Optum Health Education™

Current Approach to treatment of Migraine with the advent of CGRP therapies

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Durham, NC

Date 3/27/2024

Disclosures

- Optum
- Eli Lilly and Company
- No other disclosures

Lecture Objectives

- ***Discuss migraine pathophysiology and recognize symptoms to differentiate migraine from other headache disorders.***
- *Compare traditional migraine therapies with anti-CGRP targeted therapies to enhance decision-making in acute and preventive treatment.*
- *Apply anti-CGRP therapies to a broader spectrum of headache and facial-pain conditions, considering the evolving treatment strategies in the current anti-CGRP era.*

Review Source

Ailani J, Burch RC, Robbins MS; the Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021; 61: 1021–1039. https://doi.org/10.1111/head.14153

International Classification of Headache Disorders(ICHD-3)- Migraine without and with aura

Migraine without aura 1.1

Diagnostic criteria:

1.At least five attacks[1] fulfilling criteria B-D

2.Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)[2;3]

3.Headache has at least **two** of the following four characteristics:

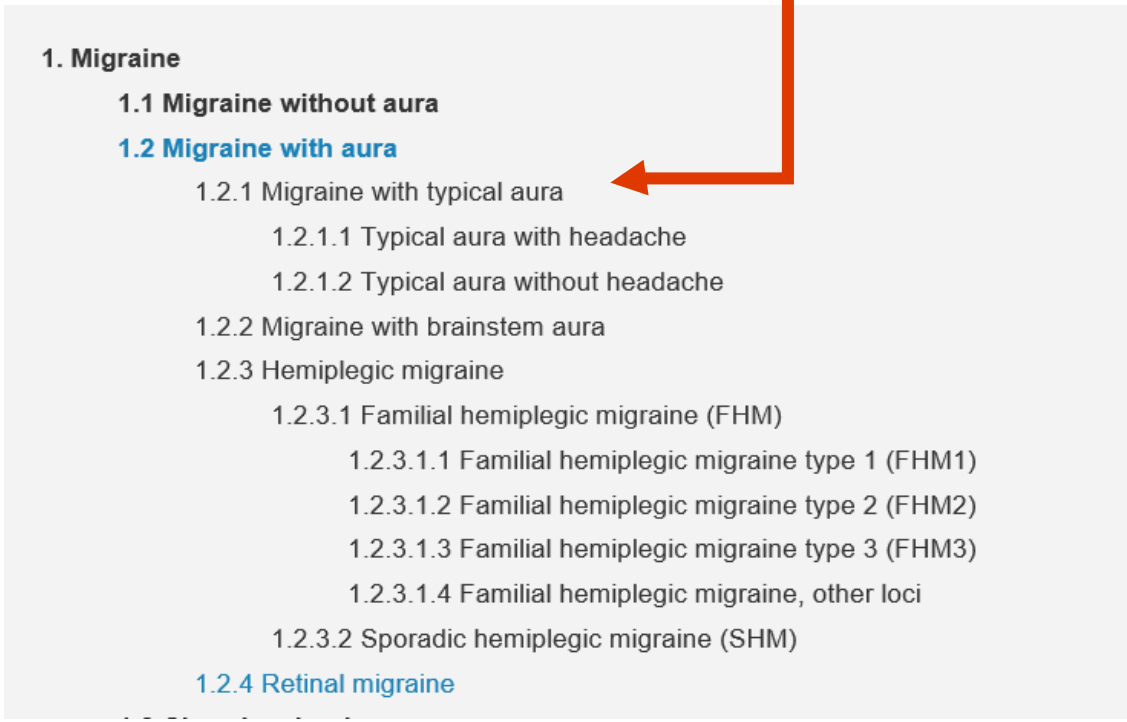
1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

4.During headache at least one of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

5.Not better accounted for by another ICHD-3 diagnosis

1. fully reversible visual, sensory and/or speech/language symptoms
2. no motor, brainstem or retinal symptoms.



https://ichd-3.org/1-migraine/

ICHD-3 Episodic versus Chronic Migraine

Chronic Migraine

(A) Migraine-like or tension-type-like headache on **≥15 days/month** for >3 months that fulfill criteria B and C

(B) Occurring in a patient who has had at least five attacks fulfilling criteria B–D for migraine without aura and/or criteria B and C for migraine with aura

(C) On **≥8 days/month** for >3 months, fulfilling any of the following:

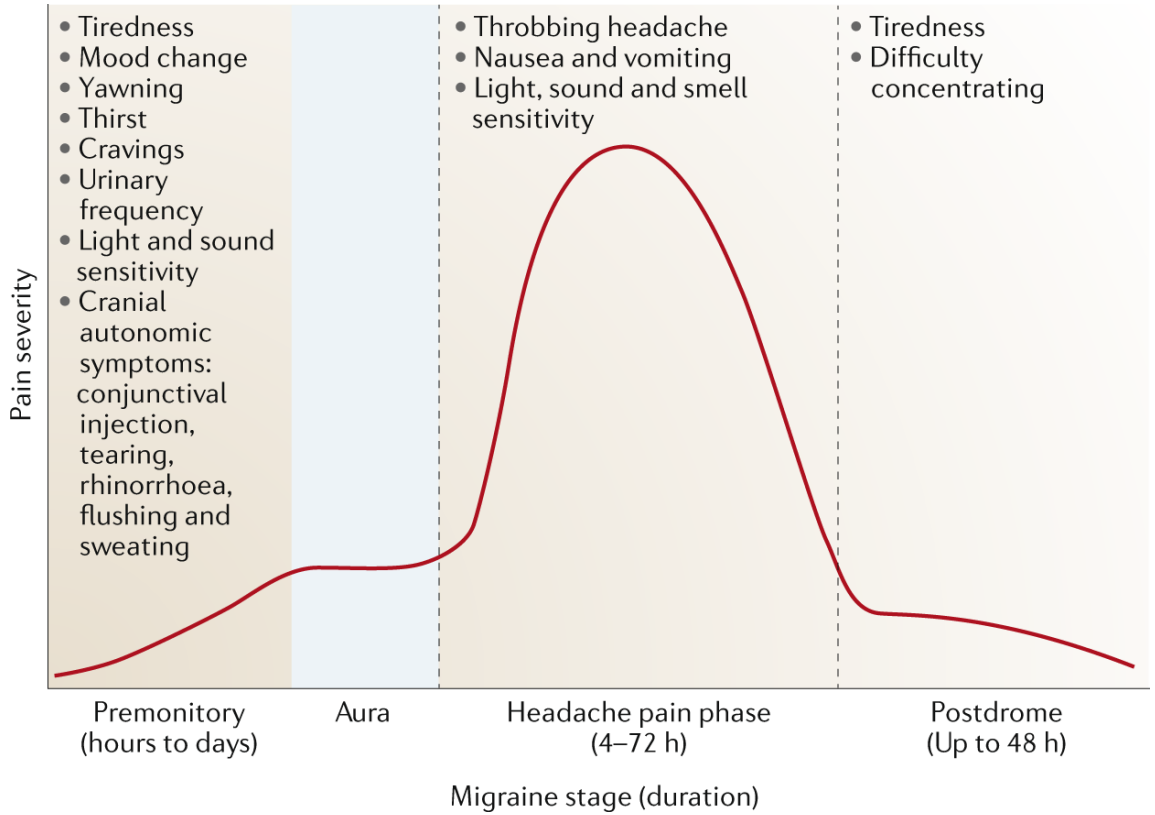
1. Criteria C and D for migraine without aura
2. Criteria B and C for migraine with aura
3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

(D) Not better accounted for by another diagnosis

https://ichd-3.org/1-migraine/

Migraine Phases

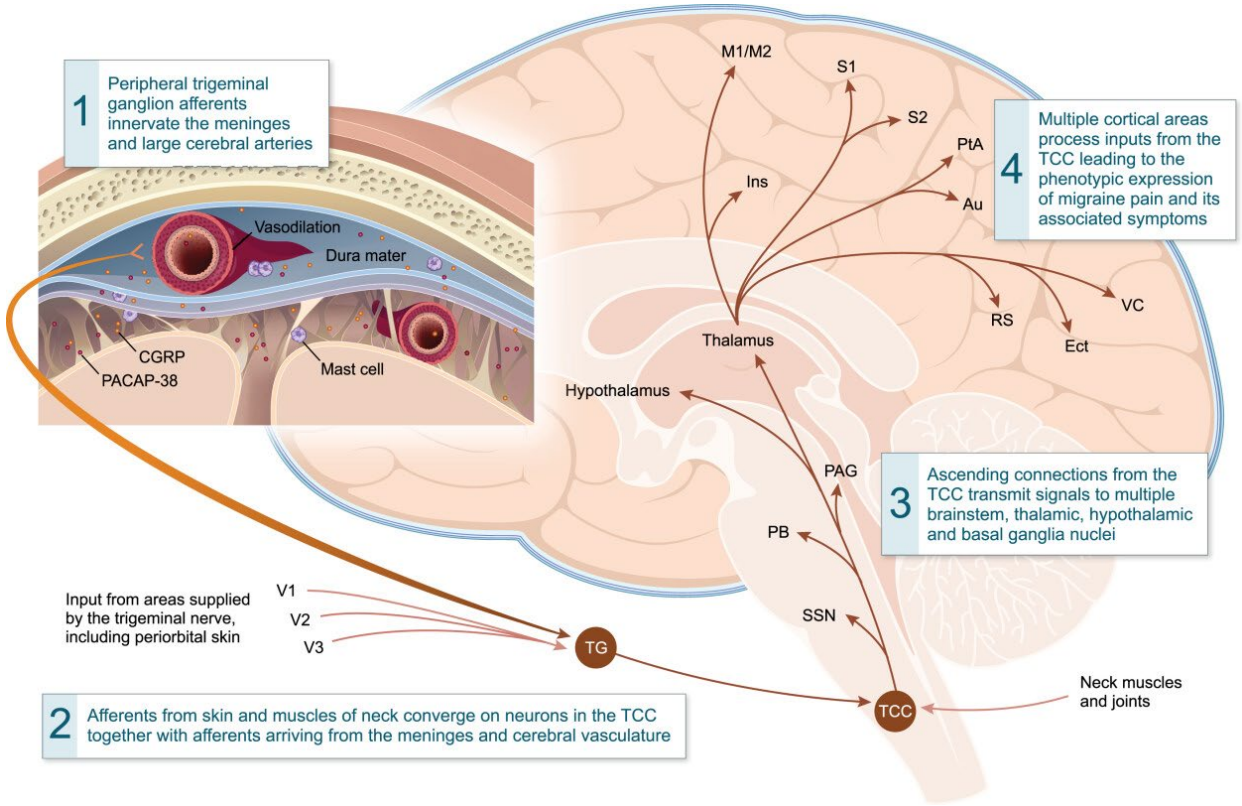
- Premonitory
- Aura
- Headache
- Postdrome



Karsan, N., Goadsby, P.J. Biological insights from the premonitory symptoms of migraine. *Nat Rev Neurol* **14**, 699–710 (2018). https://doi.org/10.1038/s41582-018-0098-4

Migraine Pathophysiology

- **“Vascular Hypothesis”**
- **Genetic Predisposition and Environmental Factors**
- **Peripheral Connections**
  - Plasma Protein extravasation
  - Central Sensitization
  - Neuropeptide release
- **Central Connections**
  - Trigeminocervical Complex
- **Higher Order Processing**
  - Thalamus
  - Periaqueductal Gray(PAG)
  - Posterior Hypothalamic Grey



Goadsby PJ. Pathophysiology of migraine. Ann Indian Acad Neurol. 2012 Aug;15(Suppl 1):S15-22. doi: 10.4103/0972-2327.99993. PMID: 23024559; PMCID: PMC3444225.

Dodick DW. A Phase-by-Phase Review of Migraine Pathophysiology. Headache. 2018 May;58 Suppl 1:4-16. doi: 10.1111/head.13300. PMID: 29697154.

Lecture Objectives

- *Discuss migraine pathophysiology and recognize symptoms to differentiate migraine from other headache disorders.*
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Basics: Acute Treatment Approach

- Acute treatment strategies:
  - **Maximal therapy at onset("Stratified")**
  - Step-care-across
  - Step-care-within
- Prevention medications
  - >2 headache days/week
  - Or missing work/life frequently because of HA

Lipton RB, Stewart WF, Stone AM, Láinez MJA, Sawyer JPC. Stratified Care vs Step Care Strategies for Migraine: The Disability in Strategies of Care (DISC) Study: A Randomized Trial. *JAMA.* 2000;284(20):2599–2605. doi:10.1001/jama.284.20.2599

Basic: Acute Treatment Approach

- Acetaminophen
  - Actually slightly better than placebo in RCT
- Sleep
- Aspirin (the original headache medication)
  - Bayer's assets auctioned after WWI, Aspirin acquired by US company at that time

Basic: Acute Treatment Approach

- NSAIDs
  - Cambia (Diclofenac potassium) FDA indicated for migraine
  - Ibuprofen 800 mg
  - Naproxen 500 mg
  - Ketorolac NS (Sprix –relatively difficult to prescribe but approved for migraine)
  - Etodolac
  - Celecoxib oral solution(Elyxyb)

Basics: Acute Treatment Approach

- NSAIDs Risks
  - GI side effects
  - Bleeding
  - Increased risk of stroke or MI with long-term use
  - Questionable in pregnancy(preferably not after 20 weeks)

Basics: Acute Treatment Approach

- Triptans
  - All FDA indicated for treatment of migraine
  - No studies suggest one product is better
  - All bind $5HT_{1b/1d}$ receptor (serotonin) except one
  - Contra-indicated after MI, stroke
  - Mild concerns with pregnancy
    - 2 studies suggest safe(2011,2013)
    - 1 study suggests slight increase risk of miscarriage(2021)
- Side effects infrequent: drowsiness, chest pressure

Bérard, A., Strom, S., Zhao, JP. *et al.* Dihydroergotamine and triptan use to treat migraine during pregnancy and the risk of adverse pregnancy outcomes. *Sci Rep* **11,** 19302 (2021). https://doi.org/10.1038/s41598-021-97092-y

Shorter half-life triptans

- Sumatriptan (Imitrex)
  - Tablet, injection, nasal spray
- Rizatriptan (Maxalt)
  - Tablet, dissolving wafer
- Zolmatriptan (Zomig) Tablet, NS
- Eletriptan (Relpax)
- Almotriptan (Axert)

Longer half-life Triptans

- Naratriptan (Amerge) ~12 hour half life
- Frovatriptan (Frova) ~25 hour half life

“Ditans”

- “Ditans”-agonist of 5HT1f receptor, no cardiac effects
- Reyvow (lasmiditan)
  - Scheduled (IV)
  - Significant cognitive side effects (warning in package insert no driving for 8 hours)

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Hum Psychopharmacol. 2020 Sep; 35(5): e2732.
Published online 2020 May 25. doi: 10.1002/hup.2732
PMCID: PMC7539914
PMID: 32449213

Effects of lasmiditan on simulated driving performance: Results of two randomized, blinded, crossover studies with placebo and active controls

Eric M. Pearlman,[1] Darren Wilbraham,[1] Ellen B. Dennehy,[1,2] Paul H. Berg,[1] Max Tsai,[1] Erin G. Doty,[1] and Gary G. Kay[3]

Dihydroergotamine(DHE)

- Binds to 5-HT1Dα and 5-HT1Dβ receptors, serotonin 5-HT1A, 5-HT2A, and 5-HT2C receptors, noradrenaline α2A, α2B and α, receptors, and dopamine D2L and D3 receptors

- DHE dihydroergotamine NS (migranal)
  - Somewhat less effective than IV, less nausea
- Caffergot ~$550/40 tablets in US
  - 1 mg ergotamine 100 mg caffeine
- Ergotamine sub lingual (Ergomar)
  - ~$1200/20 tablets (US)
- Dihydroergotamine NS(Trudhesa)
  - Approved in September 2021
  - $850


Journal of Clinical Neurology http://thejcn.com

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J Clin Neurol. 2006 Dec; 2(4): 279–282. PMCID: PMC2854981

Published online 2006 Dec 20. doi: 10.3988/jcn.2006.2.4.279 PMID: 20396534

Ergotism With Ischemia In All Four Extremities: A Case Report

Seok-Young Jeong, M.D., Eui-Seong Lim, M.D., Byoung-Soo Shin, M.D., Man-Wook Seo, M.D., Young-Hyun Kim, M.D., Hyo-Sung Kwak, M.D.,* Gyung-Ho Chung, M.D.,* and Seul-Ki Jeong, M.D.

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Anti-Emetics

- D2 receptor antagonists
- Effective for Head pain, nausea, and photophobia in ER trials (off-label)
- Prochlorperazine (Compazine) 10 mg
- Promethazine (Phenergan) 12-25 mg
- Metoclopramide (Reglan) 10 mg
- Prochlorperazine+Benadryl superior to hydromorphone in ED trial (IV use)

Neurology. 2017 Nov 14; 89(20): 2075–2082.
doi: 10.1212/WNL.0000000000004642
PMCID: PMC5711508
PMID: 29046364

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

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

Basics: Prevention Therapy Approach

FDA-indicated

- Topiramate (slow increase to 100 mg/day)
  - Tingling, weight loss
  - Acute angle-closure glaucoma
  - Kidney stones
  - Cognitive side effects 6-10%
- Depakote 500-1000 mg/day
  - Weight gain 10%
  - Teratogenic
- Propranolol 40-160 mg/day
  - Fatigue, hypotension
  - Other beta-blockers have similar effectiveness.

Loder E, Rizzoli P. Pharmacologic Prevention of Migraine: A Narrative Review of the State of the Art in 2018. Headache. 2018 Nov;58 Suppl 3:218-229. doi: 10.1111/head.13375. Epub 2018 Aug 23. PMID: 30137671.

Basics: Prevention Therapy Approach

“Standard” used off-label

- Amitriptyline 10-40 mg/day
  - Weight gain, grogginess, dry mouth, palpitations
  - Nortriptyline & other TCA probably effective
- Verapamil 120-480 mg/day
  - Constipation ~10%
- Venlafaxine 37.5-150 mg/day
  - superior to verapamil per AHS based on trial quality

Loder E, Rizzoli P. Pharmacologic Prevention of Migraine: A Narrative Review of the State of the Art in 2018. Headache. 2018 Nov;58 Suppl 3:218-229. doi: 10.1111/head.13375. Epub 2018 Aug 23. PMID: 30137671.

Basics: Prevention Therapy Approach

- Nortriptyline (few trials)
- Trazodone (few trials, may worsen headaches)
- SSRI's not effective (2 randomized trials in 1990's)
- Duloxetine-no RCTs, 1 or 2 open label trials

Loder E, Rizzoli P. Pharmacologic Prevention of Migraine: A Narrative Review of the State of the Art in 2018. Headache. 2018 Nov;58 Suppl 3:218-229. doi: 10.1111/head.13375. Epub 2018 Aug 23. PMID: 30137671.

Basics: Prevention Therapy Approach

Older meds used less often in CGRP era:

- Zonisamide 100-300 mg/day
- Imipramine 25-50 mg/day
- Candesartan 4-12 mg/day (hypotension)
- Lisinopril 5-20 mg/day (1 study)
- Gabapentin 600-1800 mg/day
- Pregabalin 150-600 mg/day

Loder E, Rizzoli P. Pharmacologic Prevention of Migraine: A Narrative Review of the State of the Art in 2018. Headache. 2018 Nov;58 Suppl 3:218-229. doi: 10.1111/head.13375. Epub 2018 Aug 23. PMID: 30137671.

CGRP….

- What is Calcitonin Gene-Related Peptide(CGRP)?
- About anti-CGRP medications used for acute therapy
- About anti-CGRP medications used for prevention therapy
- Anti-CGRP medications used for acute and prevention therapy

What is CGRP?

- CGRP is a 37-amino acid peptide and is primarily restricted to C and Aδ sensory fibers.
- The two forms of αCGRP and βCGRP are derived from genes at different sites on chromosome 11.
- αCGRP and βCGRP share >90% homology and differ by three amino acids
- αCGRP is primarily found in the central and peripheral nervous system. While βCGRP is found mainly in the GI system.
- Potent vasodilator

CGRP in Migraine

Cephalalgia
Volume 30, Issue 10, October 2010, Pages 1179-1186

https://doi.org/10.1177/0333102410368444

Original Article

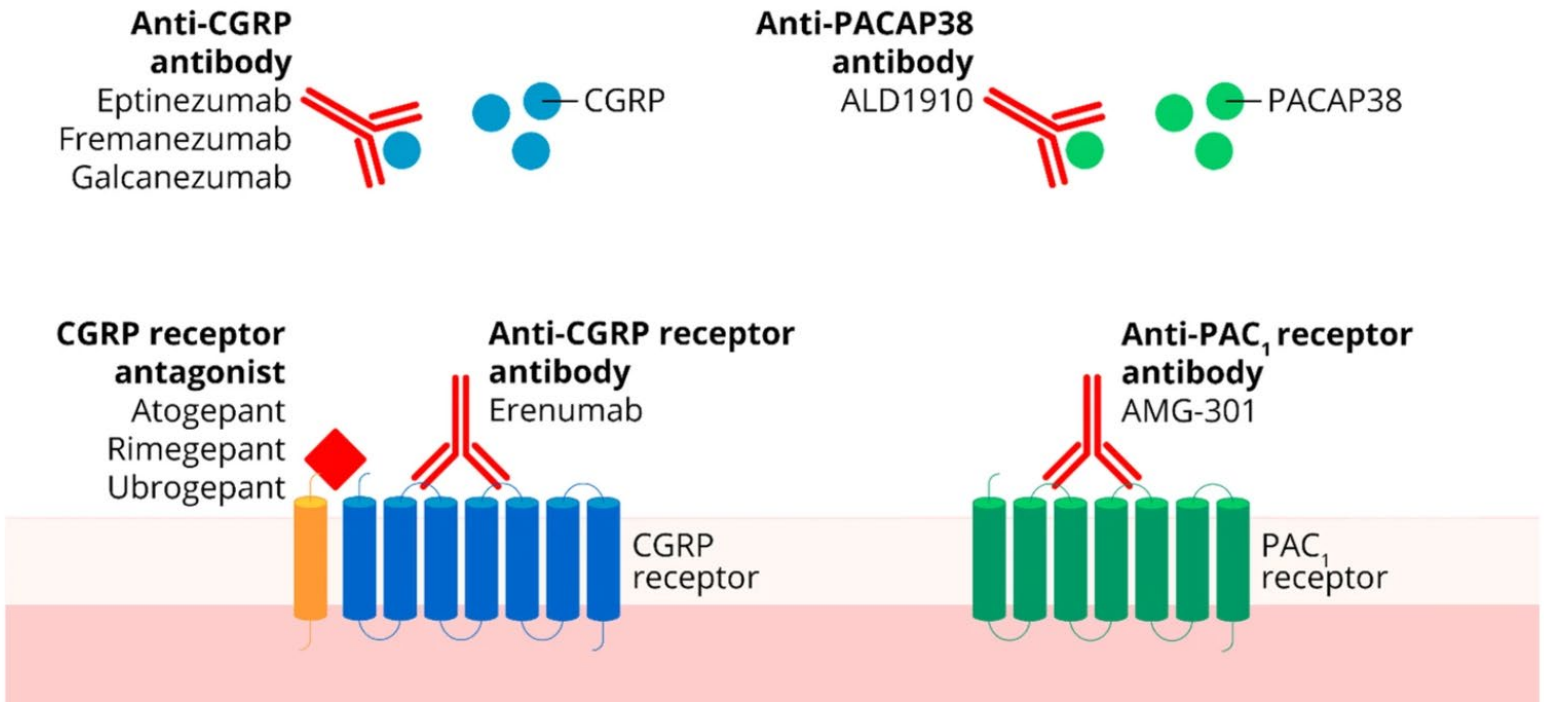
Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura

Jakob Møller Hansen, Anne Werner Hauge, Jes Olesen, and Messoud Ashina

What kind of anti-CGRP therapies are there? Gepants versus Antibodies?

Fig. 3

From: Therapeutic novelties in migraine: new drugs, new hope?



Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: new drugs, new hope? J Headache Pain. 2019 Apr 17;20(1):37. doi: 10.1186/s10194-019-0974-3. Erratum in: J Headache Pain. 2019 May 17;20(1):55. PMID: 30995909; PMCID: PMC6734360.

CGRP blocking prevention therapy antibodies

- **CGRP Blocking Ab (all FDA indicated)**
- **Aimovig**(erenumab-aooe) **70 or 140 mg/month**
  --Single injection every 28 days
  --Blocks CGRP receptor
- **Emgality**(fremanezumab-vfrm) **120 mg/month**
  --Loading dose 240 mg, then 120 mg every 28 days
  --Binds and depletes circulating CGRP
  --Also FDA indicated for cluster headache
- **Ajovy**(galcanezumab-glnm) **225 mg/month or 675 mg quarterly**
  --Binds and depletes circulating CGRP
- **Vyepti** (eptinezumab-jjmr) **100-300 mg quarterly**
  --Binds and depletes circulating CGRP

Metrics

- Mean Monthly Migraine Days(Average over 28 days)
- Most Bothersome Symptoms(Nausea, photophobia, phonophobia)
- Responder rate(50% goal reduction)

Anti-CGRP Antibody Therapies

50% MHD responder rate: 40% at 3 months

Aimovig (erenumab-aooe)

- Monoclonal Ab against CGRP Receptor
- Few side effects
  - Latex sensitivity, hypersensitivity, constipation, muscle aches, hypertension(post-marketing setting), hair loss
- Approved May 2018

Table 1: Adverse Reactions Occurring with an Incidence of at Least 2% for Either Dose of AIMOVIG and at Least 2% Greater than Placebo During the First 3 Months in Studies 1, 2, and 3

Adverse Reaction	AIMOVIG 70 mg Once Monthly N = 787 %	AIMOVIG 140 mg Once Monthly N = 507 %	Placebo N = 890 %
Injection site reactions[a,b]	6	5	3
Constipation	1	3	1
Cramps, muscle spasms	< 1	2	< 1

[a] Injection site reactions include multiple adverse reactions related terms, such as injection site pain and injection site erythema.
[b] The rate of injection site reactions reported in Table 1 is with the prefilled syringe.

In Studies 1, 2, and 3, 1.3% of patients treated with AIMOVIG discontinued double-blind treatment because of adverse events. The most frequent injection site reactions were injection site pain, injection site erythema, and injection site pruritus.

Chhabra N, Mead-Harvey C, Dodoo CA, et al. Blood pressure elevation in erenumab-treated patients with migraine: A retrospective real-world experience. *Headache*. 2024; 00: 1-10. doi:10.1111/head.14679

Anti-CGRP Antibody Therapies

Ajovy(fremanezumab-vfrm)
Ab binds CGRP
50% MHD responder rate 47%
Quarterly dosing available

Emgality(galcanezumab-glnm)
Ab binds CGRP
50% MHD responder rate 62%
Loading dose

Table 1: Adverse Reactions Occurring in Adults with Migraine with an Incidence of at least 2% for EMGALITY and at least 2% Greater than Placebo (up to 6 Months of Treatment) in Studies 1, 2, and 3

Adverse Reaction	EMGALITY 120 mg Monthly (N=705) %	Placebo Monthly (N=1451) %
Injection site reactions[a]	18	13

[a] Injection site reactions include multiple related adverse event terms, such as injection site pain, injection site reaction, injection site erythema, and injection site pruritus.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761089s002lbl.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761063s000lbl.pdf

Vyepti(Eptinezumab-jjmr)

- Designed for rapid onset and sustained activation of full preventative benefit
- Benefits have been shown to begin within 24 h of the first administration
- Delivered IV: 100% bioavailability

Table 1. Adverse Reactions Occurring with an Incidence of at Least 2% for VYEPTI and at Least 2% Greater than Placebo in Studies 1 and 2

Adverse Reactions	VYEPTI 100 mg N=579 %	VYEPTI 300 mg N=574 %	Placebo N=588 %
Nasopharyngitis	6	8	6
Hypersensitivity reactions*	1	2	0

* Hypersensitivity reactions includes multiple related adverse event terms, such as hypersensitivity, pruritus, and flushing/hot flush that occurred on the day of dosing.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761119s000lbl.pdf

Winner PK, McAllister P, Chakhava G, Ailani J, Ettrup A, Krog Josiassen M, Lindsten A, Mehta L, Cady R. Effects of Intravenous Eptinezumab vs Placebo on Headache Pain and Most Bothersome Symptom When Initiated During a Migraine Attack: A Randomized Clinical Trial. JAMA. 2021 Jun 15;325(23):2348-2356. doi: 10.1001/jama.2021.7665. PMID: 34128999; PMCID: PMC8207242.

List of monoclonal antibodies that modulate CGRP

Table 1.

Monoclonal antibodies that modulate CGRP.

Generic name	Sponsor	Patient population	Target	Route	Dose (mg)	IgG Type	$t_{1/2}$ (days)	T_{max}
Eptinezumab[a] (ALD403)	Alder Biopharmaceuticals	Episodic and chronic migraine	CGRP-α CGRP-β	IV	30 mg QTLY 100 mg QTLY 300 mg QTLY	IgG 1	26	3 hours
Erenumab[b] (AMG 334)	Novartis and Amgen	Episodic and chronic migraine	CGRP receptor	SC	70 mg QM 140 mg QM	IgG 2	28	6 days
Fremanezumab[b] (TEV-48125)	Teva Pharmaceutical Industries	Episodic and chronic migraine	CGRP-α CGRP-β	SC	225 mg QM with 675 mg LD	IgG 2	32	5 days
Galcanezumab[b] (LY2951742)	Eli Lilly and Company	Episodic and chronic migraine	CGRP-α CGRP-β	SC	240 mg LD followed by 120 mg QM	IgG 4	27	5 days

CGRP: calcitonin gene-related peptide; IV: intravenous; SC: subcutaneous; QM: once monthly; LD: loading dose; QTLY: quarterly; $t_{1/2}$: half-life; T_{max}: time of maximum observed drug concentration.

Kielbasa W, Helton DL. A new era for migraine: Pharmacokinetic and pharmacodynamic insights into monoclonal antibodies with a focus on galcanezumab, an anti-CGRP antibody. Cephalalgia. 2019 Sep;39(10):1284-1297. doi: 10.1177/0333102419840780. Epub 2019 Mar 27. PMID: 30917684; PMCID: PMC6710614.

CGRP blocking acute and prevention therapy gepants

“gepants”-small molecules blocking CGRP receptor

- Ubrelvy (Ubrogepant) 50-100 mg single dose

-- FDA approved in Jan 2020

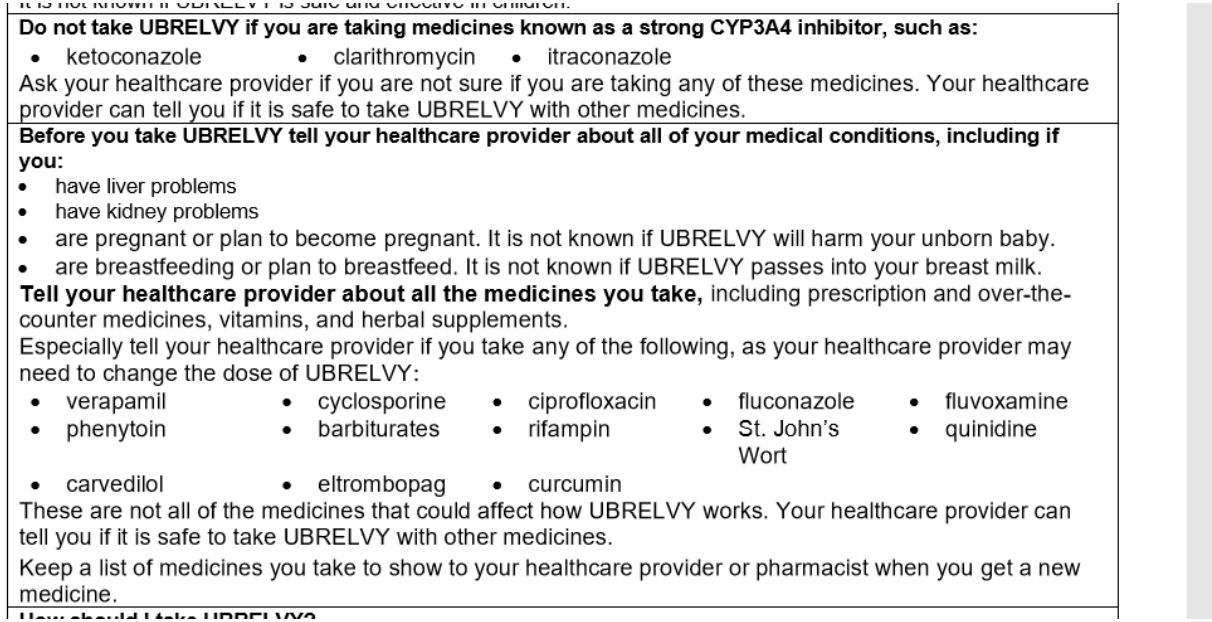
-- Metabolized by CYP3A4 which is inhibited mildly by verapamil (50 mg dose only) and strongly by antifungals.

- Nurtec (rimegepant)- Also metabolized by CYP3A4
- Qulipta (atogepant)
- Zavzepret (Zavegepant)

-- Avoid use with OATP inhibitors

Ubrelvy(ubrogepant)

- Do not take medications that are strong CYP3A4 inhibitors with ubrelvy
- 4% nausea, 3% sleepiness(at least 2% and greater than placebo)



It is not known if UBRELVY is safe and effective in children.

Do not take UBRELVY if you are taking medicines known as a strong CYP3A4 inhibitor, such as:

- ketoconazole
- clarithromycin
- itraconazole

Ask your healthcare provider if you are not sure if you are taking any of these medicines. Your healthcare provider can tell you if it is safe to take UBRELVY with other medicines.

Before you take UBRELVY tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if UBRELVY will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if UBRELVY passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take any of the following, as your healthcare provider may need to change the dose of UBRELVY:

- verapamil
- cyclosporine
- ciprofloxacin
- fluconazole
- fluvoxamine
- phenytoin
- barbiturates
- rifampin
- St. John's Wort
- quinidine
- carvedilol
- eltrombopag
- curcumin

These are not all of the medicines that could affect how UBRELVY works. Your healthcare provider can tell you if it is safe to take UBRELVY with other medicines.

Keep a list of medicines you take to show to your healthcare provider or pharmacist when you get a new medicine.

How should I take UBRELVY?

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211765s000lbl.pdf

Nurtec (rimegepant)

- Small molecule CGRP receptor antagonist for acute and prevention treatment of migraine
- Dosing: Single dosing 75 mg ODT, as needed , maximum dose in 24-hour period is 75 mg OR single dose 75 mg ODT every other day
- Does not constrict blood vessels
- Not associated with medication-overuse headache
- Avoid CYP3A4 strong inhibitors
- Safety Similar to Placebo: The most common adverse events were nausea and UTI (<=1.5%), no serious treatment-related AE were reported, and no liver safety concerns
- Hypersensitivity reactions include dyspnea and rash

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212728s006lbl.pdf

Qulipta(atogepant)

- FDA approved for headache prevention treatment
- Doses: 10mg, 30mg, 60mg
- Strong CYP3A4 inhibitor: 10mg
- Moderate and strong CYP3A4 inducers: 30mg, 60mg
- Severe renal impairment: 10mg
- Avoid severe liver impairment
- OATP Inhibitors needs dose adjustment: 10mg

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215206Orig1s000lbl.pdf

Zavzeprat(zavegepant)

- 5 to 40 mg were rapidly absorbed (T_{max} ~ 30 min)
- The recommended dose is 10 mg given as a single spray in one nostril, as needed.
- The maximum dose in a 24-hour period is 10 mg (one spray).
- The safety of treating more than 8 migraines in a 30-day period has not been established.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216386s000lbl.pdf

Triptans versus Gepants

Most triptans were associated with higher ORs for pain relief at 2 hours compared to rimegepant and ubrogepant.

The comparisons between lasmiditan, rimegepant, and ubrogepant were not statistically significant for both pain-freedom and pain relief at 2 hours.

Antibodies versus traditional headache medications: *HER-MES Protocol*

- 777 patients
- 24-week double blind phase 4 study
- >=4 migraine days monthly
- Randomized to

  --Erenumab (70 or 140 mg/month) + “Topiramate placebo”

  --Topiramate (50-100 mg/day) + “Erenumab placebo”
- **Discontinued due to AE:** Erenumab: 10.6% and Topiramate: 38.9%
- **50% reduction in monthly migraine days in last 3 months of the study:** Erenumab: 55.4% and Topiramate 31.2%

Odds ratio 2.76, 95% CI 2.06-3.71, p<0.001

Reuter U, Ehrlich M, Gendolla A, Heinze A, Klatt J, Wen S, Hours-Zesiger P, Nickisch J, Sieder C, Hentschke C, Maier-Peuschel M. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia. 2022 Feb;42(2):108-118. doi: 10.1177/03331024211053571. Epub 2021 Nov 7. PMID: 34743579; PMCID: PMC8793299.

Concurrent anti-CGRP therapies: *TANDEM Trial Results*

- 263 patients
- Phase 4, two-period, multi-center, open-label study
- Adults with migraine with or without aura, <15 headache days/month
- First phase: For first 12 weeks, participants took atogepant 60 mg daily and their non-gepant medications for breakthrough headaches.
- Seconds phase: For the second 12-week period, participants took ubrelvy up to 8 times while taking atogepant 60 mg daily.
- No hepatic safety issues arose during combination atogepant and ubrogepant period.
- Concomitant use of ubrogepant and atogepant was safe and well-tolerated over 12 week period.
- Drawbacks: They studied the combination dose for 12 weeks.

https://clinicaltrials.gov/study/NCT05264129

Which anti-CGRP therapy is better?

- 580 patients
- 3 month, double-blind, double-dummy study
- Randomized 1:1
  - 287 patients on galcanezumb and 293 on rimegepant
- Results:
  - Galcanezumab was not superior to rimegepant in achieving a 50% reduction from baseline in migraine headaches per month(62% versus to 61%; p=0.70).

Schwedt TJ, Myers Oakes TM, Martinez JM, Vargas BB, Pandey H, Pearlman EM, Richardson DR, Varnado OJ, Cobas Meyer M, Goadsby PJ. Comparing the Efficacy and Safety of Galcanezumab Versus Rimegepant for Prevention of Episodic Migraine: Results from a Randomized, Controlled Clinical Trial. Neurol Ther. 2024 Feb;13(1):85-105. doi: 10.1007/s40120-023-00562-w. Epub 2023 Nov 10. PMID: 37948006; PMCID: PMC10787669.

Botox

- Botox (brand on botulinum toxin)
- FDA indicated for chronic daily migraine
  - >14 headache days/month
- 31 injection sites, 5u per site
- Minimal cosmetic changes, no side effects
- Now requires failure of CGRP Ab product (along with 2 older medications) before authorizing Botox.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The Journal of Head and Face Pain

Review Article | Full Access

Dual Therapy With Anti-CGRP Monoclonal Antibodies and Botulinum Toxin for Migraine Prevention: Is There a Rationale?

Lanfranco Pellesi MD, Thien P. Do MD, Håkan Ashina MD, Messoud Ashina MD, PhD, DMSc, Rami Burstein PhD

First published: 21 May 2020 | https://doi.org/10.1111/head.13843 | Citations: 57

Lecture Objectives

- *Discuss migraine pathophysiology and recognize symptoms to differentiate migraine from other headache disorders.*
- *Compare traditional migraine therapies with anti-CGRP targeted therapies to enhance decision-making in acute and preventive treatment.*
- ***Apply anti-CGRP therapies to a broader spectrum of headache and facial-pain conditions, considering the evolving treatment strategies in the current anti-CGRP era.***

Anti-CGRP Therapy for Cluster Headaches and Trigeminal Neuralgia

- Cluster headaches- Emgality 300 mg (monthly if prolonged), FDA indicated
- Trigeminal Neuralgia- Small number of conflicting studies

Randomized Controlled Trial > Lancet Neurol. 2022 Nov;21(11):994-1003.
doi: 10.1016/S1474-4422(22)00294-0. Epub 2022 Sep 13.

Safety and efficacy of erenumab in patients with trigeminal neuralgia in Denmark: a double-blind, randomised, placebo-controlled, proof-of-concept study

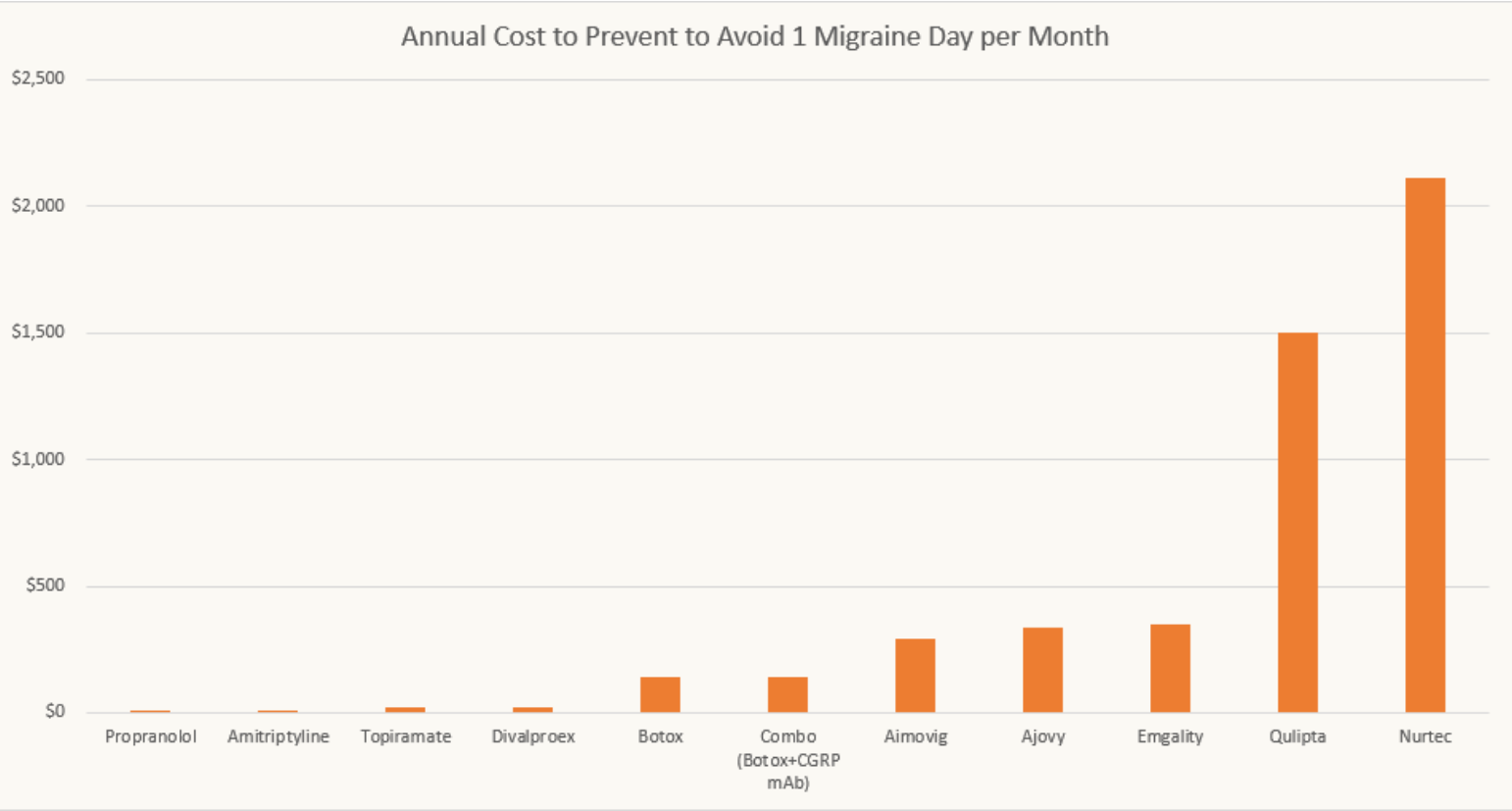
Anne Sofie Schott Andersen [1], Stine Maarbjerg [1], Navid Noory [1], Tone Bruvik Heinskou [1], Julie Lyng Forman [2], Giorgio Cruccu [3], Messoud Ashina [1], Lars Bendtsen [4]

Treatment strategy in CGRP Era- “Breaking News”

The CGRP-targeting migraine therapies are a first-line option for migraine prevention. Initiation of these therapies should not require trial and failure of non-specific migraine preventive medication approaches.

Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. *Headache*. 2024; 00: 1-9. doi:10.1111/head.14692

Annual Cost to Prevent to Avoid 1 Migraine day per month



Treatment strategies in CGRP era

- Discuss plans with patient
- Make sure they understand there is a 1st, 2nd and 3rd choice of medications
- Set expectations- duration of treatment and kind of improvement expected
- Discuss why—not every medications best for 1 patients
  - ~60% chance (roughly) of any 1 prevention medication working for the patient in front of you.
- Start with FDA indicated or "standard" medication (anticonvulsant, Beta blocker, TCA, Verapamil)

Treatment strategies in CGRP era

- If 2 of standard or FDA indicated meds not effective, recommend CGRP monthly injection
  - Choice based on insurance formulary
    - Aimovig, Emgality or Ajovy
- If patient reluctant to use injectable, work down list of meds with good evidence of effectiveness.
- Consider Melatonin or B2 for patients adverse to “meds”.

Treatment strategies in CGRP era

- Acute therapy
- Try several “Triptans” (2-3)
  - Consider longer ½ life triptan for long duration headaches or menstrual migraine
- Larger dose of NSAID
  - 500 mg naproxen
  - 800 mg ibuprofen
  - Cambia

COVID and Headaches

- Gallardo et al. analyzed 48 studies (43,169 inpatients with COVID-19) and observed a higher survival rate among COVID-19 inpatients with headache compared to those without headache.
- Between 6% and 45% of those with headache in the acute phase, the headache continued after the acute phase.
- Some cases of NDPH after covid infection


GUEST EDITORIAL | Full Access

Virtual issue: COVID-19 and headache

Edoardo Caronna MD, PhD, Patricia Pozo-Rosich MD, PhD

First published: 12 January 2023 | https://doi.org/10.1111/head.14464

Future target: PACAP

- 40% are unresponsive to anti-CGRP therapy
- Pituitary adenylate cyclase-activating polypeptide is a potential target.
- IV PACAP-38 caused a delayed migraine-like headache in 58-73% of migraine patients and rarely in those without migraine.
- Neutralizing mAb to PACAP is currently in clinical phase II development
- PACAP targets four receptors but a clinical trial that studied an antagonist to the PAC_1 receptor was negative.

Guo S, Jansen-Olesen I, Olesen J, Christensen SL. Role of PACAP in migraine: An alternative to CGRP? Neurobiol Dis. 2023 Jan;176:105946. doi: 10.1016/j.nbd.2022.105946. Epub 2022 Dec 5. PMID: 36481434.

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Thanks

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- Dr. Jodi Hawes
- Dr. Jason Pesqueira

https://natefakes.wordpress.com/2013/04/18/isnt-it-pun-ny/