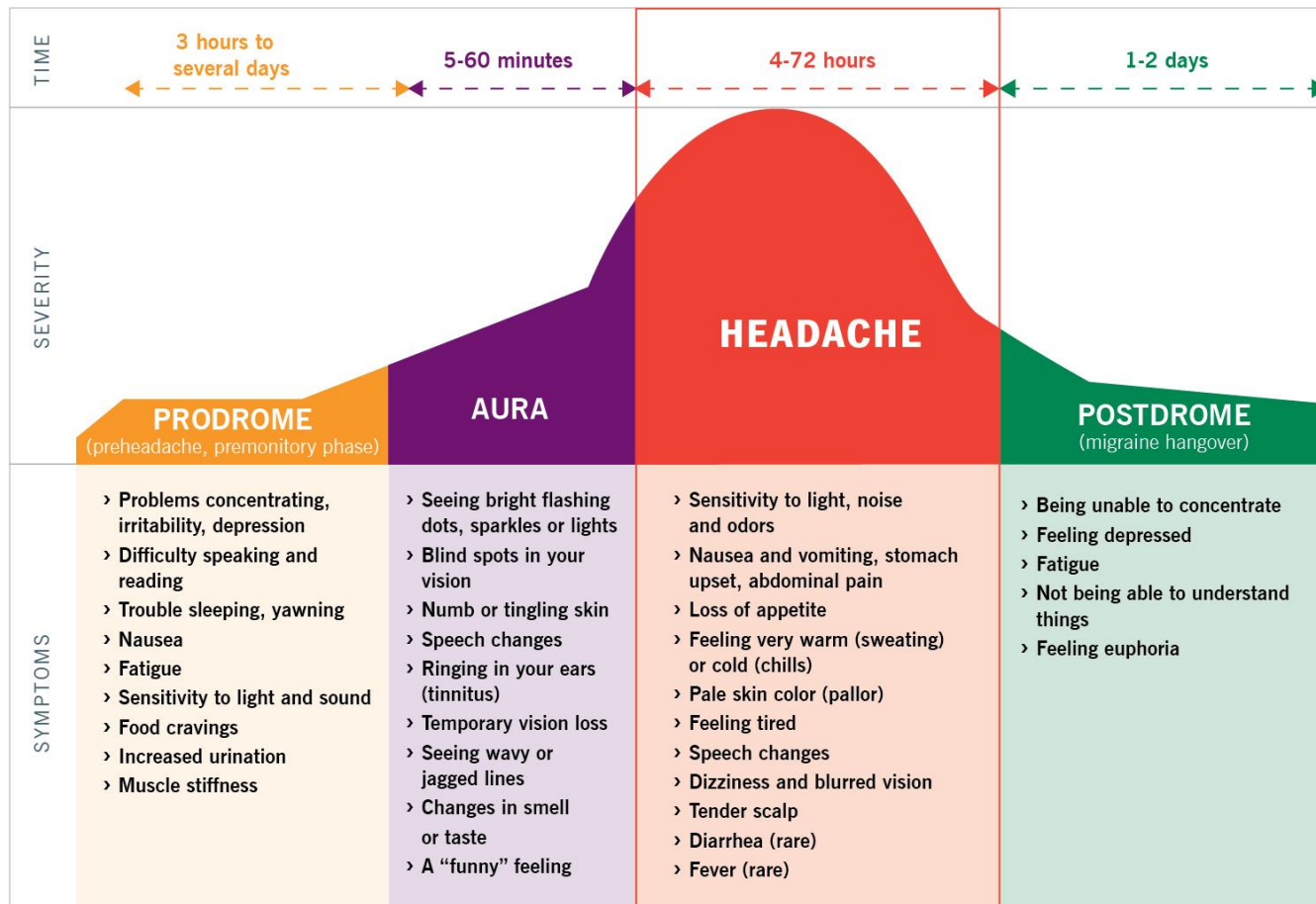




## **4. MIGRAINE IS A DISEASE – SYMPTOMS BESIDES PAIN**

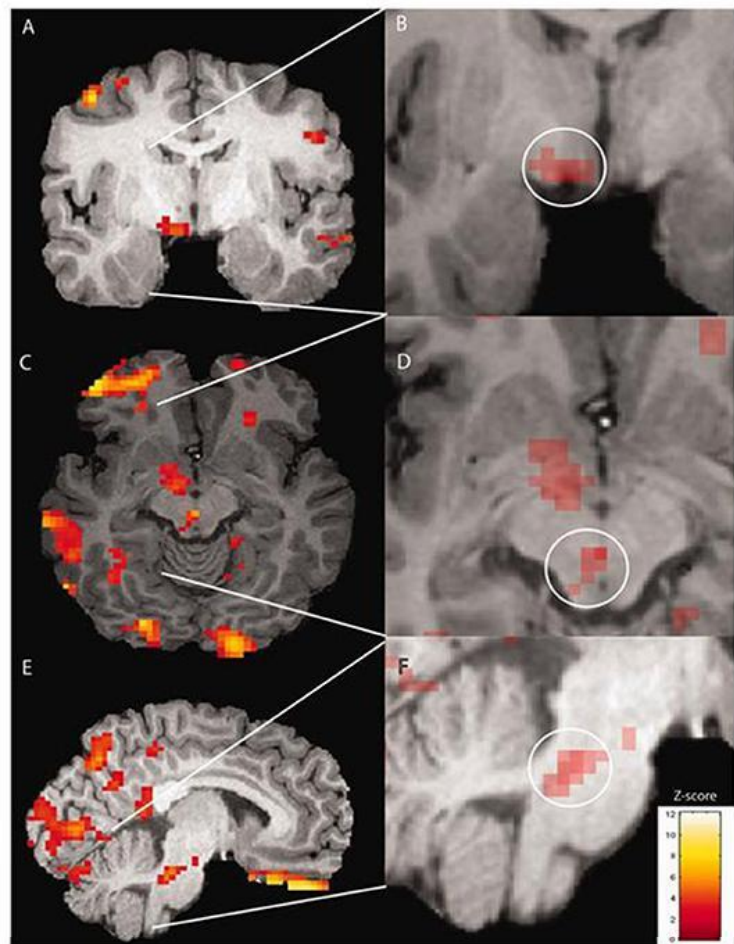


# The 4 Phases of a Migraine Headache

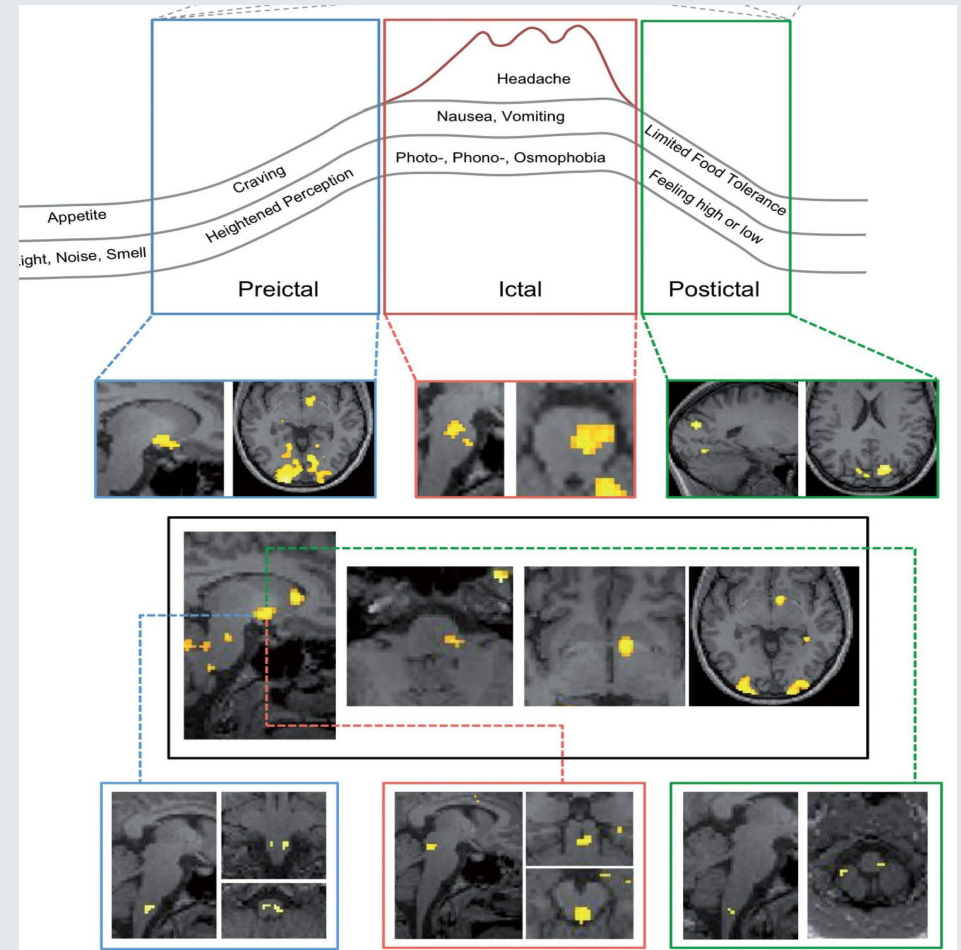


21-NEU-2074429

# Brain Activation BEFORE the Pain



Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain*. 2014 Jan;137(Pt 1):232-41. doi: 10.1093/brain/awt320



*Brain*, Volume 139, Issue 7, July 2016, Pages 1987–1993, <https://doi.org/10.1093/brain/aww097>

## Reminder: What is a Migraine?



IHS Classification ICHE-3

- At least **five** attacks
- 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
- During headache at least **one** of the following:
  - nausea and/or vomiting
  - photophobia **and** phonophobia
- Not better accounted for by another ICHE-3 diagnosis.

## Quiz: Does this patient have migraine?

33 year old 5<sup>th</sup> grade teacher with a 6 month history of 2 headaches per month:

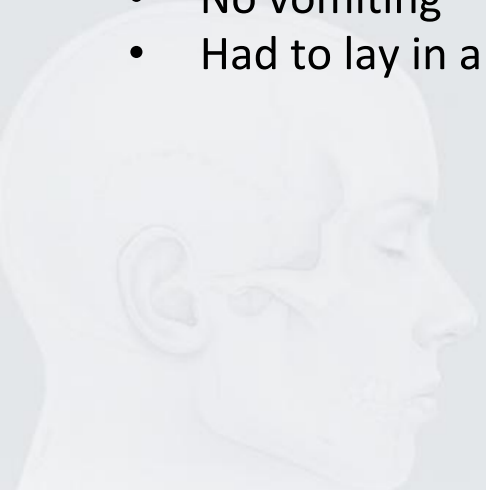
- Lasting 5 hours (after taking ibuprofen 200 mg)
- Bifrontal
- Described as dull
- Had to leave work early since the pain was so bad
- Couldn't even make her kids dinner
- No vomiting
- Had to lay in a dark, quiet room

# MIGRAINE!!!

33 year old 5<sup>th</sup> grade teacher with 6 month history of 2 headaches per month:

- Lasting 5 hours
- Bifrontal
- Described as dull
- Had to leave work early
- Couldn't even make her kids dinner
- No vomiting
- Had to lay in a dark, quiet room

- At least **five** attacks
- Lasting **4-72 hr** (untreated or unsuccessfully treated)
- 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**
- During headache at least **one** of the following:
  - nausea and/or ~~vomiting~~
  - **photophobia and phonophobia**



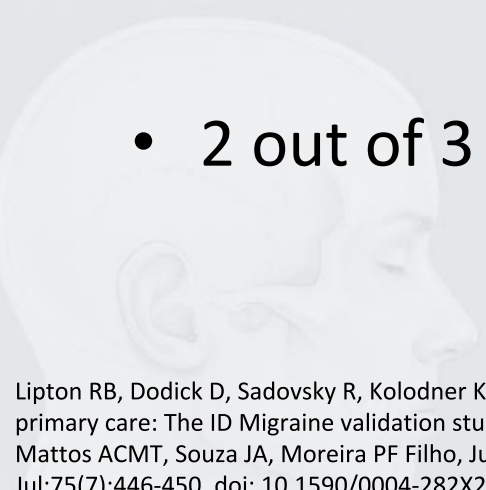
## Migraine or not? Remember to PIN the diagnosis!

**P** = Photophobia

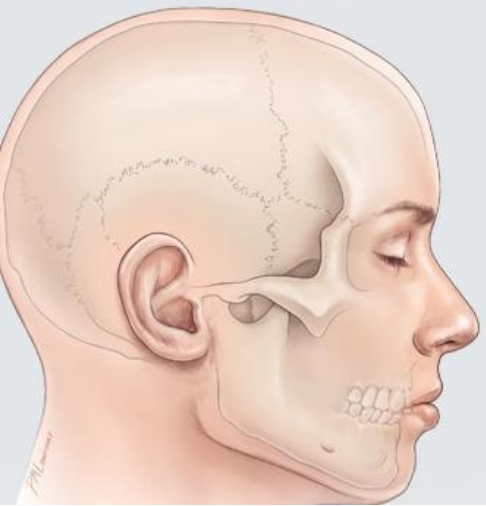
**I** = Impairment

**N** = Nausea

- 2 out of 3 positive – positive predictive value of 93%



## 5. TO IMAGE OR NOT TO IMAGE?





# Imaging for Migraine is Rarely Necessary

## American Headache Society:

There is no necessity to do neuroimaging in patients with headaches consistent with migraine who have a normal neurologic examination, and there are no atypical features or red flags present.



Research Submissions |  Free Access

### Neuroimaging for Migraine: The American Headache Society Systematic Review and Evidence-Based Guideline

Randolph W. Evans MD , Rebecca C. Burch MD, Benjamin M. Frishberg MD, Michael J. Marmura MD, Laszlo J. Mechtler MD, Stephen D. Silberstein MD, Dana P. Turner MSPH, PhD

First published: 31 December 2019 | <https://doi.org/10.1111/head.13720> | Citations: 37

# RED FLAGS!

	Clinical feature(s)	Need to exclude
<b>S</b>	Systemic symptoms: fever, chills, myalgia, weight loss	Metastasis, infection
<b>N</b>	Neurological symptoms or deficits	Stroke, mass lesion, encephalitis
<b>O</b>	Older age at onset (> 50 years)	Temporal arteritis, glaucoma, mass lesion
<b>O</b>	Onset, thunderclap headache onset	Bleed
<b>P</b>	Papilloedema	Raised intracranial pressure
<b>P</b>	Positional	Intracranial hypotension
<b>P</b>	Precipitated by Valsalva manoeuvre or exertion	Raised intracranial pressure
<b>P</b>	Progressive headache or substantial pattern change	Any secondary cause




Lee VME, Ang LL, Soon DTL, Ong JJY, Loh VWK. The adult patient with headache. Singapore Med J. 2018 Aug;59(8):399-406. doi: 10.11622/smedj.2018094.

## Is it a Brain Tumor?

- 39,534 middle-aged women, free of any cancer
- 13,022 (32.9%) reported headache
- 7,291 classified as migraine
- Mean follow-up of 15.8 years
- 52 brain tumors
- **NO correlation** with any headache history, migraine, migraine aura, non-migraine headache, or more frequent migraines.



# Resources



AAN and AHS Patient and Provider Shared Decision-making tool

## IMAGING: DO I NEED AN IMAGING STUDY FOR MY HEADACHE?

AMERICAN ACADEMY OF NEUROLOGY

AMERICAN HEADACHE SOCIETY  
www.aahs.org/131788260135201611\_010




First Contact  
**HEADACHE**  
In Primary Care  
BY THE AMERICAN HEADACHE SOCIETY

AMERICAN HEADACHE SOCIETY

## How To Diagnose Migraine


Elizabeth Ekpo Cutter, MD



## Choosing Wisely

An initiative of the ABIM Foundation

American College of Radiology



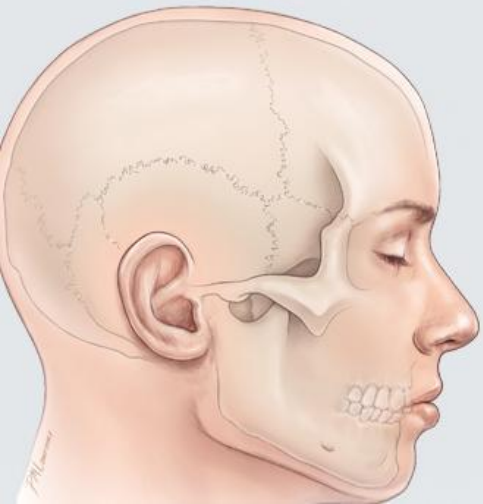
### Ten Things Physicians and Patients Should Question

---

**1 Don't do imaging for uncomplicated headache.**

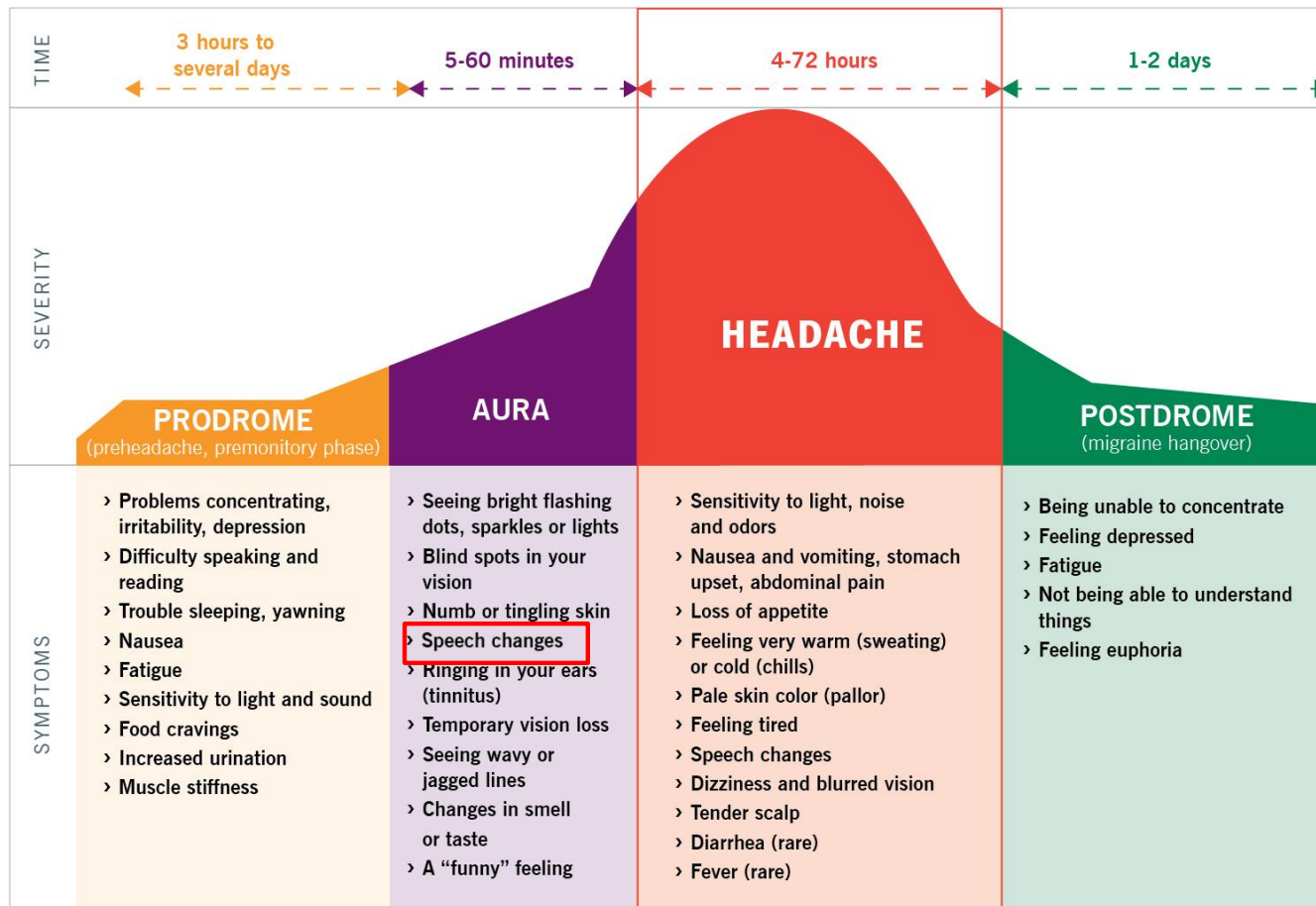
Imaging headache patients absent specific risk factors for structural disease is not likely to change management or improve outcome. Those patients with a significant likelihood of structural disease requiring immediate attention are detected by clinical screens that have been validated in many settings. Many studies and clinical practice guidelines concur. Also, incidental findings lead to additional medical procedures and expense that do not improve patient well-being.

## **6. NOT COMPLICATED, COMPLEX, OR A STROKE**





# The 4 Phases of a Migraine Headache



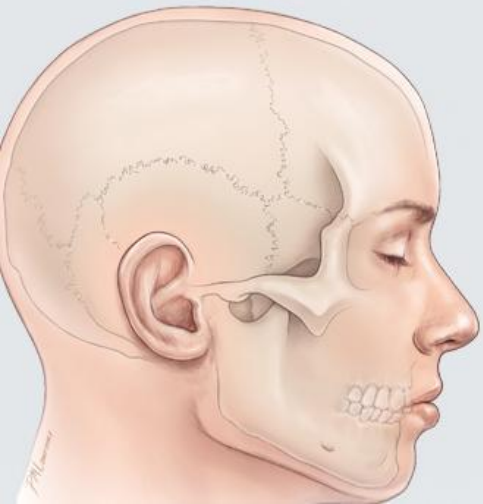
21-NEU-2074429



- AURA – speech, vision, or sensory changes
- Migraine + Aura + Motor weakness = hemiplegic migraine
  - Motor symptoms = **<72 hours** but can persist for weeks
- Can use triptans, rule out other contraindications
- Consider gepants and ditans
- Caution high dose estrogen ☐ stroke risk



## 7. BABIES CAN GET “MIGRAINE”





IHS Classification ICHE-3

## Infantile Colic



- Definition: Wessel's criteria crying for:
  - at least **3** hours a day,
  - at least **3** days a week,
  - for at least **3** weeks
- Infantile colic affects one in five babies
- Infants with colic have a **higher likelihood of developing migraine later in life.**
- Mothers with migraine  $\square$  **2.5 times** more likely to have infants with colic
- Fathers with migraine --> **2 times** more likely to have an infant with colic

Gelfand AA. Infant Colic. *Semin Pediatr Neurol*. 2016;23(1):79-82. doi:10.1016/j.spen.2015.08.003

Zhang D, Zhang Y, Sang Y, Zheng N, Liu X. The Relationship between Infant Colic and Migraine as well as Tension-Type Headache: A Meta-Analysis. *Pain Res Manag*. 2019 Jun 16;2019:8307982. doi: 10.1155/2019/830798



IHS Classification ICHD-3

## Abdominal Migraine

- Children with episodes of severe abdominal pain
- Symptom free in between attacks
- Severe  $\square$  affecting normal activities

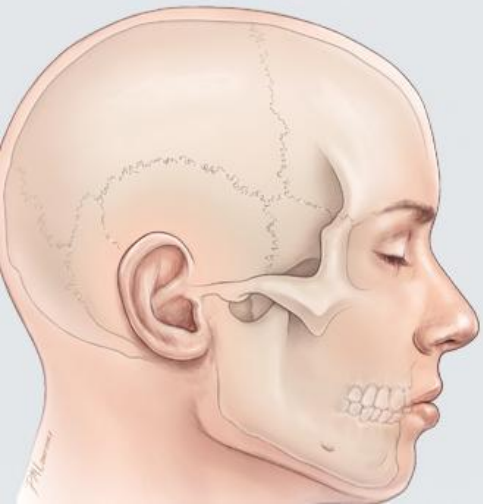
- Can come with migraine features:

- Pallor
- Anorexia

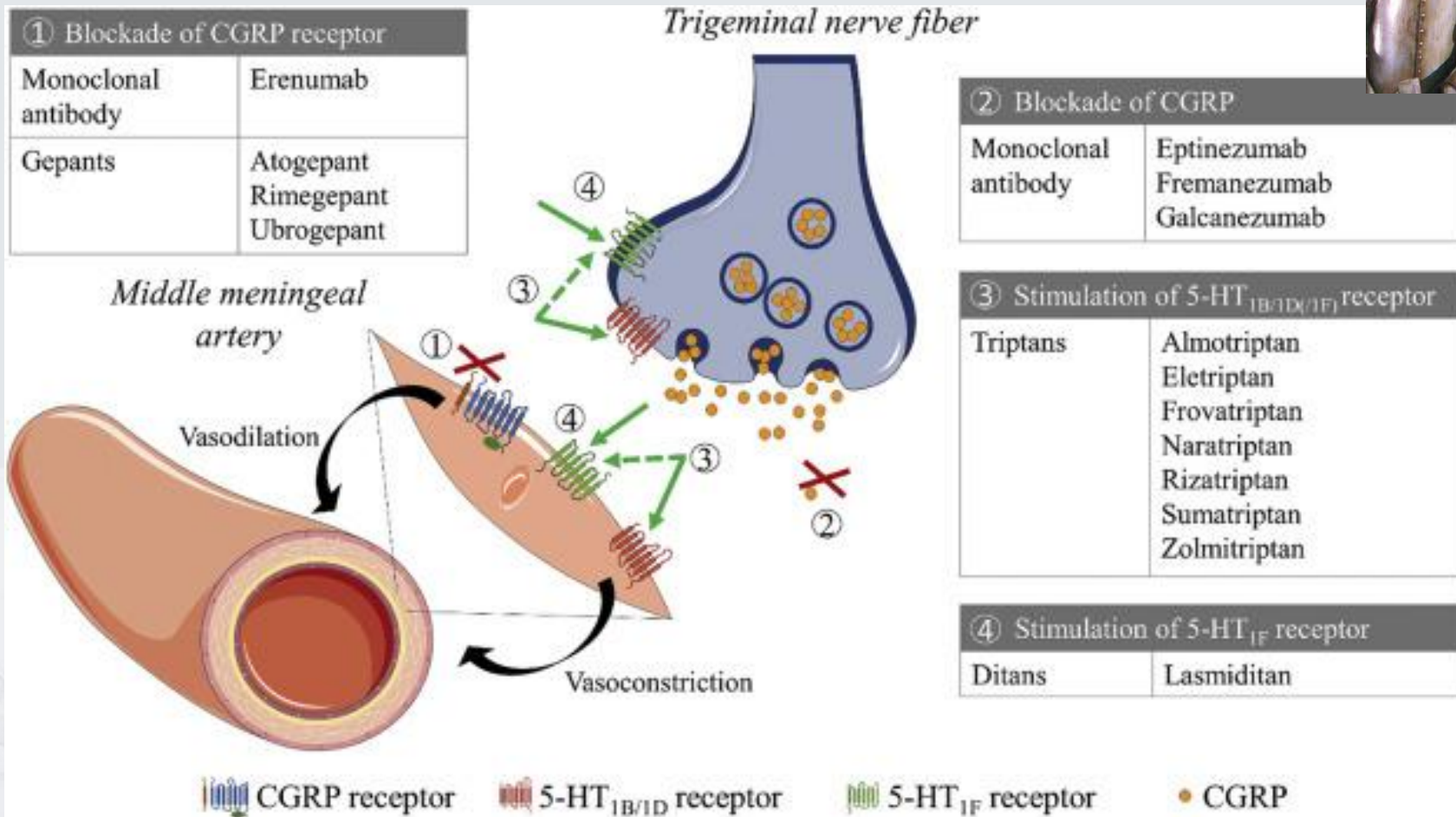
Angus-Leppan H, Saatci D, Sutcliffe A, Guiloff RJ. Abdominal migraine. *BMJ*. 2018 Feb 19;360:k179. doi: 10.1136/bmj.k179. PMID: 29459383.

- Nausea
- Vomiting

## 8. NEW ABORTIVE TREATMENTS



# Ditans, Gepants, and Monoclonal antibodies, oh my!



de Vries T, Villalón CM, MaassenVanDenBrink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. *Pharmacol Ther.* 2020 Jul;211:107528. doi: 10.1016/j.pharmthera.2020.107528.

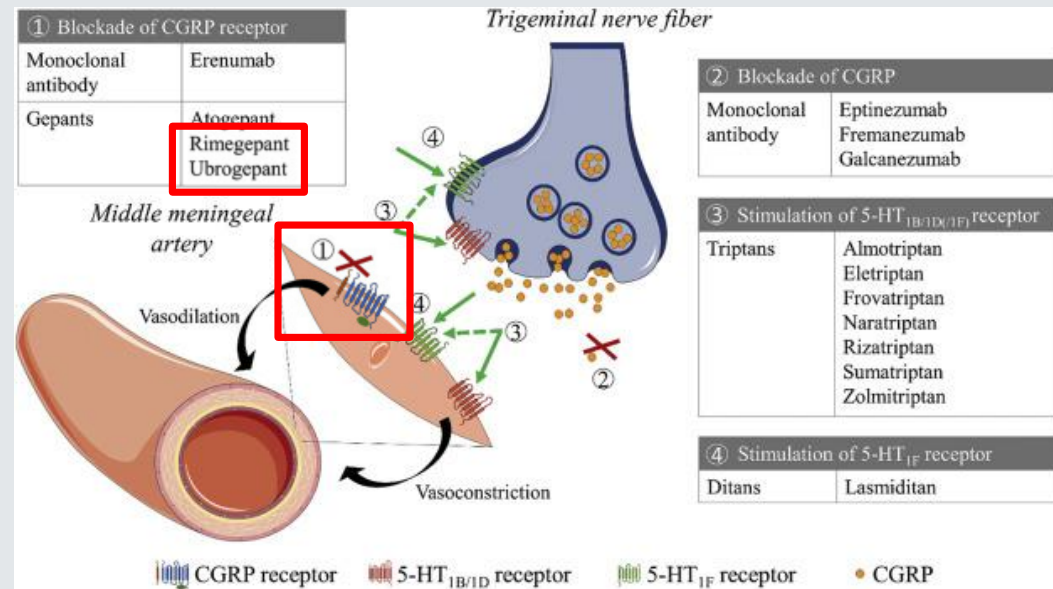
# Gepants - small molecule CGRP antagonist

- **Ubrogepant**

- 50 mg and 100 mg PO (max 200 mg/24hr)
- SE: nausea, somnolence
- No cardiovascular or medication overuse risk

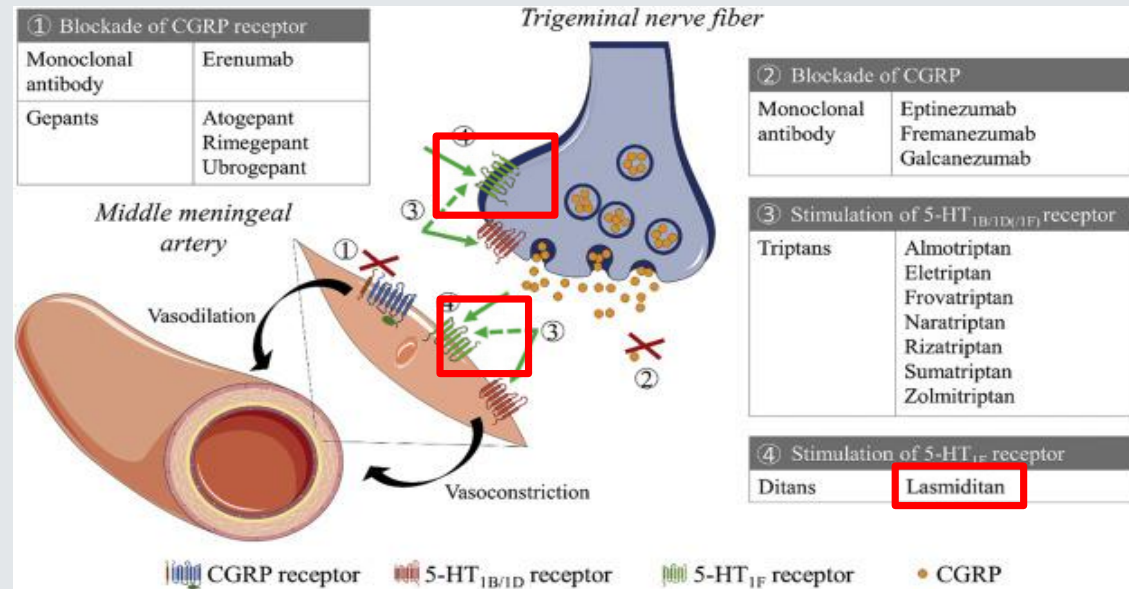
- **Rimegepant**

- 75 mg ODT (1 dose/24hr)
- SE: nausea, abdominal pain
- No cardiovascular or medication overuse risk



# Ditans – 5HT<sub>1F</sub> agonist

- Lasmiditan
  - 50 mg, 100 mg, and 200 mg (1 dose/24 hr)
  - Schedule V
  - Cannot drive for 8 hours
  - No cardiovascular risk
  - SE: dizziness, somnolence, paresthesias



# Ergotamine - 5-HT<sub>1D</sub>α/β agonists

- Dihydroergotamine mesylate
  - 0.725 mg per dose
  - Nasal spray with Precision Olfactory Delivery (POD) <sup>®</sup>
  - Contraindications – similar to triptans
  - SE: Dizziness, drowsiness, and paresthesias





## Devices

- Nerivio®
  - Arm-band Bluetooth device
  - 45 minutes, adjustable settings on app
  - Ages 12 and up
  
- Relivion®
  - Occipital and trigeminal nerve stimulator
  - 18 years and older

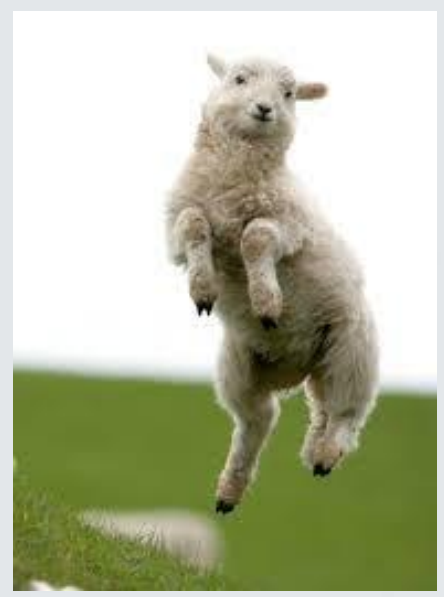
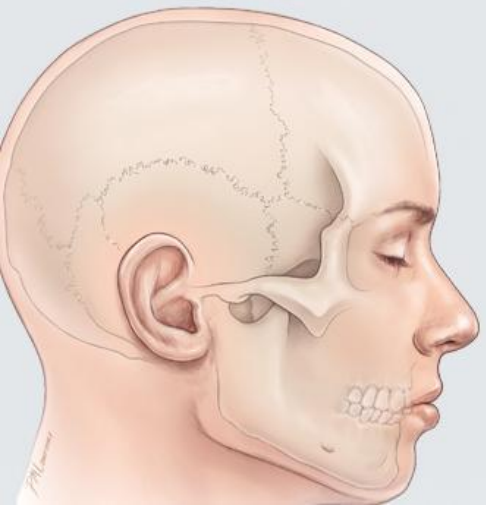


Nerivio.com



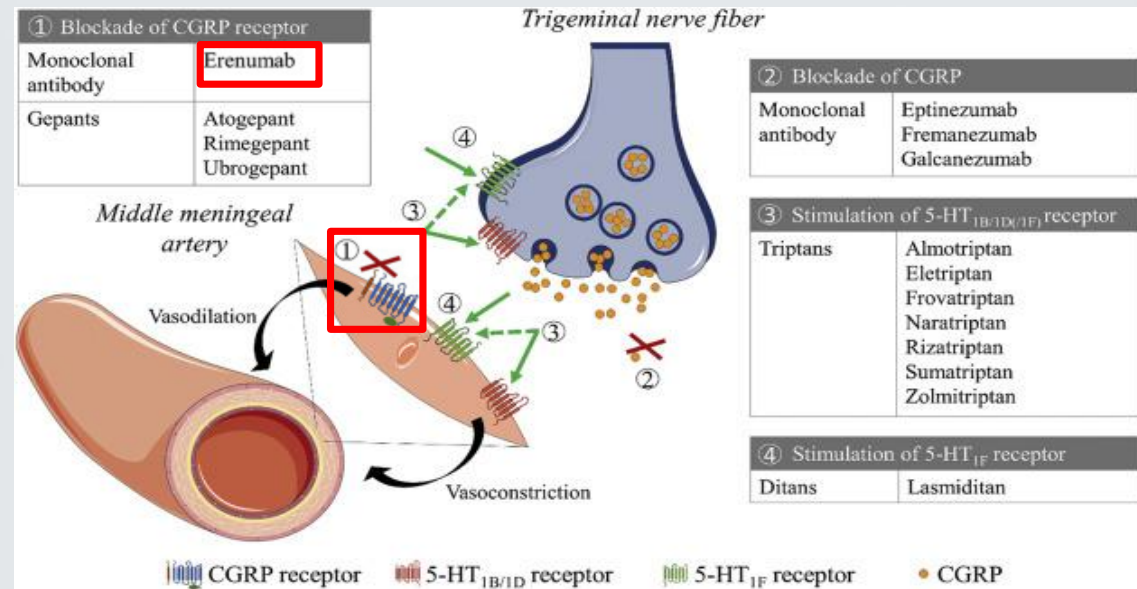
Relivion.com

## 9. NEW PREVENTATIVE TREATMENTS



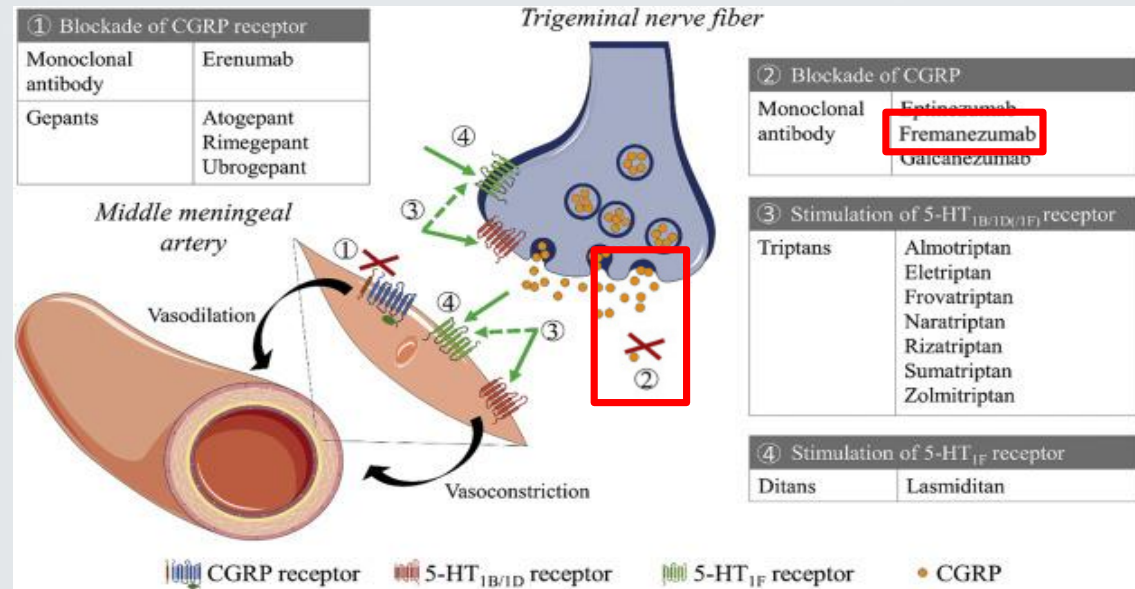
# Erenumab

- **Large molecule CGRP antibody receptor antagonist**
- Dosing
  - Two doses: 70 mg and 140mg monthly
  - Autoinjector
- Side effects:
  - Site reaction
  - Constipation
  - Cramps/spasms
  - HTN – added post-market



# Fremanezumab

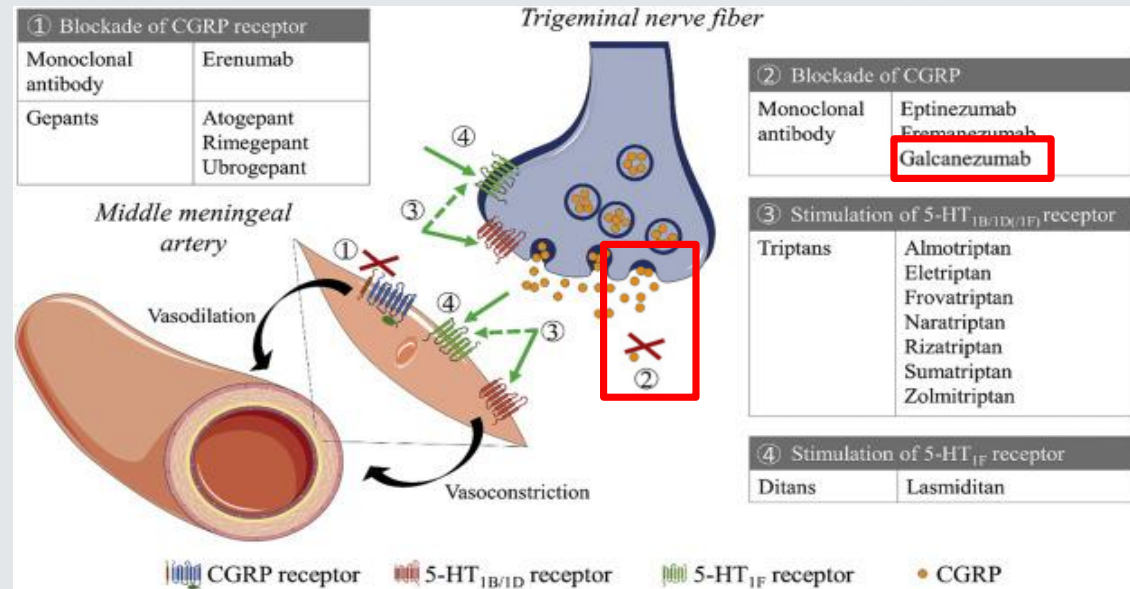
- **Large molecule CGRP antibody ligand antagonist**
- Dosing:
  - 225 mg/1.5 mL monthly or 3 injections quarterly
  - Pre-filled syringe or autoinjector
- Side effects:
  - Site reaction



# Galcanezumab

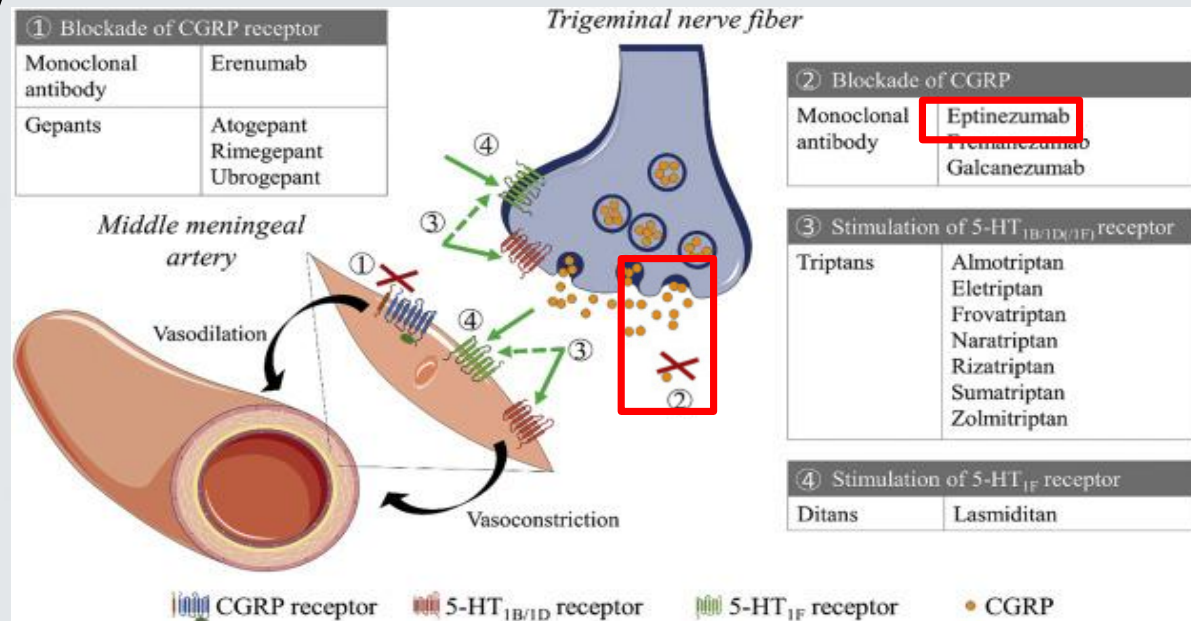
- **Large molecule CGRP antibody ligand antagonist**
- **Dosing:**
  - Month 1 (loading): two 120 mg injections
  - Month 2+ : one 120 mg injection
  - Prefilled syringe or autoinjector
- **Side effects:**
  - Site reaction

Other indication: episodic cluster headache abortive (300 mg)



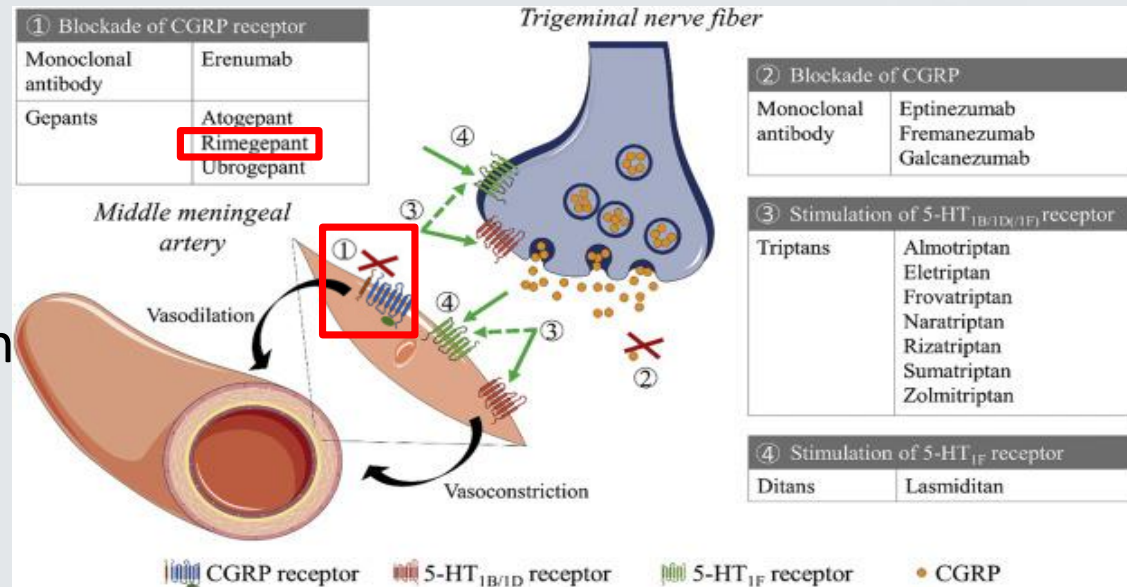
# Eptinezumab

- **Large molecule CGRP antibody ligand antagonist**
- Dosing:
  - 100 mg or 300 mg IV (30 minutes)
  - Every 3 months
- Side effects:
  - Nasopharyngitis
  - Hypersensitivity



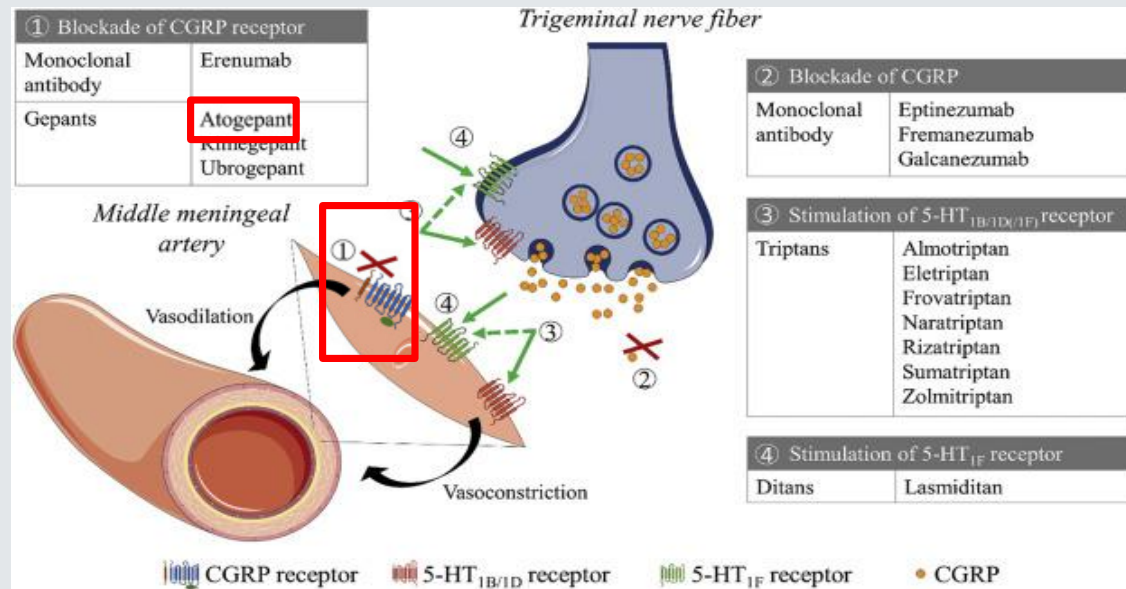
# Rimegepant

- Prevention also - 75 mg ODT (1 dose q48hr)
- SE: nausea
- No cardiovascular or medication overuse risk
- Episodic migraine only



# Atogepant

- Once daily oral
- 10 mg, 30 mg, and 60 mg
- SE: nausea, constipation, fatigue
- Episodic migraine only





# Putting it all Together

Received: 16 March 2021 | Accepted: 9 May 2021  
DOI: 10.1111/head.14159

## AHS CONSENSUS STATEMENT

### The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice

Jessica Ailani MD<sup>1</sup> | Rebecca C. Burch MD<sup>2</sup> | Matthew S. Robbins MD<sup>3</sup> | on behalf of the Board of Directors of the American Headache Society<sup>1</sup>

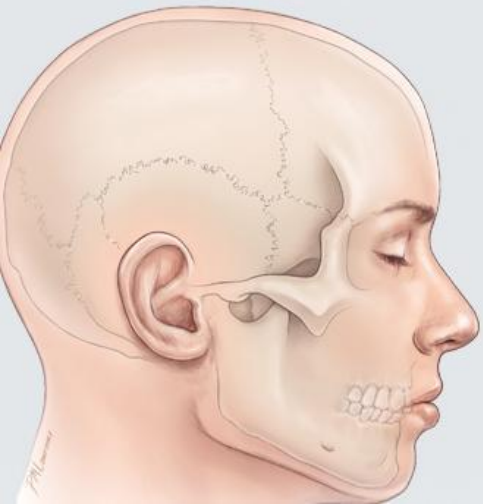
TABLE 2 Acute treatments with evidence of efficacy in migraine<sup>19,21, 23,24</sup>

Established efficacy <sup>a</sup>	Probably effective
Migraine-specific	
Triptans	Ergotamine
Ergotamine derivatives	Other forms of dihydroergotamine
Gepants	
Lasmiditan	
Nonspecific	
NSAIDs: aspirin, celecoxib oral solution, diclofenac, ibuprofen, naproxen	NSAIDs: flurbiprofen, ketoprofen, IV and IM ketorolac
Combination analgesic: acetaminophen + aspirin + caffeine	IV magnesium <sup>b</sup>
	Isometheptene-containing compounds
	Antiemetics: chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine

TABLE 3 Medications with evidence of efficacy in migraine prevention<sup>2,20,85</sup>

Established efficacy <sup>b</sup>		Probably effective <sup>c</sup>	
Oral	Parenteral	Oral	Parenteral
Candesartan	Eptinezumab	Amitriptyline	OnabotulinumtoxinA + CGRP mAb <sup>d,e</sup>
Divalproex sodium	Erenumab	Aterolol	
Ergotriptan <sup>f</sup>	Gremezumab	Lisinopril	
Metoprolol	Galcanezumab	Memantine	
Propranolol	OnabotulinumtoxinA <sup>e</sup>	Nadolol	
Luminal		Venlafaxine	
Topiramate			
Valproate sodium			

## **10. UP AND COMING TREATMENTS**



## Hot off the Press

- Celecoxib oral solution – now available
- Zavegepant – intranasal abortive – pending approval
- Zolmitriptan - topical patch – pending approval
- Rizatriptan – oral film – pending approval
- Meloxicam/rizatriptan – oral – pending approval



AMERICAN ACADEMY OF NEUROLOGY

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A Virtual Experience

September - November 2021 | Virtual

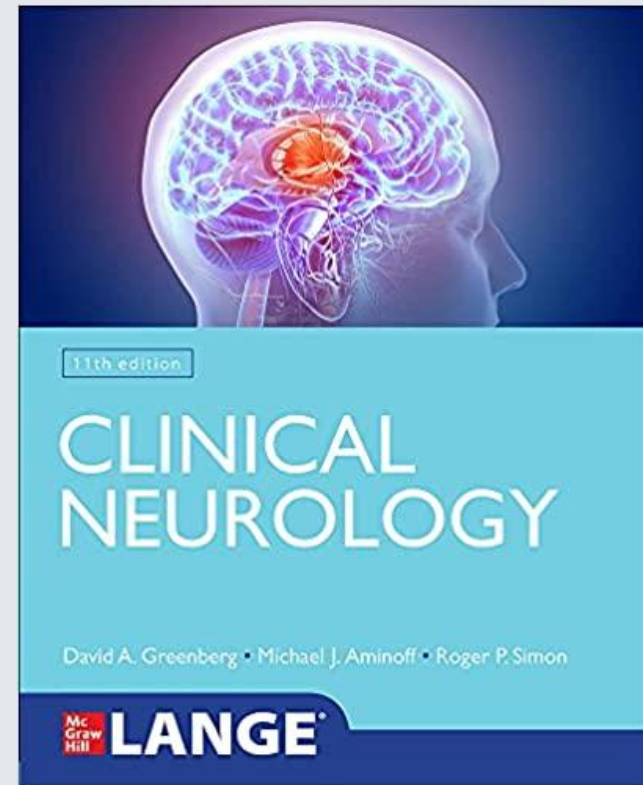
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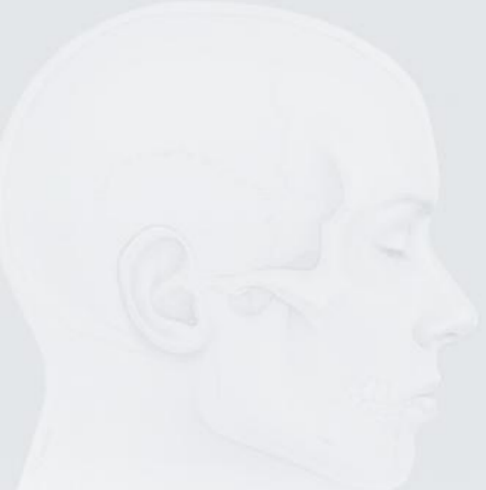
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First Contact  
**HEADACHE**  
*In Primary Care*  
BY THE AMERICAN HEADACHE SOCIETY



## Almost the End!

- Be an active listener!
- Start patients on treatment!
- Take a seat!
- Use the Force: Don't order imaging unless you're worried
- Remember why you became a PA



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