Alternative Headache Treatments

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DISCLOSURES

NONE

OBJECTIVES

- To understand the role CGRP plays in headache disorders
- To explore the current data CGRP-modulating monoclonal antibodies (mAbs) and small molecule CGRP receptor antagonists
- To introduce other novel classes of headache medications and neuromodulation devices

Novel Headache Therapies

Acute Therapies
- Gepants
  - Ubrogepant
  - rimegepant
- Ditans
  - Lasmiditan

Preventative Therapies
- mAbs
  - galcanezumab
  - erenumab
  - fremanezumab
  - eptinezumab
- Gepants
  - atogepant
  - rimegepant

Neuromodulation Therapies
- Cefaly
- Nerivio
- gammaCore
- TMS
- Dual Trigeminal/Occipital stimulators

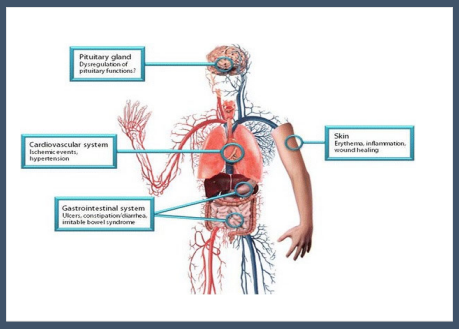
Calcitonin Gene Related Peptide (CGRP)

- 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

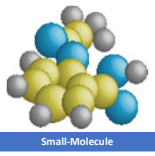
- The involvement of CGRP in migraine was suggested in the 1980s
  - Increased plasma levels of CGRP are observed in acute episodes of painful syndromes such as migraine and cluster headache.
  - Once the concentration was normalized after the attack ended, CGRP infusion could induce migraine attacks.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

CGRP receptor expression and potential SE



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

Small-Molecule Versus mAbs



Small-Molecule	Monoclonal Antibodies
Size <1 kD	Size ~150 kD
Orally administered	Must be injected
Many enter cells and cross the BBB*	Do not enter cells or cross the BBB†
Half-life hours to days	Half-life 1–4 weeks
Chemically synthesized	Manufactured in tissue culture
Hepatic metabolism and/or renal excretion	Reticuloendothelial system (peptidases)

*Not all small molecules cross the BBB in appreciable quantities.
†Antibodies may cross the BBB in very small quantities (0.1% of serum concentration).
BBB, blood–brain barrier.

CGRP Inhibitors

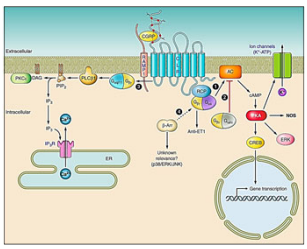
- mAbs
  - Migraine Prophylaxis
    - Emgality (galcanezumab)
    - Aimovig (erenuman)
    - Ajovy (fremanezumab)
    - Vyepti (eptinezumab)
  - Episodic Cluster Prevention
    - Emgality (galcanezumab)
- Gepant
  - Acute Migraine Therapy
    - Ubrelvy (Ubrogepant)
    - Nurtec (rimegepant)
    - Zavzpret (zavegapant)
  - Migraine Prophylaxis
    - Qulipta (atogepant)
    - Nurtec (rimegepant)

CGRP Inhibitors For Migraine Prevention

CGRP mAbs

Anti-CGRP mAbs for Migraine Prevention

- mAbs targeting CGRP ligand
  - Galcanezumab
  - Eptinezumab
  - Fremanezumab
- mAbs targeting canonical CGRP receptor
  - Erenumab



Tso AR et al. Curr Treat Options Neurol. 2017;19:27;
Russell et al. *Physiol Rev.* 2014;94:1099

	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 or autoinjector	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

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

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.

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.*

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, recommend stopping 5-6mo prior to attempts to get pregnant
- 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

Gepants for Migraine Prophylaxis

- Nurtec (rimegepant)
- Qulipta (atogepant)

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.

Qulipta (atogepant)

- FDA approved last 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
  - Special considerations: Renally dose (10mg q daily) and avoid in severe hepatic impairment

Migraine Abortive Therapies

Triptan Limitations

Inadequate Response
- Up to 55% of people do not have sufficient relief with currently available treatments

Cannot tolerate
- 43% experience AEs within 24 hours

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

Cardiovascular contraindications
- Approximately 2.6M in the US

Medication overuse headache (MOH)
- Overuse of many current acute therapies can cause MOH

New Migraine Abortive Therapies

gepants
- Ubrelvy (ubrogepant)
- Nurtec (rimegepant)
- Zavzpret (zavegepant intranasal)

ditans
- Reyvow (lasmiditan)

Approved for acute treatment of migraine with or without aura
NO VASCULAR CONTRAINDICATIONS

Gepants for Acute Migraine Treatment

	Ubrelvy (ubrogepant)	Nurtec (rimegepant)	Zavzpret (zavegepant)
Dosage and Administration	• 50mg or 100mg tablet • Can repeat dose at 2hrs, maximum dose 200mg over 24hr period • Study design limited to 8 migraines in 30-day period	• 75mg ODT • Maximum dose 75mg over 24hr period • No overuse seen with 18 doses in 30-day period	• 10mg intranasal spray • 10mg in 1 spray, Maximum dose 10mg over 24hr period
Adverse Reaction	• Nausea (2%)	• Nausea (2-4%) • Somnolence (2-4%) • Dry mouth (<1-2%)	• Dysgeusia (18%) • Nausea (4%) • Nasal discomfort (3%) • Vomiting (2%)
Clinical Pharmacology	• T_{max}= 1.5 hours • Half-life: 5-7 hrs	• T_{max}= 1.5 hours • Half-life: ~11 hrs	• T_{max}= ~30 minutes • Half-life: ~6.55 hrs

Small Molecule CGRP receptor Antagonists

Ditans- Acute Treatment of Migraine

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

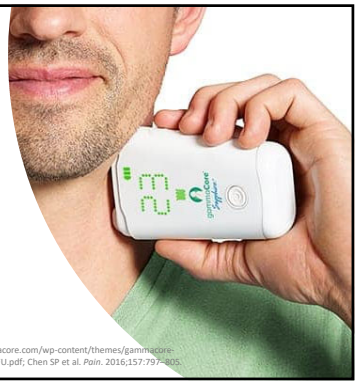
Alternative Therapies for Acute Migraine (Consider w Moderate/Severe N/V)

DRUG	PRODUCT	MAX DOSE/24HR
Zavzpret (zavegepant) 10mg	Nasal spray	10mg
Nurtec (Rimegepant) 75mg	Orally Disintegrating Tab	75mg
rizatriptan 5mg, 10mg	Orally Disintegrating Tab	30mg
Zomig (zolmitriptan) 2.5mg, 5mg	Orally Disintegrating Tab	10mg
Zomig (zolmitriptan) 2.5mg, 5mg single-use device	Nasal Spray	10mg
Imitrex Intranasal (sumatriptan) 5mg, 10mg, 20mg	Nasal Spray	40mg
Onzetra Xsail (sumatriptan) 11mg/capsule in disposable nosepiece (2 nosepieces/treatment)	Nasal powder	44mg
Imitrex (sumatriptan) 3mg/0.5mL, 4mg/0.5mL, 6mg/0.5mL	Injection (SC soln vs prefilled syringe)	12mg
Migranol (Dihydroergotamine) 0.5mg/1spray (1 treatment=1 spray in each nostril and repeat 15-30min for 4 sprays total)	Nasal Spray	6 sprays/24hr; 8 sprays/week
Trudhessa (Dihydroergotamine) 0.725 mg/1 spray (1 treatment=1 spray in each nostril)	Nasal Spray	4 sprays/24hr; 6 sprays/week
Dihydroergotamine 1mg/mL	Inj (glass ampule)	6mg
Elyxyb (celecoxib) 120mg (4.8mL)	Oral solution	120mg

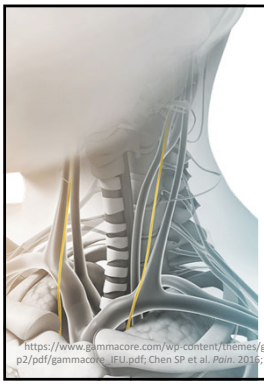
NEUROMODULATION

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 preventative treatment of migraine headaches
  - 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



https://www.gammacore.com/wp-content/themes/gammacore-p2/pdf/gammacore_IFU.pdf; Chen SP et al. *Pain*. 2016;157:797–805.



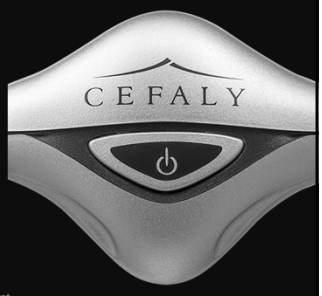
gammaCore Safety Profile

- 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)

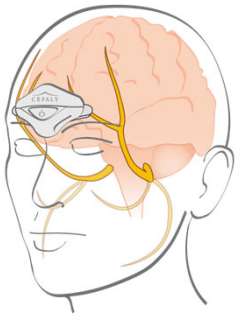
https://www.gammacore.com/wp-content/themes/gammacore-p2/pdf/gammacore_IFU.pdf; Chen SP et al. *Pain*. 2016;157:797–805.

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.



https://www.cefaly.us/en/how-to-use-it; Russo A et al. *Front Neurol*. 2017;8:282.



Cefaly Settings-Abortive and Preventative 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

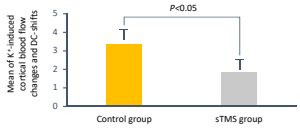
https://www.cefaly.us/en/how-to-use-it; Russo A et al. *Front Neurol.* 2017;8:282.

Single-pulse Transcranial Magnetic Stimulation (sTMS) for Migraine

sTMS mini

- Acute
  - 3 pulses at the onset of migraine pain
  - Option for 2 additional treatments (3 pulses each) at 15-minute intervals
- Prevention
  - 4 pulses twice daily (2 pulses, wait 15 minutes, then repeat 2 pulses)

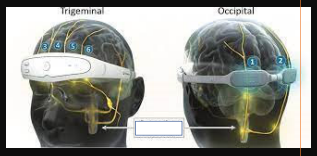
- Safe and well tolerated (contraindications similar to those for MRI)
- Data from the device is sent to the sTMS mini **Online Migraine Diary**
- **Clinical Education Specialists** will call your patients to help with their initial administrations of treatment, encourage ongoing use of the sTMS mini Online Migraine Diary, and field phone calls throughout their course of treatment with the sTMS mini.



http://www.eneura.com/wp-content/uploads/2017/03/sTMS-mini-Physicians-Instructions-for-Use-Rev-E.pdf; Andreou AP, et al. Brain. 2016;139:2002–2014.

Relivion- Acute Migraine Only*

- Non-Invasive Combined Occipital & Trigeminal Nerve Stimulation
- FDA-Approved for acute migraine therapy
- Current Studies
  - PERL Trial- migraine prevention: prospective, non-randomized, single arm, and multi-center trial
  - MOOD study-prospective, multicenter, two-arm, double-blinded, randomized, controlled trial using Relivion in patients suffering from MDD



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

- 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

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

Other Therapies to Consider for Headache Management

- In office procedures
  - Trigger point injections
  - SPG blocks
  - Peripheral nerve blocks
- Nutraceuticals
  - Riboflavin
  - Magnesium
  - Melatonin
  - CoQ 10
- Physical Therapy
- Behavioral Therapy
  - CBT
  - Biofeedback
  - mindfulness
- Integrative Medicine
  - Acupuncture
  - Yoga

QUESTIONS?