Emerging Treatments for Migraine

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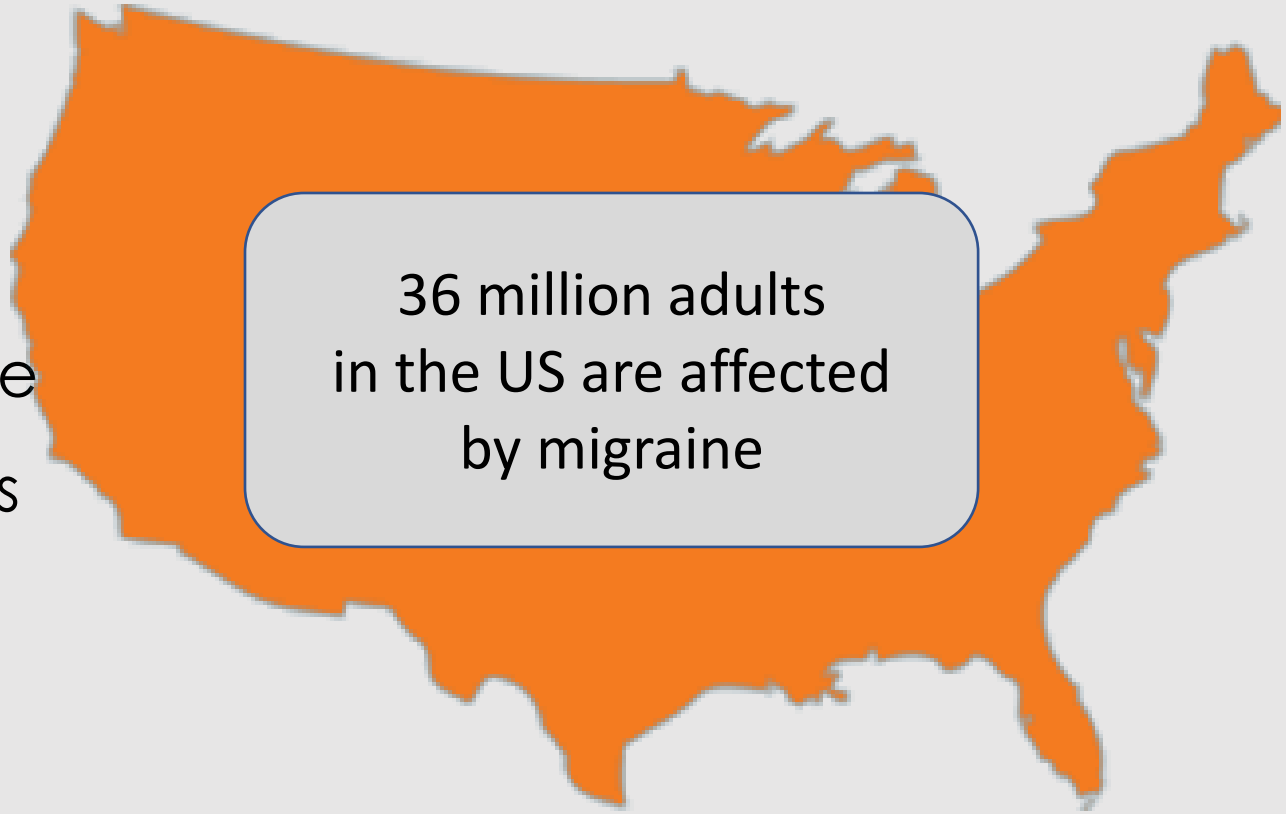
Disclosures

- Speakers Bureau: Allergan, Amgen, Teva
- Advisory Board: Lilly, Impel

Migraine Is a Highly Prevalent Disease

- 2nd leading cause of years lived with disability worldwide
- Effective treatment can reduce migraine frequency and risk of progression to more severe disease
- Our understanding of what causes migraine has allowed for the development of migraine-specific therapies



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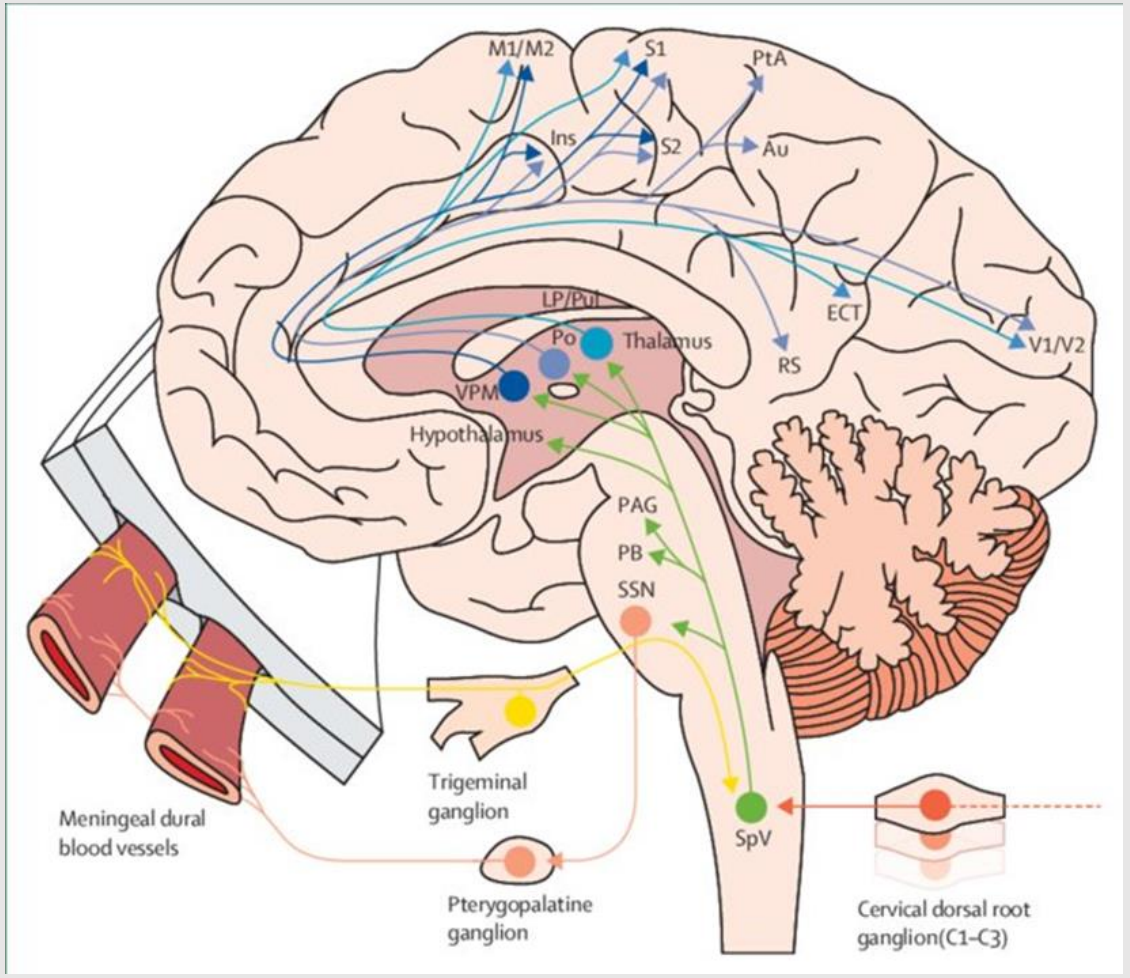
Migraine Activation of the Trigeminovascular Complex

Peripheral components:

- **Trigeminal Ganglion**
  - **Innervate cerebral and meningeal blood vessels in the dura**
  - **Relay pain signals to CNS**
- **Meningeal vasculature**
- **Resident immune cells**

Central components:

- **Trigeminoncervical Complex (TCC)**
  - **Sensory information is related from periphery to CNS**
- **Thalamus**
- **Cortex**



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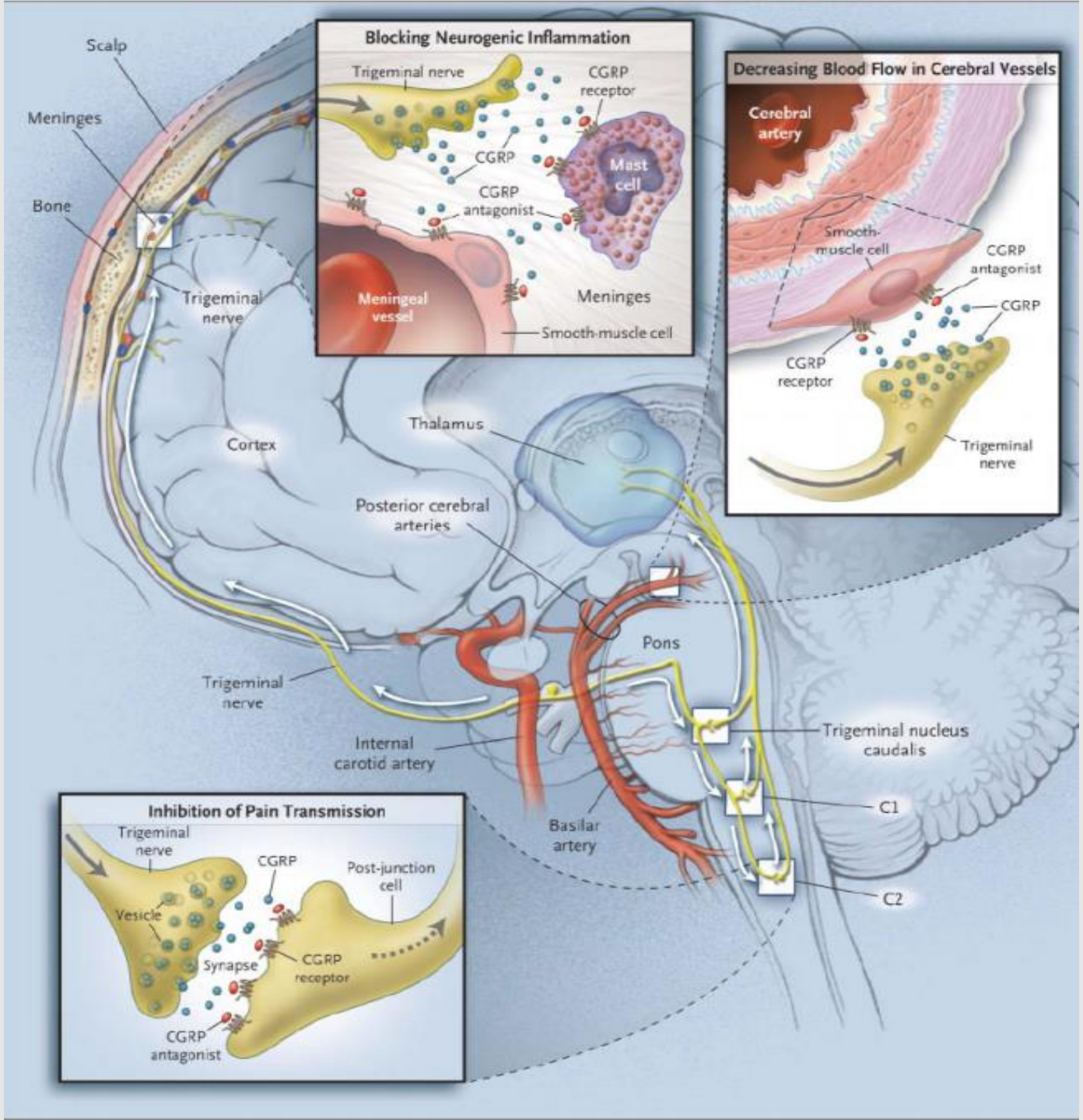
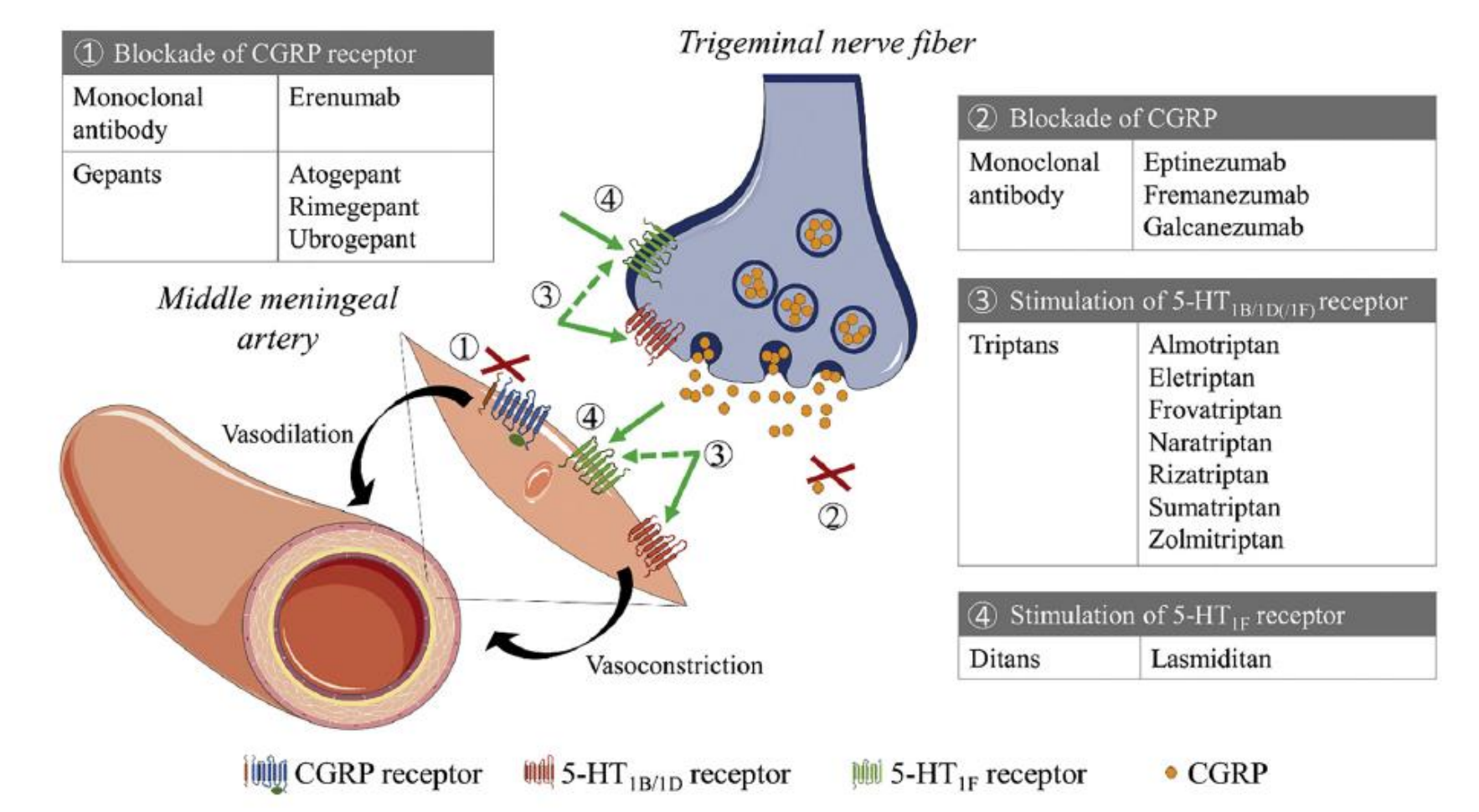
Calcitonin Gene Related Peptide (CGRP)



Levin M. Headache. 2018 Nov-Dec; 58(10): 1689–1696.

Overview of Possible Targets of Migraine-specific Medications



Reviewed in: Negro A, Martelletti P, Lionetto L, Guglielmetti M, Simmaco M, Martín-Escalón CM, MaassenVanDenBrink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. Pharmacol Ther. 2020;211:107528. doi: 10.1016/j.pharmthera.2020.107528

Acute Treatment

Patient Expectations for Acute Migraine Treatments

- "I want attacks to be treated rapidly, consistently without risk of headache returning"
- "I want to function normally"
- "I don't want to rely on other rescue medications"
- "I don't want to have to go to the doctor or ER"
- "I want to be able to afford it"
- "Minimal or no side effects would be gre

Step Care vs Stratified care

Step Care

1. • OTC Analgesics
2. • NSAIDS
3. • Triptan, DHE →
   • Ditans, Gepants
4. • Rescue Therapy
   • Corticosteroid, Neuroleptic

Stratified Care

1

- Treatment based on attack profile, associated symptoms, and level of disability

MILES FOR MIGRAINE

Factors to Consider when Choosing an Abortive

- Consider comorbid disease
  - History of heart attacks, strokes, vascular or kidney disease, and pregnancy
- Past use of meds- their efficacy and any sensitivities
- Types of attacks
  - Fast build up
  - Wake up with
  - Associated nausea/ vomiting
- Patient's comfort level with injections or nasal sprays

Acute Treatments for Migraine

OTC Analgesics

NSAID

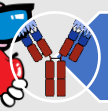
Triptan

DHE, Ergots

Neuromodulation

Rescue Therapies

Opioids


Gepants

Ditans

- Most people with migraine have never used acute prescription medications for migraine attacks
- Triptan discontinuation rate: 55%
  - Lack of efficacy (38%) and side effects (23%)
- 36.3% of patients report current opioid use or keep opioids on hand to manage their migraines
- Risk of medication overuse headache (MOH

Lipton RB, et al. *Headache.* 2019 Nov;59(10):1762-1772.
Lipton RB, et al. *Headache*. 2019;59(8):1310-1323
Alam A, et al. *Neurology*.2019; 92 (15 Supplement
Lipton RB, et al. *Neurology*. 2020;94:e1-e12.

For Patients, each Migraine is a Difficult Choice

2/3 of pts delay or avoid taking their prescription

Is it a migraine?

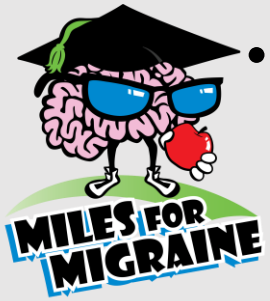
Limited number of pills prescribed

Side Effects are intolerable

MILES FOR MIGRAINE

Migraine assessment of current therapy

- Consistency of response:
  - *Does your migraine medication work consistently in the majority of your attacks?*
- Global assessment of relief:
  - *Does the headache pain disappear within 2 hours?*
- Impact:
  - *Are you able to function normally within 2 hours?*
- Emotional response:
  - *Are you comfortable enough with your medication to be able to plan your daily activities?*



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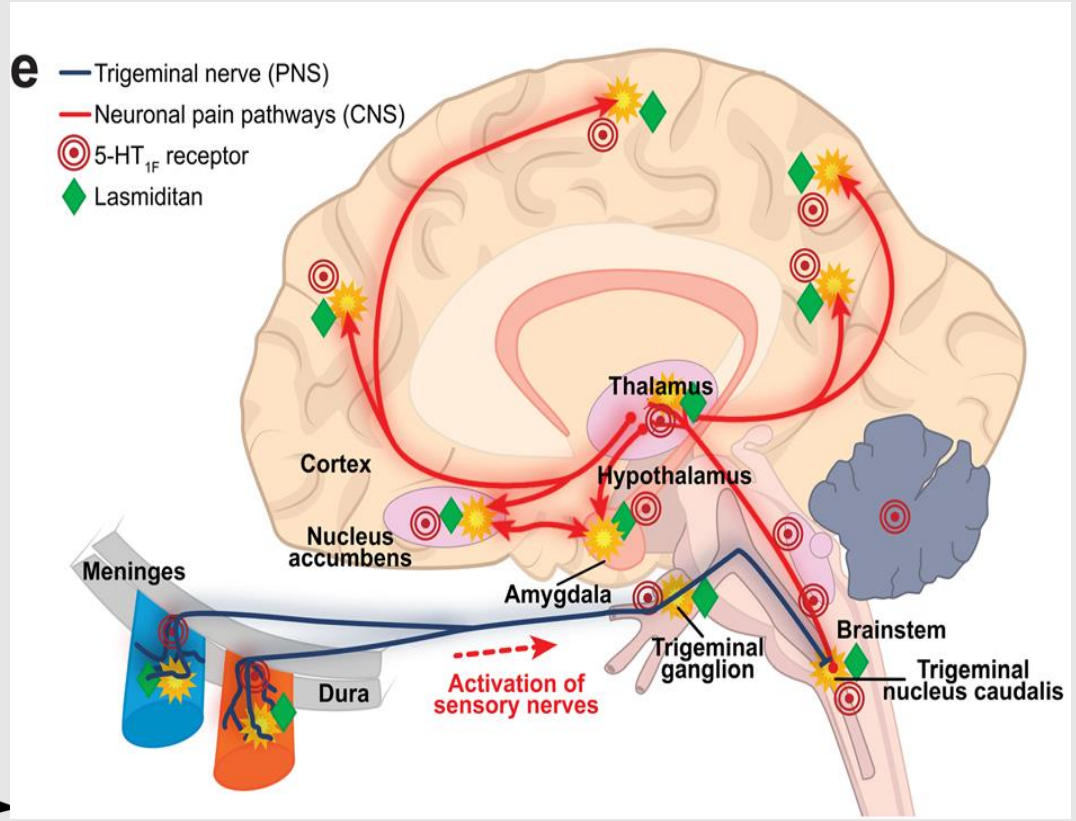
DITANS
Lasmiditan (Reyvow)
5-HT1 F receptor agonist

5-HT_{1F} Receptor and Lasmitidan



5-HT1F receptors, involved in modulating pain signaling, are present on both peripheral and central pain pathways.

- Inhibit pain pathways, including the trigeminal nerve
- Inhibit the release of neurotransmitters and neuropeptides
- Does not cause vasoconstriction of blood vessels

Clemow et al. The Journal of Headache and Pain (2020) 21:71
Rubio-Beltrán E,et al. *Pharmacol Ther*. 2018;186:88-97. Vila-Pueyo M.. *Neurotherapeutics*. 2018;15:291-303

Gepants

Oral small molecule calcitonin gene-related peptide receptor antagonist

Available

Ubrogepant	• **Ubrelvy** • **Acute**
Rimegepant	• **Nurtec ODT** • **Acute (+preventative 2021?)**

Clinical trials

Atogepant	• **Migraine prevention in daily dose**
Zavegepant	• **Nasal spray (10 and 20 mg)** • **Acute treatment**

MILES FOR MIGRAINE

CLASS	GEPANT		DITAN
Brand Name	UBRELVY	NURTEC ODT	REYVOW
Generic Name	ubrogepant	rimegepant	lasmitidan
Manufacturer	Allergan	Biohaven	Eli Lilly
Dosage	50 or 100 mg May repeat in 2 hour Max dose is 200 mg /24 hr	75 mg as needed Max dose 75 mg in 24hr	50, 100 or 200 mg Max dose is 1 dose in 24hr
Efficacy	2 hr Pain Free (Pain relief) 19.2% at 50 mg (60.7%) 21.2% at 100 mg (61.4%)	2 hr post dose Pain Free 21.2 % Normal function: 38.1% Pain Relief: 59.3%:	2 hr Pain Free (Pain relief) 29% at 50 mg (56%) 31% at 100 mg (61%) 39% at 200 mg 61%)
Delivery Administration	Oral Tablet	Orally dissolving tablet	Oral tablet
Half Life	5-7	11 hours	5.7 hours
Primary Side Effects	Nausea and drowsiness	Nausea	Dizziness, fatigue, paresthesias, sedation, nausea, muscle weakness
Warnings	None provided	Hypersensitivity reactions including dyspnea and rash	Driving impairment, CNS depression, serotonin syndrome,

Precautions

Gepants

- Drug interaction caution due to same liver processing pathway (CYP3A4) as a number of medications,
  - of these medications could either increase or decrease the effectiveness of medications using the same pathway
- None of the gepants is recommended in pregnancy or when nursing.

Ditans

- Driving Impairment:
- Advise patients not to drive or operate machinery for 8 hours after taking REYVOW
- Patients who can't follow this advice should not take REYVOW
- Patients may not be able to assess their own driving competence and degree of impairment
- REYVOW is a Schedule V controlled substance.

Consider Prevention When…

Significant Interference
with routine activities —
despite use of acute treatment

Attack Frequency
> 1/week

Elevated Risk:
Medication overuse

Acute Medications
Ineffective
Contraindicated
Troublesome AEs
Overused

Uncommon Subtypes Present
Hemiplegic
Brainstem
Prolonged aura
Migrainous infarction

Patient Preference

MILES FOR MIGRAINE

Preventative Treatments for Migraine

Antidepressants

Antihypertensives

Antiepileptics

Neurotoxins

Nutraceuticals

Neuromodulation

Nonpharmacological

Anti-CGRP

- ~ 40% of episodic migraine should be on preventative therapy
- ~45% of patients on preventive therapy experience a reduction in the mean monthly frequency of migraine attacks by ≥50%
- ~2 of 3 of people who are candidates for preventive treatment don't actually use it
- ~70% of patients are non-adherent with oral preventive therapy after 6 months of treatment
- Lack of efficacy and side effects is top reasons for discontinuation

PREVENTION:
MONOCLONAL ANTIBODIES

Migraine Preventative Therapy
CGRP mAbs

- Extended biological half-life
  - administered either monthly or quarterly either SQ/IV
- Require minimal or no dose titration
- Rapid onset of effect compared to conventional oral preventive drugs
- Highly selectivity and target an important mediator in the pathogenesis of migraine
- Studies have all yielded + results with a favorable adverse event profile
- This tolerability profile promises to improve adherence and, possibly, long-term outcomes

What has Changed in Migraine Prevention?

Prevention prior to mAbs

- Preventative therapies were borrowed from other therapeutic areas
- Numerous adverse effects, poor adherence
- 4-6 weeks + to become effective
- ≥50% responder rates ~45%
- Uncertain effectiveness in setting of medication overuse headache
- Not always effective at lowering acute medication use

Prevention with use of mAbs

- Specifically designed for migraine prevention
- Wide therapeutic targets: episodic and chronic migraine, medication overuse headache, episodic cluster
- Effective: < 1 week to 1 month
- Lower all acute medication use
- Side effect profile similar to placebo
- Responder rates at ≥75% or more

MILES FOR MIGRAINE

Monoclonal Antibodies Targeting the CGRP Pathway for Episodic and Chronic Migraine Prevention

Erenumab	• CGRP Receptor
Fremanezumab	• CGRP Ligand
Galcanezumab*	• CGRP Ligand
Eptinezumab	•CGRP Ligand

MILES FOR MIGRAINE

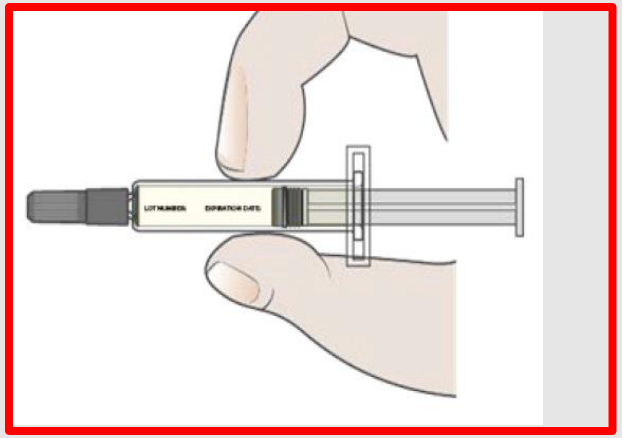
*Also for episodic cluster headache

CGRP mAbs
Migraine Prevention Dosing

Erenumab	• Aimovig (Amgen FDA approved 5/17/18)) • SQ Autoinjector: 70 or 140 mg monthly
Fremanezumab	• Ajovy (Teva FDA approved 9/14/18) • SQ and SQ autoinjector: 225 mg monthly or 675 mg quarterly
Galcanezumab	• Emgality (Lilly FDA approved 9/26/18, 6/4/19 eCH) • SQ Autoinjector:240 mg initial dose followed by 120 mg monthly • Cluster: 300 mg: 3 x 100 mg prefilled syringes
Eptinezumab	• VYEPTI (Lundbeck FDA approved 2/21/20) • IV: 100 mg and 300 mg quarterly

Methods of Injections

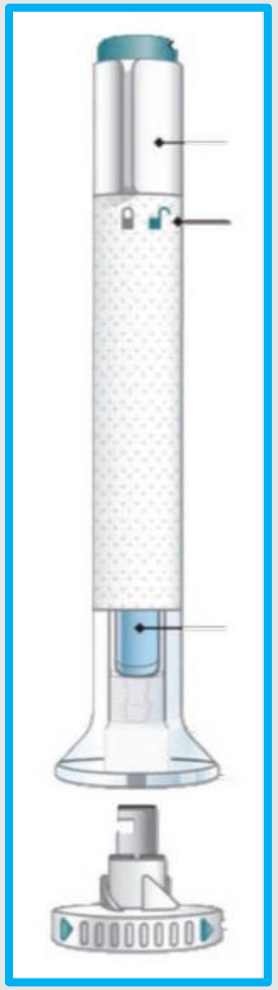
Erenumab: monthly



Galcanezumab: monthly

Cluster HA dosing

Fremanezumab: monthly or q3 months



Eptinezumab: IV q 3 months

CGRP mAbs for Migraine Prevention

Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
• PROMISE-1 in **EM**: reduced mean MMD with eptinezumab 30, 100, and 300 mg vs placebo (-4.0, -3.9, -4.3 d, respectively, weeks 1-12; $P < .0001$)[a] • PROMISE-2 in **CM** reduced mean MMD with eptinezumab 100 mg and 300 mg vs placebo (-7.7, -8.2, -5.6 d, respectively, weeks 1-12; $P < .0001$)[b]	• STRIVE in **EM**: reduced mean MMD with erenumab 70 mg (-3.2 d) and 140 mg (-3.7 d) vs placebo (-1.8 d); $P < .001$[c] • ARISE in **EM**: reduced mean MMD with erenumab 70 mg (-2.9 d) vs placebo (-1.8 d); $P < .001$[d] • In **CM**: reduced mean MMD with erenumab 70 mg (-6.6 d) and 140 mg (-6.6 d) vs placebo (-4.2 d); $P < .0001$[e]	• HALO EM in **EM**: reduced mean MMD with fremanezumab quarterly (-3.5 d) or monthly (-3.7 d) vs placebo (-2.4 d) at week 12; $P < .001$[f] • HALO CM in **CM** reduced mean HDM with fremanezumab quarterly (-4.3 d) and monthly (-4.6 d) vs placebo (-2.5 d) at week 12; $P < .001$[g]	• EVOLVE-1 in **EM**: reduced mean MMD with galcanezumab 120 mg (-4.7 d) and 240 mg (-4.6 d) vs placebo (-2.8 d) at 6 months; $P < .001$[h] • EVOLVE-2 in **EM**: reduced mean MMD with galcanezumab 120 mg (-4.3 d) and 240 mg (-4.2 d) vs placebo (-2.3 d) at 6 months; $P < .001$[i] • REGAIN in **CM**: reduced mean HDM with galcanezumab 120 mg (-4.8 d) and 240 mg (-4.6 d) vs placebo (-2.7 d) at 3 months; $P < .001$[j]

a. Silberstein S, et al. AHS 2018. Poster PF108LB; b. Lipton RB, et al. AHS 2018. Poster PF110LB; c. Goadsby P, et al. *N Engl J Med.* 2017;377:2123-2132; d. Dodick DW, et al. *Cephalalgia*. 2018;38:1026-1037; e. Tepper S, et al. *Lancet Neurol*. 2017;16:425-434; f. Dodick DW, et al. *JAMA*. 2018;319:1999-2008; g. Silberstein SD, et al. *N Engl J Med*. 2017;377:2113-2122; h. Stauffer VL, et al. *JAMA Neurol*. 2018;75:1080-1088; i. Skljarevski V, et al. *Cephalalgia*. 2018;38:1442-1454; j. Detke HC, et al. *Neurology*. 2018;91:e2211-e2221.

Adverse Events

- The most common treatment-emergent adverse events (AEs) were mild injection site pain or erythema
- On the preclinical and clinical studies, no differences seen in cardiovascular parameters
- So far, LFT abnormalities have not been seen in excess of placebo
- Erenumab- Constipation and HTN postmarketing
- Avoid if planning pregnancy

CONSENSUS STATEMENT: PREVENTIVE AND ACUTE TREATMENT OF MIGRAINE

American Headache Society

American Headache Society. Headache. 2019;59:1-18.

Who Should Receive the mAbs

AHS Consensus Statement

Should be available to be prescribed by any licensed provider to patients who meet

the following criteria:

1. Lower frequency EM (4-7 headache days/month)

- Lack of success with 2: AEDs (VPA, TPM), TCAs (amitriptyline, nortriptyline), beta-blockers, SNRIs, other Level A or B migraine preventive medications
- Documented at least moderate disability or impact by the migraines

2. High frequency EM (8-14 days/month)

- Same requirements as 1, but no need to document disability, as they are clearly impacted

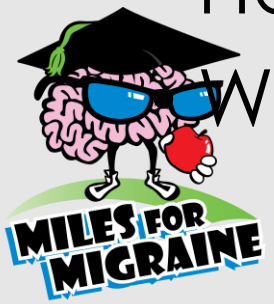
3. CM (≥15 days/month)

- Same requirements as 1, or onabotulinumtoxinA as an additional choice, and no need to document disability, as they are clearly impacted

American Headache Society. Headache. 2019;59:1-18.

Anti-CGRP Therapy: Where Does It Fit In Our Clinics?

- Who to prescribe it to?
- Who is likely to respond?
- Is it better to target ligand or receptor?
- Are there side effects noted in real life experience not seen in clinical studies?
- Does the medication wear off before the next dose?
- How long will patients need anti-CGRP therapy?
- What is longer term effect of CGRP antagonism?



Other Practical Considerations

- Age, long term safety (>5 years)
- Efficacy in other types of migraine
- Switching between CGRP MAB
  - Timing between starting and stopping
- Use of CGRP receptor antagonists with CGRP MAB to ligand
- Use of CGRP MAB with onabotulinum toxin

Thank You!

Hope Your Thanksgiving
is filled with peace, love and great joy.
Have a wonderful time...
Happy Thanksgiving!
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