Headache Medicine: A New Era

E. Lane Schlitz Fortenberry, M.D.

DISCLOSURES

NONE

OBJECTIVES

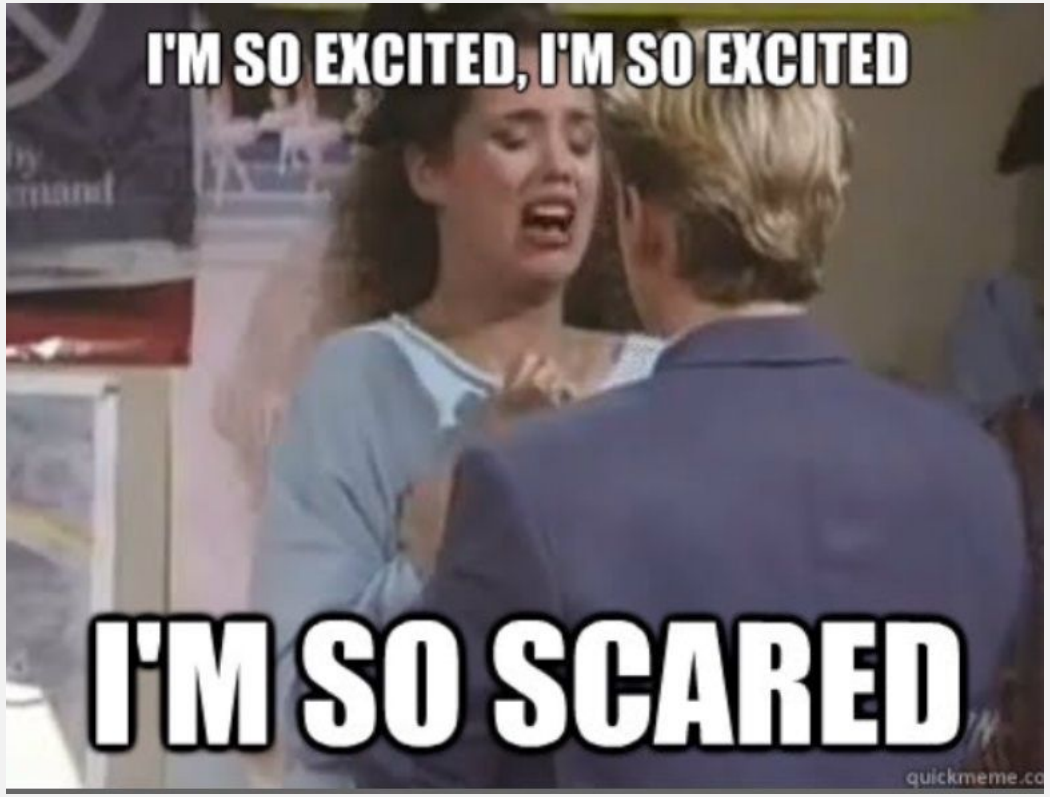
To understand the role CGRP plays in headache disorders

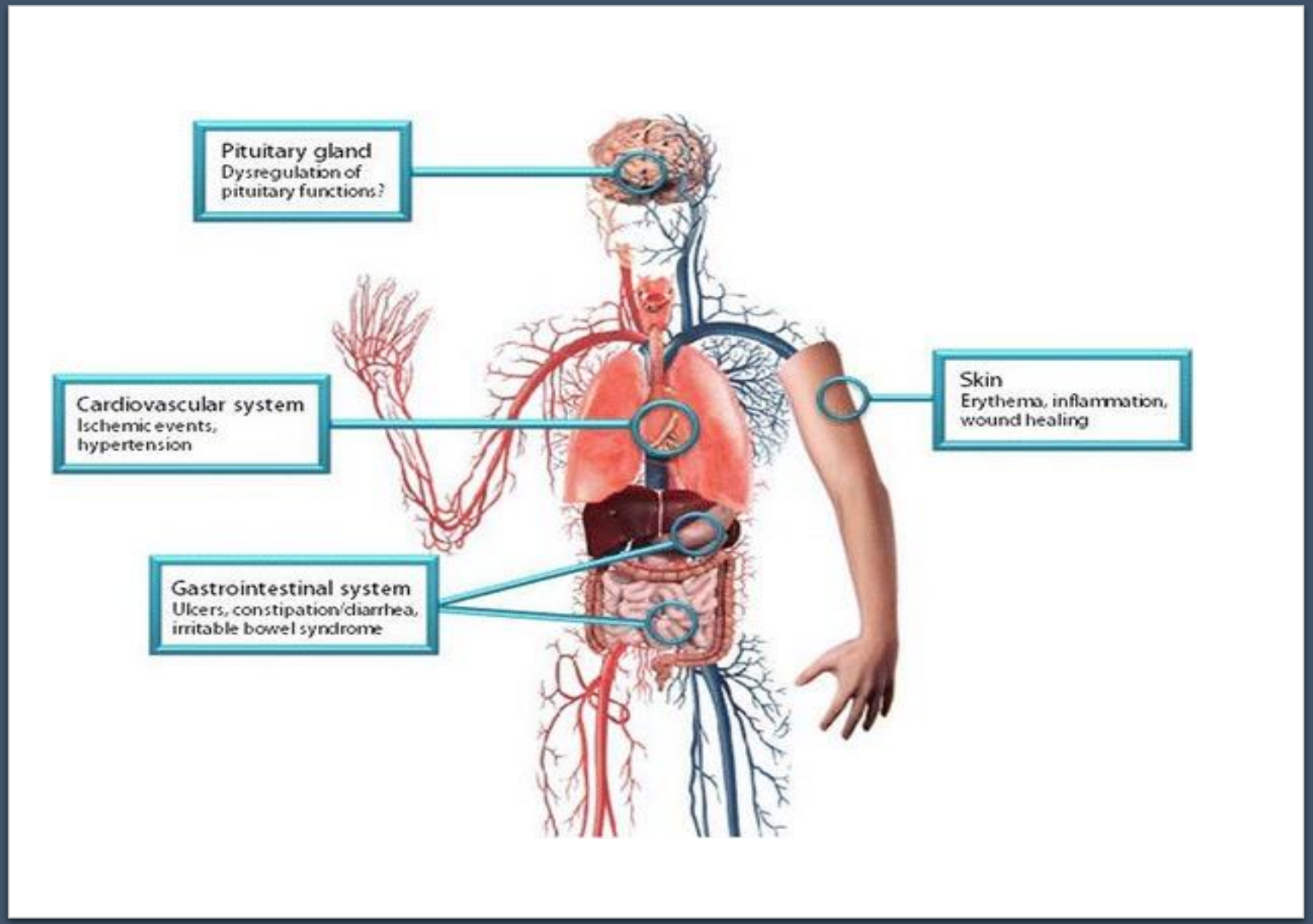
To explore the extended data for CGRP-modulating monoclonal antibodies (mAbs)

To introduce two novel classes of medications

Calcitonin Gene Related Peptide (CGRP)

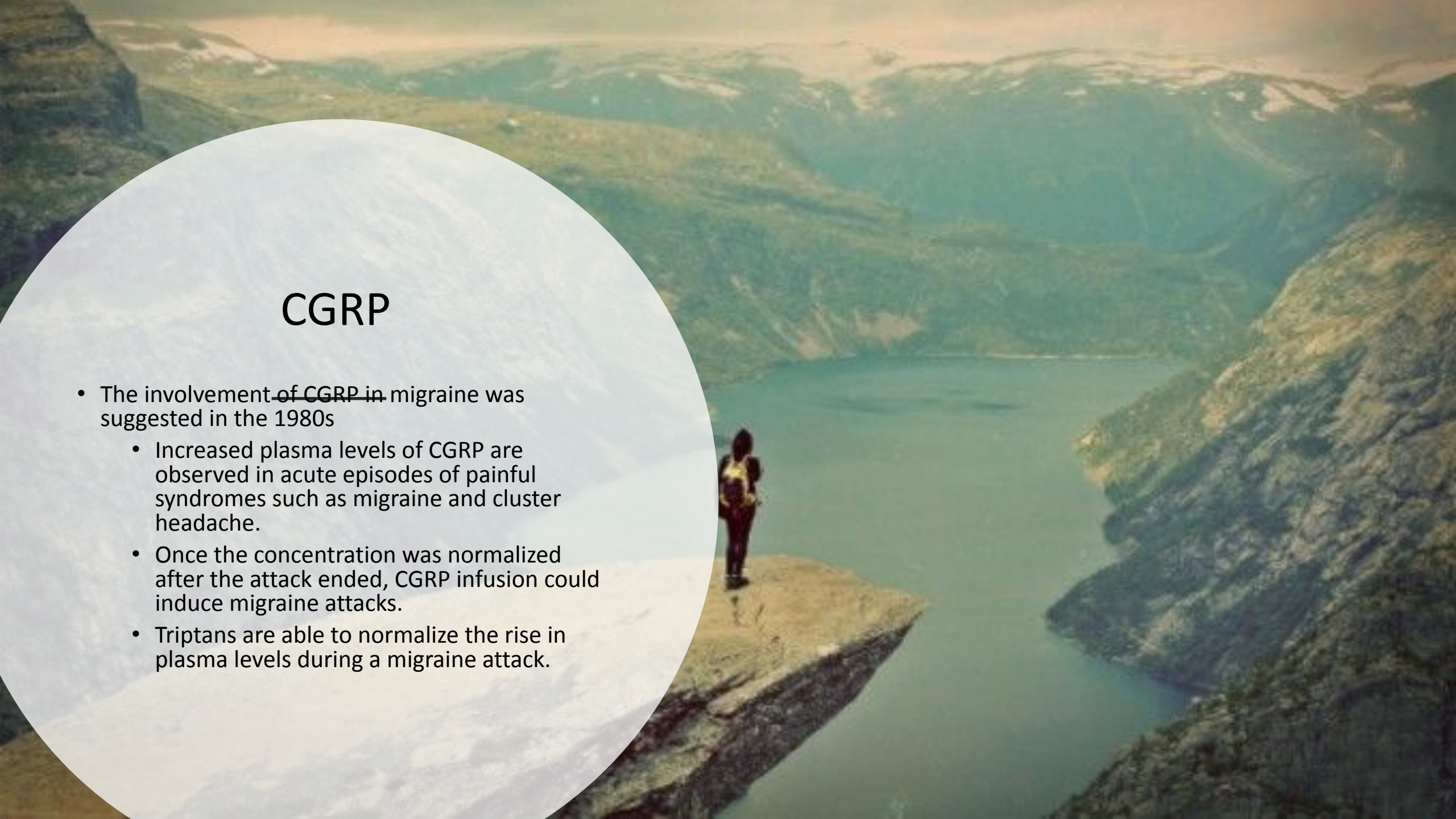
- CGRP is a 37-amino acid peptide and functions as a neuropeptide involved in nociception and neurogenic inflammation in the CNS and PNS and is also a potent vasodilator.
- The CGRP pathway plays an important role in headache disorders including migraine and cluster headache.
  - CGRP is released from the trigeminal ganglia neurons that innervate the cranial vessels and is associated with control of cerebrovascular tone
  - CGRP also released from terminal neurons in trigeminal system that innervate the meninges and face
- CGRP binding to its receptor is involved in pain, inflammation, and vasodilation in various systems of the body (nervous system, gastrointestinal, integument, cardiovascular)





CGRP receptor expression and potential SE

Deen et al. The Journal of Headache and Pain (2017) 18:96



CGRP

- The involvement ~~of CGRP in~~ migraine was suggested in the 1980s
  - Increased plasma levels of CGRP are observed in acute episodes of painful syndromes such as migraine and cluster headache.
  - Once the concentration was normalized after the attack ended, CGRP infusion could induce migraine attacks.
  - Triptans are able to normalize the rise in plasma levels during a migraine attack.

CGRP Infusions to Induce Headache

Migraine

- Migraine without aura: A study in 2002 with 12 patients showed CGRP induced migraine in 100% of patients within 11hr of infusion compared to 1 in placebo group (P=0.004)
- Migraine with aura: CGRP triggered delayed headache (12/14 compared to 1/11 controls; p=0.001) majority fulfilled migraine criteria without aura (11/14 compared to 0/11 controls; p=0.003), and 4 patient (28%) reported migraine with their typical aura
- Hemiplegic Migraine: CGRP infusion did not trigger more migraine like attacks in studies with patients with known and unknown FHM mutation compared to control groups.
- This suggests similar neurobiological pathways responsible for triggering migraine headache in MA and MO patients, and differences between MA/MO and FHM.

Cluster Headache

- Episodic Cluster/Active Phase: Attack triggered in 8/9 active cluster patients compared to 1/9 in placebo group (p=0.05)
- Episodic Cluster/Remission Phase: no patients with episodic cluster in remission phase reported headache after CGRP or placebo
- Chronic Cluster: attack triggered in 7/14 patients with chronic cluster vs none in the placebo group (p=0.02)

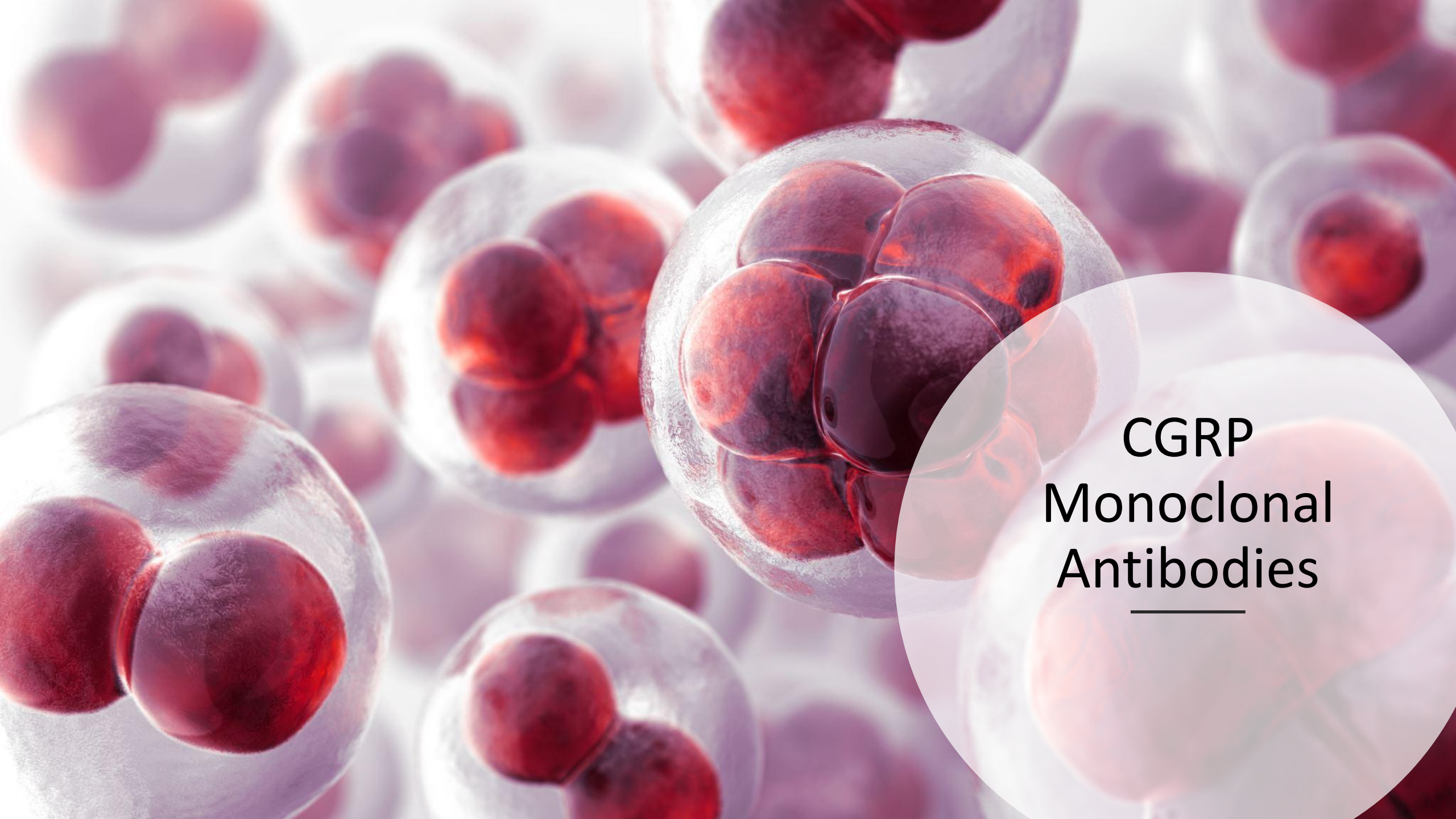
JAMA Neurol. 2018 Oct 1;75(10):1187-1197. doi: 10.1001/jamaneurol.2018.1675.

Cephalalgia. 2002 Feb;22(1):54-61.

Cephalalgia. 2010 Oct;30(110.1177/03331024103684440):1179-86. doi:. Epub 2010 May 12

CGRP Inhibitors: Treatment Approaches

1. Small molecule CGRP-receptor antagonists
   - they proved to have adequate efficacy both in acute migraine and in migraine prophylaxis
   - Until recently, none were approved for clinical use because of the risk of liver toxicity after chronic exposure
   - Ubrelvy (ubrogepant)
   - Nurtec (rimegepant)
2. Monoclonal antibodies targeting CGRP or its receptor
   - FDA approved Monoclonal antibodies
     1. Aimovig (erenumab-aooe)- targets CGRP receptor
     2. Ajovy (fremanezumab-vfrm)- targets CGRP ligand
     3. Emgality (galcanezumab-gnlm)- targets CGRP ligand
     4. Vyepti (eptinezumab)**- targets CGRP ligand
   - All are approved for both chronic and episodic migraine prevention



CGRP Monoclonal Antibodies

Pharmacokinetics (CGRP mAbs)

- They are administered parenterally because of their large dimensions, and their instability in the gastrointestinal tract.
- They have long half-lives which allows for longer dosing intervals.
- They are not metabolized by the liver; elimination is primarily by catabolism into smaller peptides and individual amino acids via the reticuloendothelial system (similar to endogenous IgGs).
    - There is a low risk of drug–drug interactions
    - There is no danger of raising creatinine or the hepatic enzymes.

Immunogenicity

- As with all therapeutic proteins there is potential for immunogenicity with all CGRP-modulating mAbs
- The FDA cautions against comparison of antidrug antibodies (ADA) incidence between different mAbs, even for products that share sequence or structural homology
    - Detection of ADA formation is highly dependent on the sensitivity and specificity of the assay
    - observed incidence of ADAs may be influenced by factors such as method, sample handling, timing of sample collection, concomitant medications, and disease condition.
- Reported data for ADAs for CGRP-modulating mAbs is limited, but no impact of ADA development on efficacy or safety has been demonstrated

	AIMOVIG	AJOVY	EMGALITY
RETAIL COST	$575/MO	$575/MO	$575/MO
INDICATION	Migraine prevention in Adults	Migraine prevention in Adults	Migraine prevention in Adults
HALF-LIFE	28 days	31 days	27 days
MODE OF ACTION	Blocks CGRP **receptor**	Blocks CGRP ligand	Blocks CGRP ligand
STORAGE	Refrigeration required. Do not freeze. Use within 7 days after removal from refrigerator.	Refrigeration required. Do not freeze. Use within 24 hours after removal from refrigerator.	Refrigeration required. Do not freeze. Use within 7 days after removal from refrigerator.
DOSAGE	70mg monthly or 140mg monthly	225mg monthly or 675mg quarterly	240mg loading dose then 120mg monthly
FREQUENCY	Monthly (1-2 doses)	Monthly (1 dose) Quarterly (3 doses)	Initial loading dose (2 doses) Monthly (1 dose)
MODE OF INJECTION	Autoinjector	Prefilled syringe	Autoinjector or prefilled syringe
INJECTION SITE	Abdomen or thigh (self-injection) Upper arm (injection by others)	Abdomen or thigh (self-injection) Upper arm (injection by others)	Abdomen or thigh (self-injection) Upper arm or buttocks (injection by others)
LISTED SIDE EFFECTS	Injection Site Irritation, Constipation, HTN	Injection Site Irritation	Injection Site Irritation
CLINICAL SUCCESS	1-3 fewer migraine days/mo	4.3 (given monthly)-4.6 given quarterly days/mo	3.91-5.27 fewer days/mo
ALLERGIES	Needle shield and cap contain dry natural rubber (a derivative of latex)	Latex-free	Latex-free
NOTABLE RESULTS	First Drug Available-published 5 year open label data		Found to help those who failed botox Approved for **Episodic** cluster headache

Emgality (galcanezumab) for EPISODIC Cluster Headaches

- **Emgality provided a ≥50% reduction from baseline** in weekly cluster headache attacks **in most patients (71.4%) at Week 3**
- **Emgality reduced the number of weekly cluster headache attacks by an average of 8.7** vs. **5.2 with placebo** over Weeks 1 to 3 (baseline **17.8** vs **17.3**) (*p*=0.036)
- Dosing: 300 mg administered as 3 consecutive subcutaneous injections of 100 mg each, at the onset of the cluster period, and then monthly until the end of the cluster period.

Sustained Efficacy and Long-Term Safety of Erenumab in Patients With Episodic Migraine: 4+ Year Results of a 5-Year, Open-Label Treatment Period

Conclusions

- In a 4+ year interim analysis, patients continuing to receive long-term erenumab treatment experienced sustained efficacy through year 4.5 in the open-label treatment phase:
- Reduction of 5.8 monthly migraine days (from baseline of 8.8 days)
- 76.5% of patients achieved ≥ 50% response, 55.7 achieved ≥ 75% response, and 32.9% achieved 100% response in monthly migraine days reduction
- Reduction of 4.6 monthly acute migraine-specific medication use days (from a baseline of 6.2 days)
- Erenumab was well tolerated and safe, with no new safety signals detected over the extended treatment period, no dose dependency of adverse events, and with infrequent discontinuation due to adverse events

•Messoud et al. ***American Headache Society, 61st Annual Meeting; Philadelphia, PA; July 11–14, 2019***

Vascular Concerns of CGRP mAbs

- In physiological conditions CGRP has important vasodilating effects and is thought to protect organs from ischemia
- CGRP and its receptors are not only distributed throughout the CNS and PNS but also in the cardiovascular system (both in blood vessels and the heart)
- CGRP does not appear to play an acute role in demand ischemia or acute blood pressure changes but may have chronic role in terms of cardioprotective effects
- So far we are not seeing an increased incidence of cardiovascular or cerebrovascular adverse events

Headache. 2018 May;58(5):715-723. doi: 10.1111/head.13316.

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Erenumab on Exercise Time During a Treadmill Test in Patients With Stable Angina.

Depre C[1], Antalik L[2], Starling A[3], Koren M[4], Eisele O[1], Lenz RA[1], Mikol DD[1].
Author information

Abstract

OBJECTIVE:
To determine the potential impact of erenumab, a human anti-calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, on total exercise time (TET), time to exercise-induced angina, and ST depression in a double-blind, placebo-controlled study in patients with stable angina due to documented coronary artery disease.

METHODS:
An exercise treadmill test was conducted following a single IV infusion of erenumab 140 mg or placebo. The primary endpoint was the change from baseline in exercise duration as measured by TET with a noninferiority margin of -90 seconds. Safety follow-up visits occurred through week 12. Eighty-eight participants were included in the analysis.

RESULTS:
TET change from baseline in the erenumab group was non-inferior to placebo. There was no difference in time to exercise-induced angina in erenumab and placebo groups (median [90% CI] time of 500 [420, 540] vs 508 [405, 572] seconds; hazard ratio [90% CI]: 1.11 [0.73, 1.69], P = .69) or time to onset of ≥1 mm ST-segment depression (median [90% CI] time of 407 [380, 443] vs 420 [409,480] seconds; hazard ratio [95% CI]: 1.14 [0.76, 1.69], P = .59). Adverse events were reported by 27% and 32% of patients in erenumab and placebo groups.

CONCLUSIONS:
Erenumab did not adversely affect exercise time in a high cardiovascular risk population of patients, supporting that inhibition of the canonical CGRP receptor does not worsen myocardial ischemia.

Neurology. 2020 Feb 4;94(5):e497-e510. doi: 10.1212/WNL.0000000000008743. Epub 2019 Dec 18.

Vascular safety of erenumab for migraine prevention.

Kudrow D[1], Pascual J[2], Winner PK[2], Dodick DW[2], Tepper SJ[2], Reuter U[2], Hong F[2], Klatt J[2], Zhang F[2], Cheng S[2], Picard H[2], Eisele O[2], Wang J[2], Latham JN[2], Mikol DD[2].
Author information

Abstract

OBJECTIVE:
To examine the cardiovascular, cerebrovascular, peripheral vascular safety of erenumab across migraine prevention studies.

METHODS:
Vascular adverse events (AEs) and blood pressure data were integrated across 4 double-blind, placebo-controlled studies of erenumab and their open-label extensions in patients with chronic or episodic migraine. Subgroup analyses were conducted by acute migraine-specific medication use and number of vascular risk factors at baseline. Standardized search terms were used to identify vascular AEs (cardiovascular, cerebrovascular, or peripheral). An independent committee adjudicated whether targeted events were vascular in origin.

RESULTS:
In placebo-controlled studies, 2,443 patients received placebo (n = 1,043), erenumab 70 mg (n = 893), or erenumab 140 mg (n = 507) subcutaneously once monthly. Regardless of acute migraine-specific medication use or vascular risk factors at baseline, AE incidence was similar across the placebo and erenumab treatment groups. Hypertension AEs were reported for 0.9% (placebo), 0.8% (erenumab 70 mg), and 0.2% (erenumab 140 mg) of patients. Vascular AEs, which were similar across double-blind and open-label treatment, generally were confounded, with plausible alternative etiologies. In 18 patients with events reviewed by the independent committee, 4 events were positively adjudicated as cardiovascular in origin: 2 deaths and 2 vascular events. All 4 positively adjudicated cardiovascular events occurred during open-label erenumab treatment.

CONCLUSION:
Selective blockade of the canonical calcitonin gene-related peptide receptor with erenumab for migraine prevention had a vascular safety profile comparable to that of placebo over 12 weeks, with no increased emergence of events over time. Further study of long-term safety of erenumab in patients with migraine is needed.

CLASSIFICATION OF EVIDENCE:
This analysis provides Class II evidence that for patients with migraine, erenumab does not increase the risk of vascular AEs.

Table 1 Determination of baseline vascular risk factors from reported data

Category	Description
Diabetes mellitus	History of diabetes mellitus
Hypertension	Medical history of hypertension or high blood pressure at screening (≥2 occasions with systolic >140 mm Hg or diastolic >90 mm Hg)
Obesity	Body mass index >30 kg/m^2
Dyslipidemia	Total cholesterol >200 mg/dL or low-density lipoprotein cholesterol >130 mg/dL or high-density lipoprotein cholesterol <40 mg/dL or triglycerides >150 mg/dL or medical history of dyslipidemia
Cigarette use	History of smoking
Coronary artery disease	Ischemic heart disease (as reported in case report forms for dedicated vascular medical history or for general medical history)
Cerebrovascular or peripheral artery disease	Cerebrovascular disease or peripheral artery disease (as reported in case report forms for dedicated vascular medical history or for general medical history) or medical history of peripheral vasoconstriction, necrosis, or vascular insufficiency

Table 2 Patient demographic and clinical characteristics at baseline in 4 migraine prevention studies

Baseline characteristic	Placebo QM (n = 1,043)	Erenumab 70 mg QM (n = 893)	Erenumab 140 mg QM (n = 507)
Age, y	41.8 ± 11.1	41.7 ± 11.2	41.3 ± 11.2
Female	869 (83.3)	755 (84.5)	431 (85.0)
White	934 (89.5)	813 (91.0)	475 (93.7)
North America	544 (52.2)	471 (52.7)	248 (48.9)
Body mass index, kg/m^2	26.8 ± 5.8	26.9 ± 5.8	26.7 ± 6.0
Disease duration, y	20.7 ± 12.2	20.8 ± 12.4	20.5 ± 12.2
History of migraine with aura	481 (46.1)	429 (48.0)	231 (45.6)
History of migraine without aura	925 (88.7)	788 (88.2)	450 (88.8)
Monthly migraine days	11.1 ± 5.5	10.3 ± 5.0	11.9 ± 5.8
Acute headache medication use			
Any	1,024 (98.2)	872 (97.6)	498 (98.2)
Migraine-specific[a]	690 (66.2)	572 (64.1)	339 (66.9)
Non-migraine-specific	822 (78.8)	705 (78.9)	416 (82.1)
Any hypertension medication use	68 (6.5)	33 (3.7)	22 (4.3)
History of vascular disorders	77 (7.4)	59 (6.6)	50 (9.9)
No. of vascular risk factors			
0	310 (29.7)	233 (26.1)	148 (29.2)
1	423 (40.6)	377 (42.2)	199 (39.3)
≥2	310 (29.7)	283 (31.7)	160 (31.6)
Vascular risk factors			
High cholesterol level[b]	489 (46.9)	438 (49.0)	241 (47.5)
Obesity[c]	253 (24.3)	230 (25.8)	133 (26.2)
High lipid level[d]	250 (24.0)	227 (25.4)	122 (24.1)
History of diabetes mellitus	21 (2.0)	17 (1.9)	6 (1.2)
History of dyslipidemia	93 (8.9)	69 (7.7)	31 (6.1)
History of hypertension	93 (8.9)	51 (5.7)	34 (6.7)
High blood pressure at screening[e]	73 (7.0)	58 (6.5)	34 (6.7)
History of cigarette use			
Current	64 (6.1)	67 (7.5)	41 (8.1)
Former	114 (10.9)	93 (10.4)	51 (10.1)
Never	430 (41.2)	437 (48.9)	227 (44.8)
Unknown	435 (41.7)	296 (33.1)	188 (37.1)

Abbreviation: QM = once monthly.
Data are presented as mean ± SD or number (%) of patients.
[a] Includes triptan-based or ergot-based medications (<1% received ergot-based medications).
[b] High cholesterol level is defined as one of the following: total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >130 mg/dL, or high-density lipoprotein cholesterol <40 mg/dL.
[c] Obesity is defined as a body mass index >30 kg/m^2.
[d] High lipid level is defined as triglycerides >150 mg/dL.
[e] High blood pressure at screening is defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg measured on at least 2 occasions.

Table 3 Treatment-emergent vascular adverse events in migraine prevention studies

Category Preferred term	During 12 weeks of double-blind treatment Placebo QM (n = 1,043)	 Erenumab 70 mg QM (n = 893)	 Erenumab 140 mg QM (n = 507)	During any exposure to erenumab 70 mg QM (n = 2,128)	 140 mg QM (n = 1,223)
Ischemic CNS vascular conditions	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0) 2,068.2 [0.0]	4 (0.3) 1,015.1 [0.4]
Cerebral venous thrombosis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0) 2,068.2 [0.0]	2 (0.2) 1,016.2 [0.2]
Cerebrovascular disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) 2,068.2 [0.0]	1 (<0.1) 1,015.4 [<0.1]
TIA[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) 2,068.2 [0.0]	1 (<0.1) 1,016.3 [<0.1]
Ischemic heart disease	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2) 2,066.2 [0.2]	0 (0.0) 1,016.4 [0.0]
Myocardial ischemia[a]	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1) 2,067.5 [<0.1]	0 (0.0) 1,016.4 [0.0]
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1) 2,067.7 [<0.1]	0 (0.0) 1,016.4 [0.0]
Arteriosclerosis coronary artery	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1) 2,067.8 [<0.1]	0 (0.0) 1,016.4 [0.0]
Blood CPK-MB increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1) 2,067.8 [<0.1]	0 (0.0) 1,016.4 [0.0]
Peripheral arterial disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1) 2,067.9 [<0.1]	1 (<0.1) 1,015.7 [<0.1]
Raynaud phenomenon	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1) 2,067.9 [<0.1]	1 (<0.1) 1,015.7 [<0.1]
Hypertension	9 (0.9)	7 (0.8)	1 (0.2)	50 (2.3) 2,034.8 [2.5]	17 (1.4) 1,007.1 [1.7]
Hypertension	9 (0.9)	7 (0.8)	0 (0.0)	41 (1.9) 2,039.4 [2.0]	15 (1.2) 1,008.9 [1.5]
Diastolic hypertension	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0) 2,068.2 [0.0]	1 (<0.1) 1,015.1 [<0.1]
Blood pressure increased	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.3) 2,063.8 [0.3]	1 (<0.1) 1,015.9 [<0.1]
Blood pressure diastolic increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1) 2,068.1 [<0.1]	0 (0.0) 1,016.4 [0.0]
Hypertensive heart disease[a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1) 2,068.2 [<0.1]	0 (0.0) 1,016.4 [0.0]

Abbreviations: CPK-MB = creatine phosphokinase–muscle/brain; QM = once monthly.
Data for double-blind treatment are presented as number (%) of patients who received at least 1 dose of 70 mg or 1 dose of 140 mg (the same patient could have received both doses). Data for any exposure to erenumab are presented as number (%) of patients/total time at risk in years [exposure-adjusted incidence rate per 100 patient-years], where total time at risk was the time from the patient's first dose of erenumab 70 mg or 140 mg to onset of the first event or, if no event occurred, to the earliest of patient's end of safety follow-up (12 or 16 weeks after last dose of 70 mg or 140 mg, respectively), end of study, or data cutoff date. Each erenumab dose group includes adverse events while the patient received that dose. Multiple events of the same preferred term are only counted once per patient.
[a] Four patients had a positively adjudicated vascular event, including 1 patient each with a vascular adverse event of TIA, myocardial ischemia, and hypertensive heart disease, plus 1 patient without a reported vascular adverse event.

Aimovig and Hypertension

- Prescribing Information (USPI) was updated on April 30, 2020.
- *Development of hypertension and worsening of pre-existing hypertension have been reported following the use of Aimovig® in the postmarketing setting. Many of the patients had pre-existing hypertension or risk factors for hypertension. There were cases requiring pharmacological treatment and, in some cases, hospitalization. Hypertension may occur at any time during treatment but was most frequently reported within seven days of dose administration. In the majority of the cases, the onset or worsening of hypertension was reported after the first dose. Aimovig® was discontinued in many of the reported cases.*

Aimovig and Hypertension

- As of January 31 2020, with an estimated 245,682 person-years of Aimovig® exposure in the US in the postmarketing setting, 362 events (355 cases) of hypertension were identified from postmarketing safety reports in the Amgen Global Safety Database including 95 serious events (94 cases)
- A medical history of hypertension was reported in 62 (17.1%) of the events and another 96 events (26.5%) had pre-existing risk factors for hypertension or transient increase in blood pressure (e.g., concomitant use of vasoactive acute migraine medications, diabetes, obesity)[3]
- Among the 185 events for which there were reports of action taken regarding Aimovig® use, 106 (57.3%) discontinued Aimovig® treatment, 64 (34.5%) did not change treatment, and 15 (8.1%) temporarily withheld treatment or changed dose, if possible[3]
- There was a total of 20 events reported with hospitalization. Thirteen (13) events were hospitalized primarily for hypertension, of which 8 had pre-existing risk factors (hypertension, diabetes, obesity, etc). The remaining 7 of the 20 events were hospitalized for other reasons with hypertension or increased blood pressure noted as an incidental finding[3,5]
- In Aimovig's® pivotal clinical trials, high cardiovascular risk patients were excluded (i.e., myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening; > 65 years of age upon entry into screening)[6]

Neurology. 2019 May 14;92(20):e2309-e2320. doi: 10.1212/WNL.0000000000007497. Epub 2019 Apr 17.

Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial.

Tepper SJ[1], Diener HC[2], Ashina M[2], Brandes JL[2], Friedman DI[2], Reuter U[2], Cheng S[2], Nilsen J[2], Leonardi DK[2], Lenz RA[2], Mikol DD[2].

- A double-blind, placebo-controlled study, 667 adults with chronic migraine were randomized (3:2:2) to placebo or erenumab (70 or 140 mg), stratified by region and medication overuse status.
- MO was defined as the monthly use of ≥ 15 days of analgesics, ≥ 10 days of triptans, and ≥ 10 days of combination therapy
- Patients with CM and MO who were treated with erenumab 70 mg or 140 mg had a difference from placebo of -3.1 monthly migraines days (MMD) by week 12 ($P < 0.001$ for both).
- Reductions of ≥ 50% in MMD were more than twice as likely for erenumab-treated patients at week 12 compared to patients who were treated with placebo ($P \leq 0.007$).
- Patients who were treated with erenumab had greater daily reductions in the use of acute migraine-specific medication (triptans and ergot derivatives) at week 12 compared to placebo.
- A greater proportion of patients who were treated with erenumab had a status change from MO to non-MO by medication category compared to placebo at week 12.3
- Exclusion criteria included opioid overuse of more than 6 days during the 3 months prior to screening, or more than 2 days during baseline, and the use of preventive migraine drugs 2 months before baseline and during the study.

Lancet. 2019 Sep 21;394(10203):1030-1040. doi: 10.1016/S0140-6736(19)31946-4. Epub 2019 Aug 16.

Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomized, double-blind, placebo-controlled, phase 3b trial.

Ferrari MD[1], Diener HC[2], Ning X[3], Galic M[4], Cohen JM[3], Yang R[3], Mueller M[4], Ahn AH[3], Schwartz YC[5], Grozinski-Wolff M[3], Janka

- Investigated the efficacy and tolerability of Ajovy in patients with migraine who had previously not responded to two to four classes of migraine preventive medications.
- The primary outcome was mean change from baseline in the monthly average number of migraine days during the 12-week treatment period.
- 838 participants with episodic (329 [39%]) or chronic (509 [61%]) migraine were randomly assigned to placebo (n=279), quarterly fremanezumab (n=276), or monthly fremanezumab (n=283).
- Reductions from baseline in monthly average migraine days over 12 weeks were greater versus placebo (least-squares mean [LSM] change -0·6 [SE 0·3]) with quarterly fremanezumab (LSM change -3·7 [0·3]; LSM difference vs placebo -3·1 [95% CI -3·8 to -2·4]; p<0·0001) and with monthly fremanezumab (LSM change -4·1 [0·34]; LSM difference vs placebo -3·5 [-4·2 to -2·8]; p<0·0001).
- Adverse events were similar for placebo and fremanezumab.
- Interpretation: Fremanezumab was effective and well tolerated in patients with difficult-to-treat migraine who had previously not responded to up to four classes of migraine preventive medications

Vyepti (eptinezumab) Infusion

- Monoclonal antibody binding the CGRP ligand
- Delivered by quarterly infusions
- Studies have shown that its bioavailability is 100% by the end of its half-hour infusion
- Both phase 3 clinical trails PROMISE-1 in episodic migraine and PROMISE-2 in chronic migraine both met their primary end points of mean monthly migraine day (MMD) reduction

Special Considerations for using CGRP mAbs

Elderly

- Safety and efficacy of CGRP antibodies is unknown in patients >70 years

Patients with significant vascular risk factors

- a hx of stroke/TIA or MI, Known CAD or cerebrovascular disease, EKG abnormalities, strong family hx, and significant PVD

Women of childbearing age

- No adequate data on pregnancy risk
- Long half lives: emgality 27 days, aimovig 28 days, and ajovy 31 days
- It is not known if CGRP is present in breast milk.

Hemiplegic Migraines

- Many pivotal trials excluded patients with hemiplegic migraines
- In Hemiplegic Migraine patients, CGRP infusion did not trigger more migraine like attacks in studies with patients with known and unknown FHM mutation compared to control groups.

Botox

New Migraine Abortive Therapies

Triptan Limitations

Inadequate Response

- Up to 55% of people do not have sufficient relief with currently available treatments1

Cannot tolerate

- 43% experience AEs within 24 hours2

Recurrence

- 17% to 40% experience return of migraine pain/symptoms within 24 hours3

Cardiovascular contraindications

- Approximately 2.6M in the US4

Medication overuse headache (MOH)

- Overuse of many current acute therapies can cause MOH5

New Migraine Abortives

gepants

- Ubrelvy (ubrogepant)
- Nurtec (rimegepant)

ditans

- Reyvow (lasmiditan)

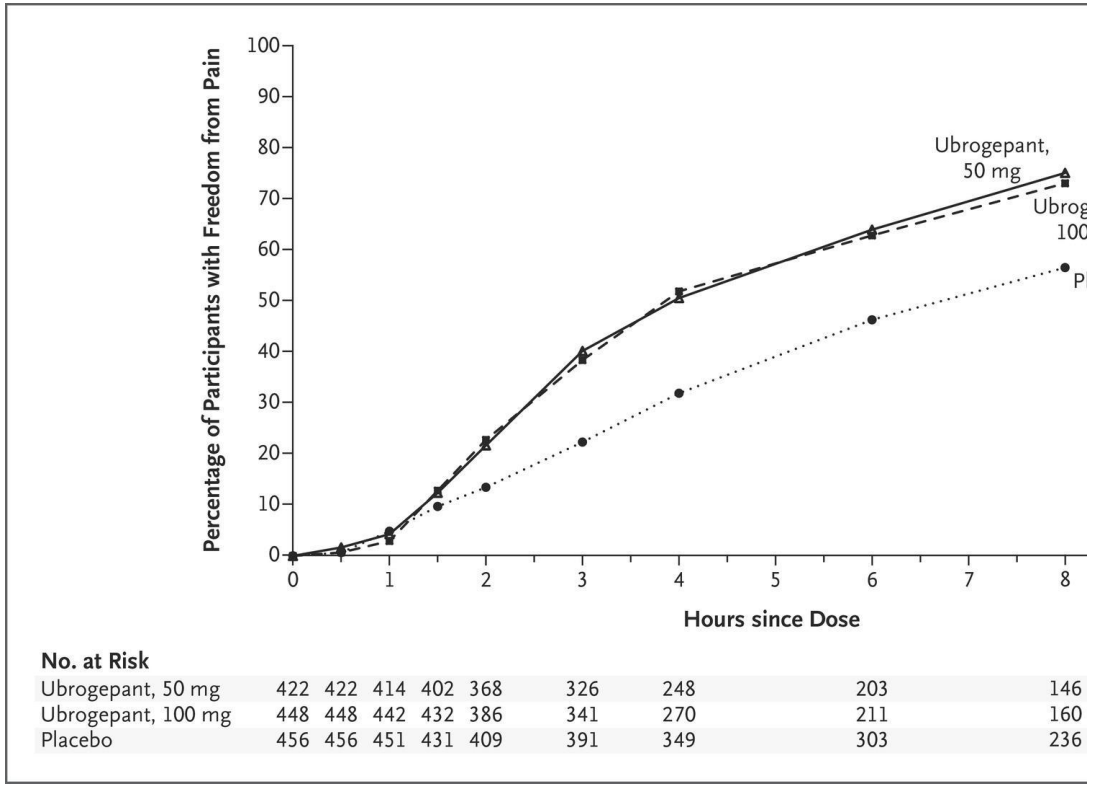
Approved for acute treatment of migraine with or without aura

gepants

- Small-molecule CGRP receptor antagonists
- Both Ubrelvy and Nurtec had similar safety profiles to that of placebo in clinical trials.
- Do not result in vasoconstriction/no contraindications thus far for patients with significant vascular risk factors or hx of vascular disease.

Ubrelvy (ubrogepant)

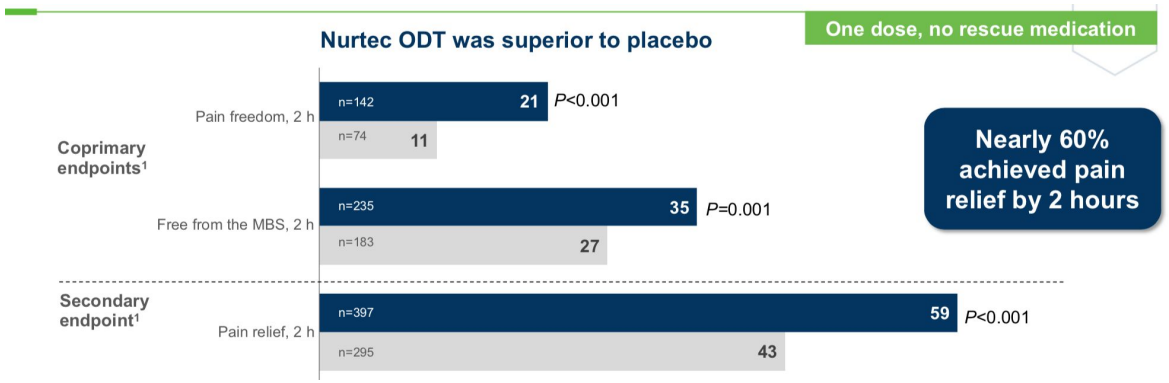
- ACHIEVEI and II met Co-primary endpoints were pain freedom and relief of most bothersome symptom. Secondary Endpoint was pain relief
- Contraindication: Concomitant use of strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, **CBD, barbiturates**, phenytoin).
- Adverse Reactions: The most common adverse reactions were nausea (4% vs 2% placebo) and somnolence (3% vs 1% placebo).
- Comes in a 50mg and 100mg tablet. Can give a second dose 2 hours after the initial dose. The maximum dose in a 24-hour period is 200 mg.
- The safety of treating more than 8 migraines in a 30-day period has not been established.
- Pharmacokinetics
    - time to reach pharmacologically available concentration: 11 minutes
    - time to peak plasma concentrations (T_{max}): 1.5 hours
    - elimination half-life: 5-7 hours



No. at Risk									
Ubrogepant, 50 mg	422	422	414	402	368	326	248	203	146
Ubrogepant, 100 mg	448	448	442	432	386	341	270	211	160
Placebo	456	456	451	431	409	391	349	303	236

Nurtec (rimegepant)

- Comes in 75mg ODT, max dose 75mg in 24 hrs
- Study 303: **Cmet oprimary endpoints:** Freedom from pain and MBS associated with migraine at 2 hours post-dose and secondary enpoint of pain relief at 2 hr
- Contraindication: Concomitant use of strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, **CBD, barbiturates**, phenytoin).
- **Pain relief** beginning at 15 min with statistical significance at 1 hour2 Sustained efficacy through **2 days with a single dose** (pain relief, freedom from pain, and MBS)
- **Return to normal function** by 60 min and sustained to 2 days with a single dose.2 **Reduced total migraine disability** (MIDAS) by ~50% in 1-year study.3
- **86%** of rimegepant-treated patients did not use rescue medication within 24 hours.
- Trials with patients receiving Nurtec daily or EOD did not result in MOH.
- Adverse Reactions: The most common adverse reactions were nausea (2% Nurtec vs 0.4% placebo)
- Pharmacokinetics:
    - Time to peak concentration (Tmax) = 1.5 hours
    - Half-life: approximately 11 hours



Nurtec (rimegepant) for Migraine Prophylaxis

- Study 201: Open label extension with rimegepant 75mg ODT assigned patients with **episodic** migraine to 2 different treatment groups: PRN up to 1×/day dosing vs Fixed dosing up to 12 weeks (EOD+PRN dosing).
  - Not only was MOH not observed, but **48.4%** of subjects in the EOD+PRN cohort during month 3 **achieved ≥50% reduction, from baseline, of moderate-to-severe migraine days per month** with rimegepant 75 mg (n=244)
- A recent randomized, placebo-controlled pivotal clinical trial (NCT03732638) evaluating the efficacy and safety of oral rimegepant 75 mg for the preventive treatment of migraine in both episodic and chronic migraine patients met the primary endpoint, demonstrating a statistically significant reduction from baseline in monthly migraine days in patients treated with rimegepant compared with placebo.

Emerging Treatments: NURTEC™ ODT (rimegepant) and UBRELVY™ (ubrogepant)

	NURTEC™ ODT (RIMEGEPANT)[1]	UBRELVY™ (UBROGEPANT)[2]
DOSAGE AND ADMINISTRATION	▪ 75 mg single dose, as needed ▪ Maximum dose in a 24-hour period: 75 mg ▪ 15 migraines in a 30-day period	▪ 50 mg or 100 mg, as needed ▪ If needed, a second dose may be administered at least 2 hours after the initial dose ▪ Maximum dose in a 24-hour period: 200 mg ▪ 8 migraines in a 30-day period
ADVERSE REACTIONS	▪ The most common adverse reaction was nausea (2% NURTEC ODT vs. 0.4% Placebo) ▪ Long-term safety evaluated in 1,798 patients, dosing intermittently for up to one year	▪ The most common adverse reactions (>2%) were nausea, somnolence, and dry mouth. ▪ Long-term safety assessed in 813 patients, dosing intermittently for up to 1-year. Patients were permitted to treat up to 8 migraines per month with UBRELVY.
CLINICAL PHARMACOLOGY	▪ T_{max} = 1.5 hours ▪ Half-life: approximately 11 hours	▪ T_{max} = 1.5 hours ▪ Half-life: 5-7 hours
CLINICAL STUDIES	▪ Rescue medication (ie NSAIDs, acetaminophen, and/or an antiemetic) was allowed 2 hours after the initial treatment. Other forms of rescue medication such as triptans were not allowed within 48 hours of initial treatment. ▪ Efficacy Endpoints: Pain Free at 2 hours, Most Bothersome Symptom Free at 2 hours, Pain Relief at 2 hours, Sustained Pain Freedom 2-48 hours, Use of Rescue Medication within 24 hours, Percentage of Patients Reporting Normal Function at 2 hours	▪ A second dose of study medication (UBRELVY or placebo) or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours. ▪ Efficacy Endpoints: Pain Free at 2 hours, Most Bothersome Symptom Free at 2 hours, Pain Relief at 2 hours, Sustained Pain Freedom 2-24 hours

*These are cross-trial comparisons and no head-to-head studies between NurtecTM ODT and competitors have been conducted.

References: 1. Nurtec ODT USPI 2020. **2.** UBRELVY USPI 2019.

Qulipta (atogepant)

- FDA approved this week for episodic migraine prophylaxis
  - 60mg q daily (phase 3 trial multidose study 10mg, 30mg, 60mg daily and BID dosing groups)
  - Strong CYP3A4 inhibitors give 10mg daily dosing
  - Most common adverse reactions: nausea, constipation, fatigue
  - Renally dose (10mg q daily) and avoid in severe hepatic impairment

Reyvow (lasmiditan)

- **First and only FDA-approved ditan, a high-affinity 5-HT_{1F} receptor agonist**
  - A number of triptans have been shown to act on this subtype as well, but only after their affinity for 5-HT_{1B} and 5-HT_{1D}
- indicated for the acute treatment of migraine with or without aura in adults
- Across 2 clinical studies and 3 doses (50 mg, 100 mg, 200 mg), **28%-39%** of patients achieved **complete elimination of migraine pain** at 2 hours with REYVOW compared to 15% and 21% with placebo
- Reyvow is a **Schedule V controlled substance**
- The most common adverse reactions associated with REYVOW (≥2% and greater than placebo in clinical studies) were dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, and muscle weakness.

Reyvow (lasmiditan): Safety Indications

- **Driving Impairment:** REYVOW may cause significant driving impairment. More sleepiness was reported at 8 hours following a single dose of REYVOW compared to placebo
- **Central Nervous System Depression:** REYVOW may cause central nervous system (CNS) depression, including dizziness and sedation.
- **Serotonin Syndrome:** In clinical trials, reactions consistent with serotonin syndrome were reported in patients treated with REYVOW who were not taking any other drugs associated with serotonin syndrome as well as those who were on serotonergic drugs.
- **Medication Overuse Headache** potential was demonstrated
- **Abuse** In a human abuse potential study in recreational poly-drug users subjects reported statistically significantly higher “drug liking” scores than placebo
    - Reyvow is a **Schedule V controlled substance**
- No vascular contraindications

NEUROMODULATION

gammaCore

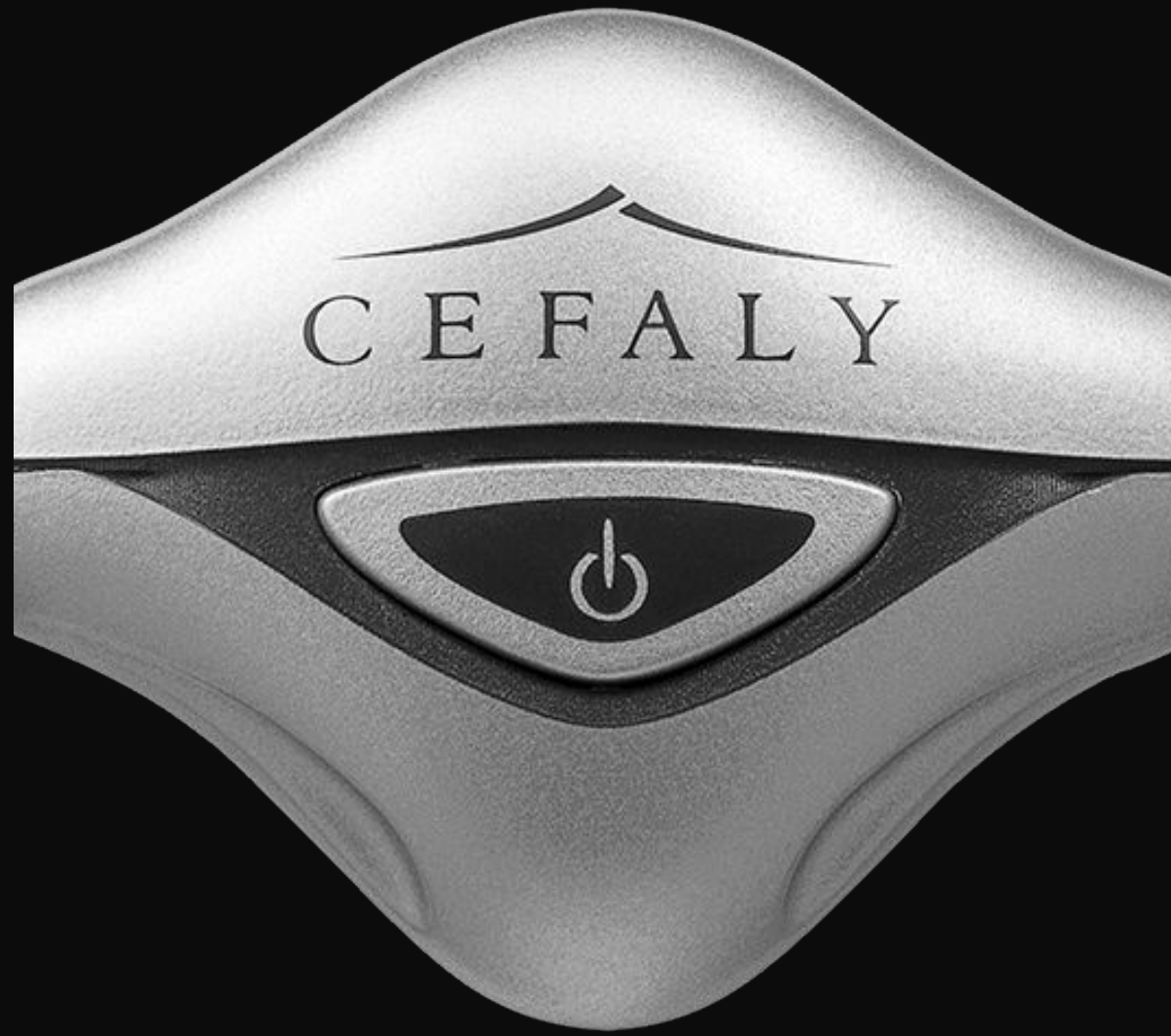
- Uses electrical stimulation to activate the vagus nerve
- Non-invasive
- The gammaCore Sapphire device is indicated for:
  - The preventative treatment of episodic cluster headaches
  - The acute treatment of pain associated with episodic cluster headache in adult patients.
  - The acute treatment of pain associated with migraine headache in adult patients.
- Safe and well tolerated
  - most common adverse device-related events were mild and transient, and occurred primarily during administration

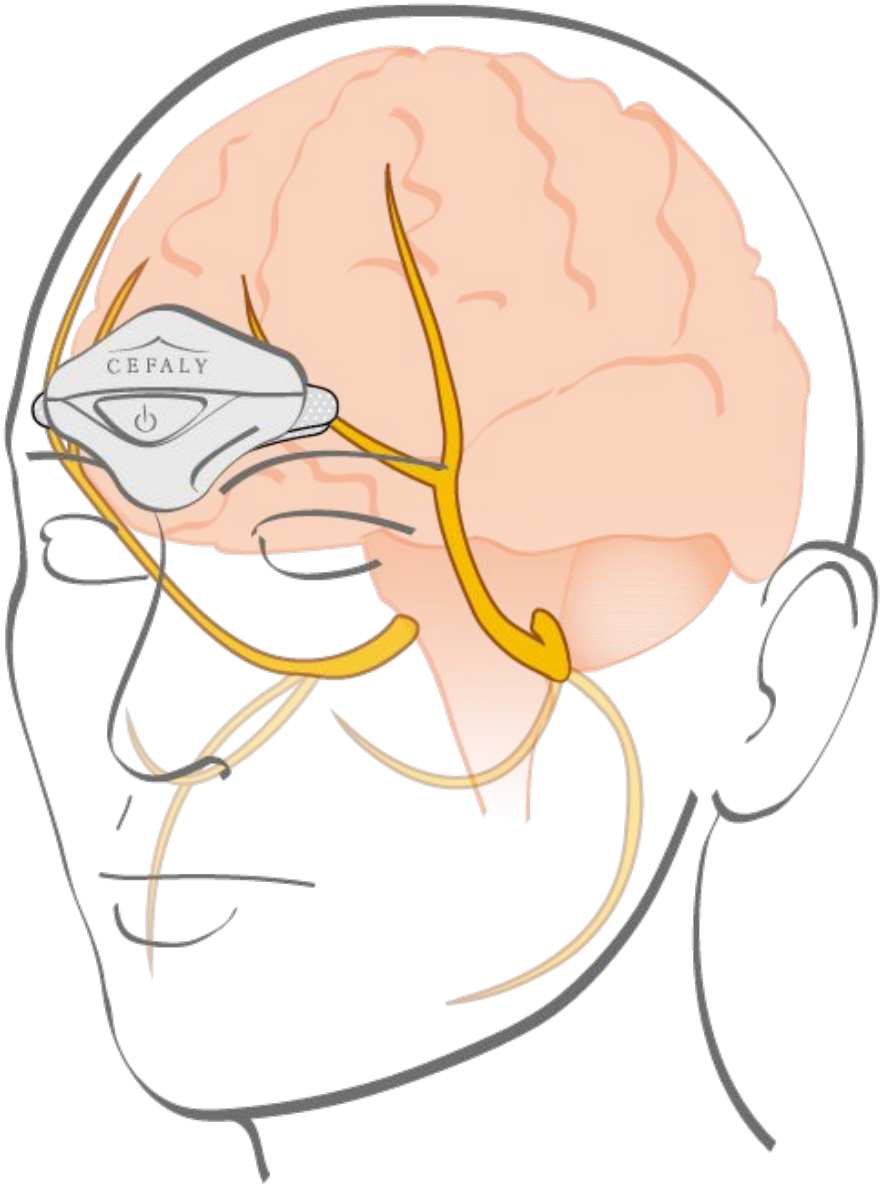
gammaCore Safety Profile

- Safety and efficacy of gammaCore have not been evaluated in the following patients, and therefore it is NOT indicated for:
  - Patients with an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device
  - Patients diagnosed with narrowing of the arteries (carotid atherosclerosis)
  - Patients who have had surgery to cut the vagus nerve in the neck (cervical vagotomy)
  - Pediatric patients
  - Pregnant women
  - Patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia
- Patients should not use gammaCore if they:
  - Have a metallic device such as a stent, bone plate, or bone screw implanted at or near their neck
  - Are using another device at the same time (eg, TENS Unit, muscle stimulator) or any portable electronic device (eg, mobile phone)

Cefaly

- Cefaly is an External Trigeminal Nerve Stimulation device (e-TNS) for migraine treatment.
- Precise micro-impulses are then sent through the electrode to the upper branch of the trigeminal nerve to either relieve the headache pain during a migraine attack (Acute setting) or to prevent future migraine attacks (Prevent setting).
- FDA approved for treatment of migraine with or without aura.
- Can be used for patients with episodic or chronic migraine.





Cefaly Settings

- Neurostimulation of the supraorbital nerve bilaterally with via two different modes:
  - Cefaly acute setting (high frequency, single long session) produces a sedative effect on the nervous system that relieves headache pain.
  - Cefaly prevent setting (low frequency, daily short sessions) restores progressively a normal metabolism in the fronto-temporal cortex of migraineurs; that is to say an improvement of the migraine-triggering threshold, which consequently reduces the frequency of migraine attacks.
- Adverse Events
  - **All were mild and completely reversible**
  - Most Common: Intolerance to the feeling of Cefaly on the forehead: 1.25%
- Contraindications
  - Implantable stimulators in the head or neck
  - Pacemaker

Alpha Stim- Cranial Electrotherapy Stimulation (CES)

- FDA approved for treatment of:
  - Chronic pain
  - Anxiety
  - Depression
  - Insomnia
- A meta-analysis of Cranial electrostimulation for headache demonstrated benefit for multiple headache types specifically migraine and tension headache

J Nerv Ment Dis. 1997 Dec;185(12):766-7.

Alpha Stim: Treatment Mechanisms of CES

- The exact mechanism is not fully understood.
- Functional MRI results showed CES stimulation is associated with cortical deactivation for 0.5 Hz and 100 Hz frequencies in bilateral frontal, parietal and posterior midline regions.
- CES induces EEG changes by increasing alpha-wave activity and decreasing delta-wave activity
- Neurotransmitter studies have shown CES leads to increased concentrations of beta-endorphin, serotonin, and melatonin, and decreasing levels of cortisol in the brain. These effects are thought to reduce pain, insomnia, and the response to stress, while improving mood.

Alpha Stim

- Out of over 100 clinical research studies, less than 1% of patients reported mild and self-limiting side effects, including dizziness (6 cases or 0.07%), skin irritation/electrode burns (6 cases or 0.07%), and headaches (9 cases or 0.10%)
- **Contraindications:** Pacemaker or implanted defibrillator, implanted brain stimulator. Do not stimulate directly on the eyes, or press the probes over the carotid sinus
    - seizures are not a contraindication but increase in dosage should be done slowly and with caution

eNeuro

- **Single Pulse Transcranial magnetic stimulator (sTMS) for the acute treatment of migraine with or without aura**
- Mechanism is not fully understood but studies have demonstrated sTMS inhibits cortical spreading depression and significantly inhibits spontaneous and evoked firing rate of third order thalamocortical projection neurons (Andreou et al., Brain; 2016:1-13)
- Safe and well tolerated (contraindications similar to those for MRI)
- Data from the device is sent to the sTMS mini **Online Migraine Diary**
- **Clinical Education Specialists** will call your patients to help with their initial administrations of treatment, encourage ongoing use of the sTMS mini Online Migraine Diary, and field phone calls throughout their course of treatment with the sTMS mini.

Nerivio

- A a wireless non-invasive **remote electrical neuromodulation** (REN) wearable for the acute treatment of migraine (with or without aura) applied to the upper-arm
- smartphone-controlled by an easy-to-use app that provides personalized treatments and offers an advanced migraine diary
- stimulates C and Aδ nociceptive sensory fibers of the upper arm above their depolarization thresholds but below the perceived pain threshold to activate the descending pain inhibitory pathway and the release of serotonin and noradrenalin, which inhibit incoming messages of pain in the trigeminal cervical complex (TCC) that occur during a headache of a migraine attack
- conditioned pain modulation (CPM) – an endogenous analgesic mechanism in which conditioning stimulation inhibits pain in remote body regions.
- 66.7% of patients achieve pain relief at 2 hours (Yarnitsky et al., Headache, 2019; 58:1240-1252)
- Contraindications: CHF, severe cardiac or cerborovascular disease, uncontrolled epilepsy, and active implantable medical device









THANK YOU!

QUESTIONS?