UT Southwestern
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Brain Institute

New Therapies for Migraine 2021

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Disclosures (past year)

Role	Organization
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Bold = relevant to content

It’s Almost Lunch time – What’s on the Menu?

- Discuss new and emerging medications for acute and preventive treatment of migraine and cluster headache
- Compare them to some of the existing medications
- Describe their indications and limitations

New and Emerging Therapies

- Monoclonal antibodies targeting CGRP
- Small molecules vs. CGRP
- 5-HT 1F receptor agonist (“ditans”)
- PACAP-38 receptor antagonist
- Devices
- Reformulations

Acute Treatment Should Be Offered To All Migraine Patients

Rest

Biofeedback

Caffeine

Heat/cold

Medications

Devices

McGregor EA. Ann Int Med 2017;166:ITC49-ICT64
Vargas BB. Continuum 2018;24:1032-51

Acute Treatment Home Medication Options

- Ditans
- Triptans
- Ergots
- NSAIDs
- Anti-CGRP
- OTC Combination Analgesics
- Prescription Combination Analgesics
- ~~Opioids~~
- Neuro-modulation
- Antiemetics
- High Flow Oxygen (Cluster)
- Sedatives

Go For the Gold With Acute Treatment

STEPPED CARE

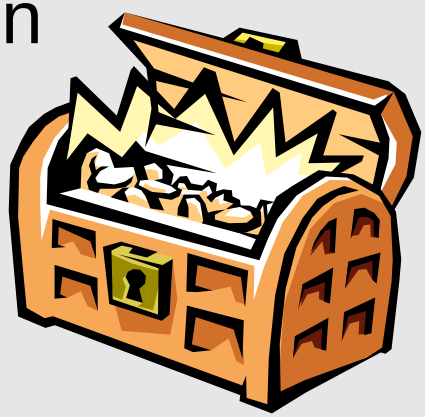
1. Acetaminophen (45 min)
2. Ibuprofen (45 min)
3. Butalbital/APAP (45 min)
4. Triptan (2 hours)
5. Repeat triptan

INCOMPLETE RELIEF

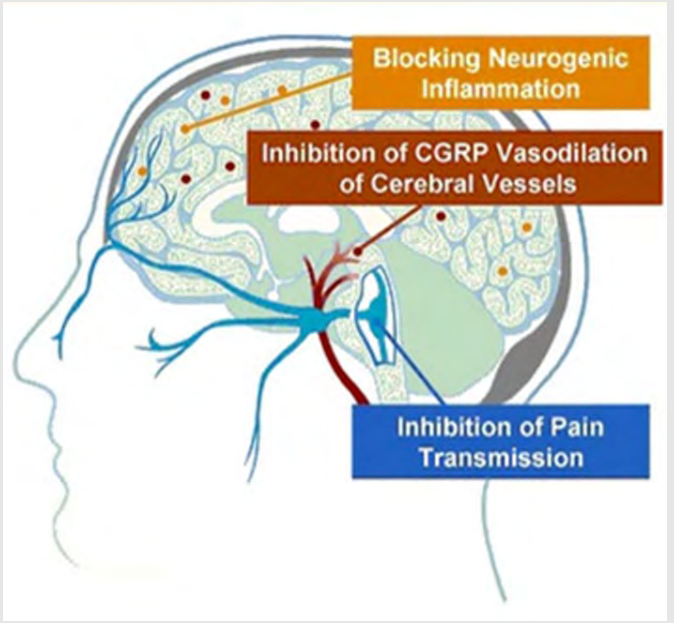
STRATIFIED CARE

1. Start with the treatment most likely to work for the patient
2. Treat early before central sensitization begins

RELIEF



Calcitonin Gene-Related Peptide

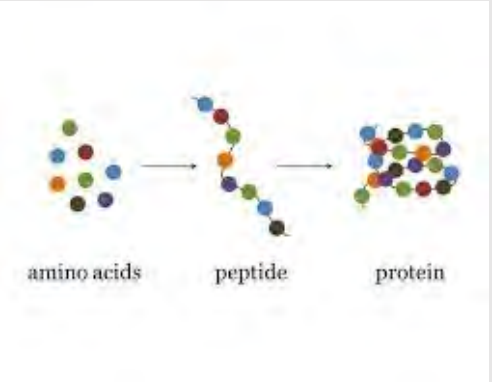


- 37 amino acid peptide
- Vasodilator and key mediator of neurogenic inflammation
- Expressed in trigeminal system
- Released from peripheral and central nerve endings during migraine and cluster headache

Russell FA et al. Physiol Rev 2014:1099-1142
Granstein RD et al. Acta Physiol (Oxf) 2015;213:586-94

What's a Peptide, anyway?

- Comes from the Greek "peptós" – "digested"
- A compound consisting of 2 to 50 amino acids



Did I hear digestion? I'm still hungry!

What's an amino acid?

The building blocks of proteins (>50 amino acids)

When you eat proteins, they are broken down into amino acids

Composed of nitrogen, carbon, hydrogen and oxygen with a side chain group

Some of them are used to form neurotransmitters and histamine

MILES FOR MIGRAINE

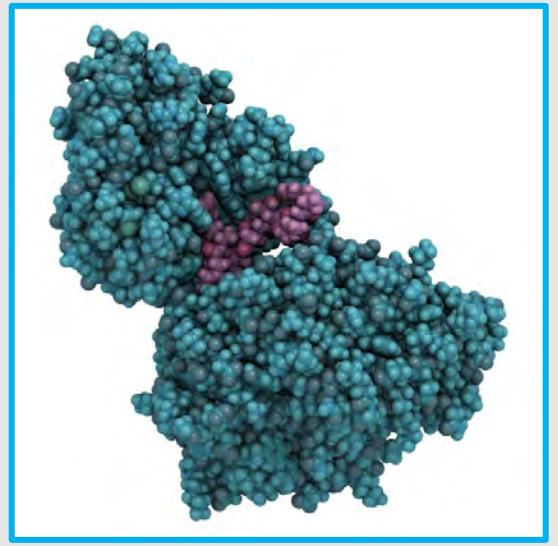
Acute Medications That Target CGRP

Acute Treatment

Rimegepant ODT (Nurtec™ 75 mg ODT)

Ubrogepant (Ubrelvy™ 50 mg, 100 mg)

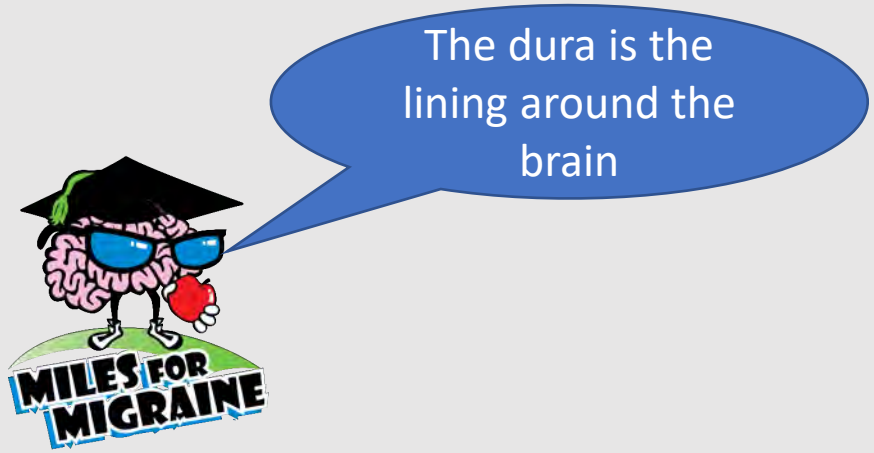
Zavegepant (intranasal, Phase 3 clinical trials)

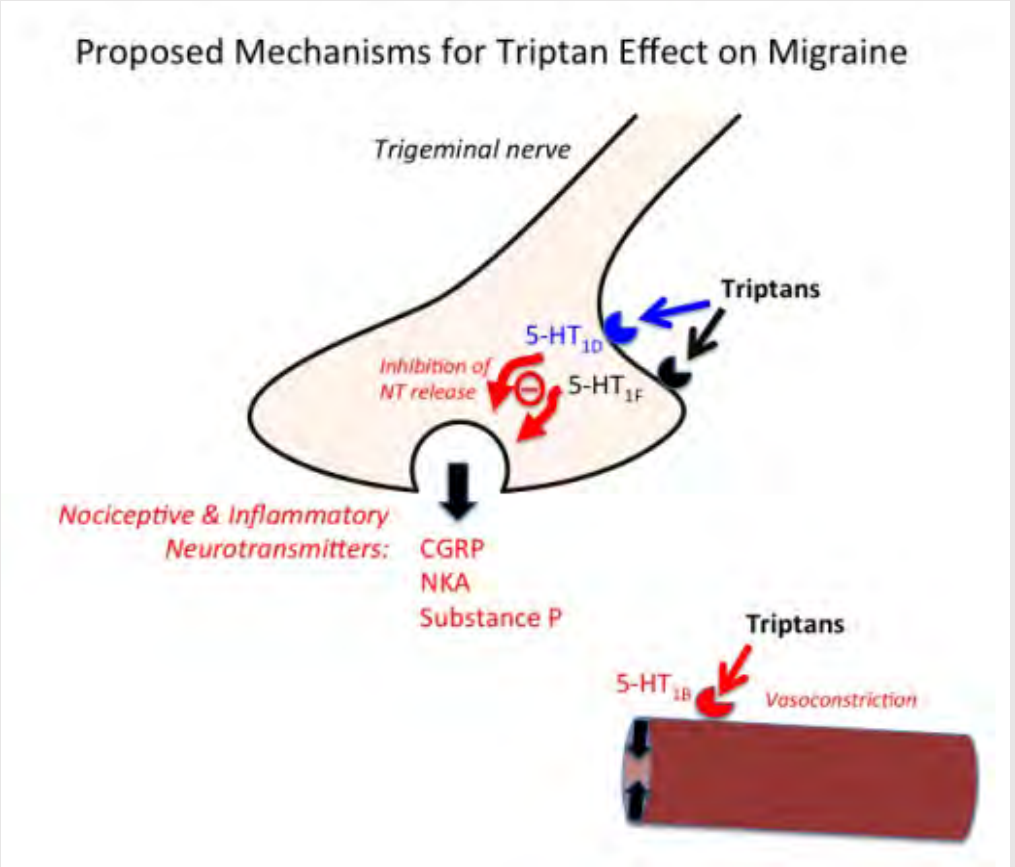


MILES FOR MIGRAINE

5HT-1F Receptor Antagonists

- Does not constrict blood vessels – an option for those in whom triptans (affect 5HT-1B/1D receptors) cannot be used
- Enters the brain
  - Effects and side effects
- Block neurogenic inflammation in the dura





Lasmiditan (5HT-1F receptor agonist)

- Acute oral migraine treatment – Revow™
- Clinical Trial Results
  - Patients with some vascular risk factors included
  - 2 hour pain free 38.8% (200 mg) vs 21% PBO
  - Benefit for pain freedom at 2 hours and relief of most bothersome symptom (48.7% vs 33.5% PBO)
  - No significant cardiovascular side effects (dizziness most common)
  - CV risk factors did not affect outcomes
  - Avoid driving for 8 hours after administration

MILES FOR MIGRAINE

Shapiro RE et al. J Headache Pain 2019;20

When to Offer Preventive Treatment

- 4 or more migraine attacks or ≥ 8 migraine days per month
  - Fewer if they negatively impact quality of life
- Patient preference (to have as few attacks as possible)
- Unacceptable migraine-related disability despite trigger management, appropriate use of acute medications, lifestyle modification
- Failure of, contraindication to, overuse of, or intolerable side effects from acute medications
- Migraine with brainstem aura or hemiplegic migraine
- Short-term prevention for predictable menstrual migraine, prolonged aura, history of migranous infarction

Silberstein SD. Continuum 2015:21(4):973-989

Preventive Treatment Medication Options

- Antidepressants Mood stabilizers
- Antihypertensives
- Antiepileptics
- Neuromodulation
- Nutraceuticals
- Onabotulinum-toxinA
- Anti-CGRP monoclonal antibodies

Adherence to Oral Preventives is a Problem

- Annual discontinuation rates of 40% or more
- Most common reasons:
  - Lack of efficacy (39-49%, depending on class)
  - Side effects (34-53%, depending on class)
  - Headaches resolved (1-9%, depending on class)
- Strategies for improvement:
  - Provider and patient monitoring
  - Patient education
  - Cognitive behavioral therapy
- Better treatments are needed!

Hepp Z et al. J Manag Care Pharm 2014;20:22-33

Monoclonal Antibodies Against CGRP

Block CGRP, without causing blood vessel constriction

CGRP mAbs do not enter the brain

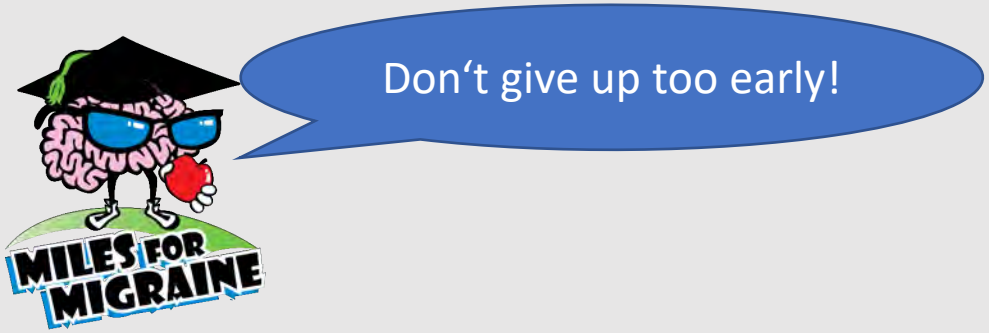
Reduce the amount of CGRP available without affecting other target

Eliminated through reticuloendothelial system (not liver or kidney)

Shuster NM, Rapoport AM. Clin Neuropharm 2017;40:169-74

	Galcanezumab	Eptinezumab	Erenumab	Fremanezumab
Antibody vs:	IgG4	IgG1	IgG2	IgG2a
Derivation	Fully humanized	Genetically engineered	Human	Fully humanized
Binding site	Molecule	Molecule	Receptor	Molecule
Administration	SC	IV	SC	SC
Dosing interval	monthly	every 3 months	monthly	Every month/3 months
Studied in:				
HF EM (4/5-14d)	Yes	Yes	Yes	Yes
CM (≥15 d)	Yes	Yes	Yes	Yes
Episodic Cluster	Yes	No	No	Yes (abandoned)
Chronic Cluster	Yes (negative study)	No	No	Yes (abandoned)
FDA-approved	Yes	Yes	Yes	Yes
Trade name	Emgality™	Vyepti™	Aimovig™	Ajovy™

- All studied in episodic, high-frequency episodic and chronic migraine
- One FDA-approved for episodic cluster headache prevention (galcanezumab 300 mg)
- May have rapid onset of action, sometimes within days (up to 6 months)
- All were superior in reducing headache days vs. placebo
- All reduced acute medication usage
- Average improvement over placebo treatment: 1-2 migraine days/month for EM (50% decrease overall) and 3-4 days/month for CM
- Well tolerated
- Effective with prior treatment failures
- No contraindications (unknown effect during pregnancy)



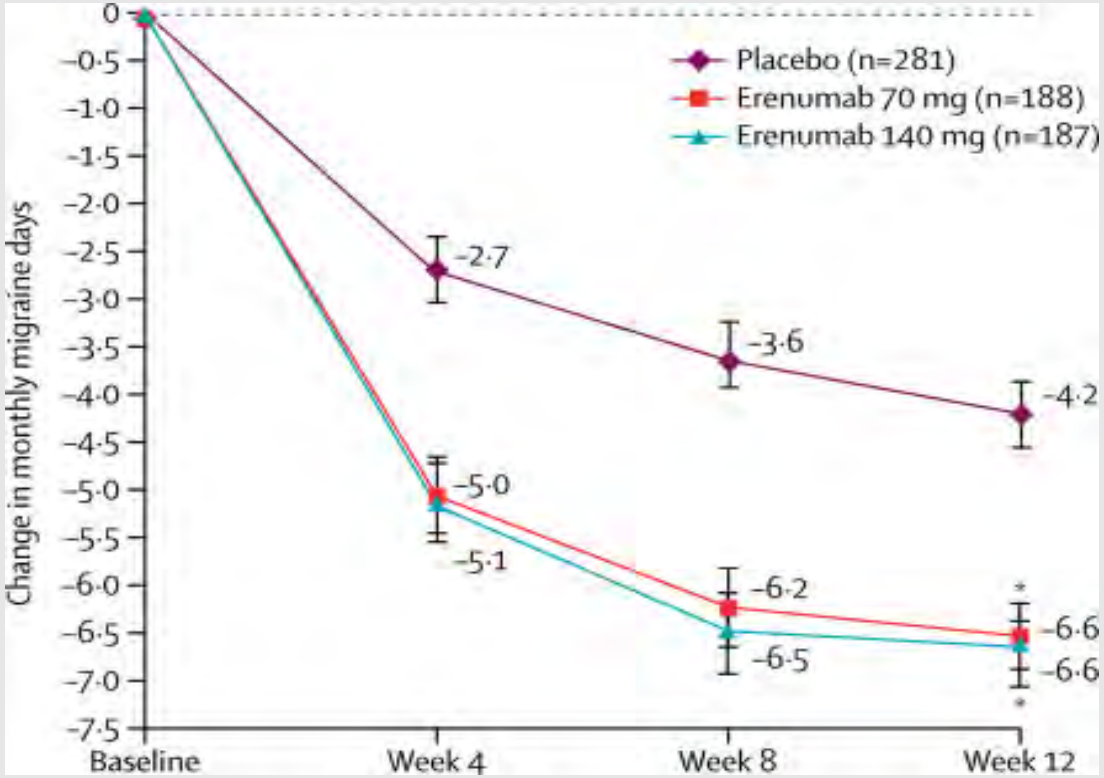
Ashina H et al. Neurol Sci 2017;38:2089-93
Schwedt T. Continuum 2018;24:1052-65

Common Adverse Events Reported in Clinical Trials with CGRP mAbs

- Injection site pain, redness
- Constipation (especially erenumab 140 mg → ileus)
- Other adverse events were not different than those occurring with the placebo injections
  - Upper respiratory tract infection, joint pain, “flu-like”
  - Nausea
  - Urinary tract infection
  - Some reports of abdominal, back pain, hair loss
- No signal of cardiovascular adverse events to date

Skljarevski V et al. Cephalalgia 2018;38:1442-54
Giamverardino MA et al. J Pain Res 2017;10:2751-60
Xu D et al. Cephalalgia 2019;39:1164-79
Kudrow D et al. Neurology 2020;94(5)

Erenumab CM Phase 2

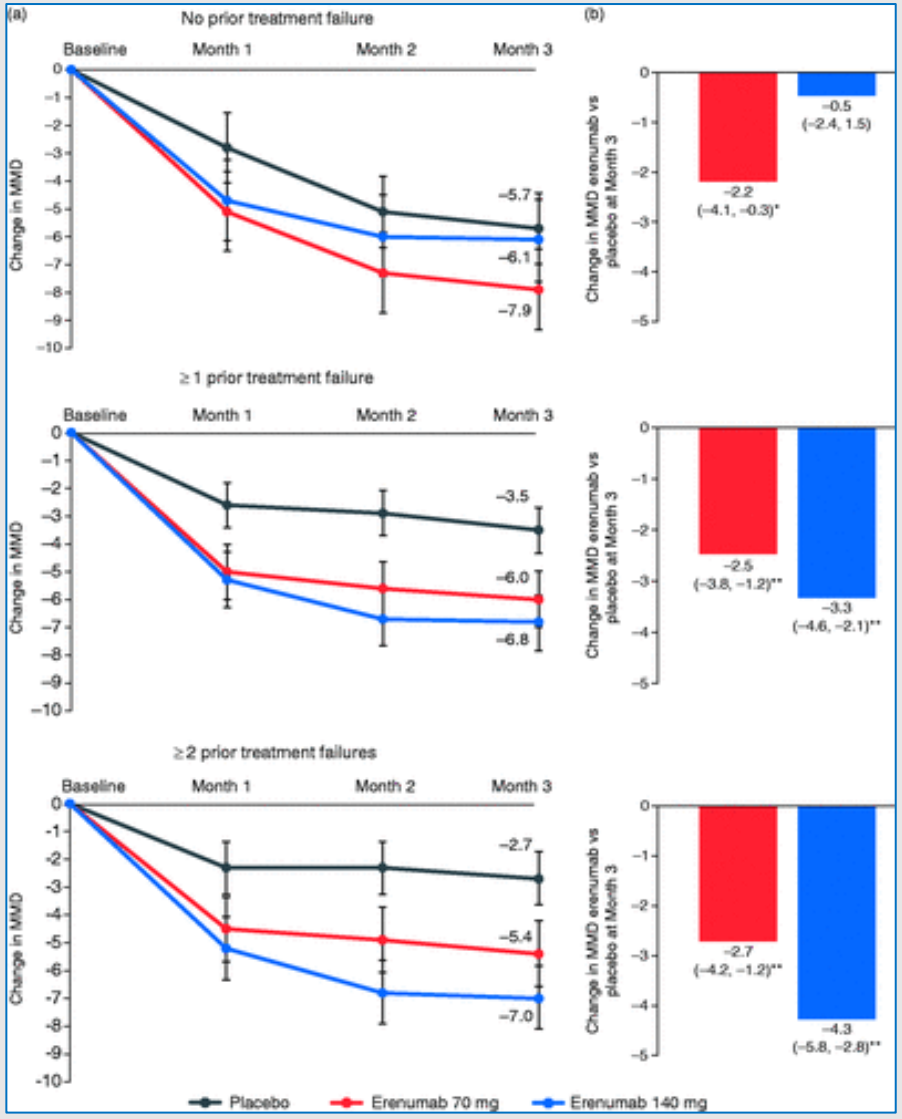


* p<0.05

Baseline ~18 migraine days

Tepper SJ et al. Lancet Neurol 2017;16::425-34

Effective in Some Patients with Prior Treatment Failure



Erenumab for CM (n=667)

- Exclusion: No response to more than 3 preventive treatment categories (intolerance OK)
- 73.8% received previous preventive treatment

Never failed (32.1%)

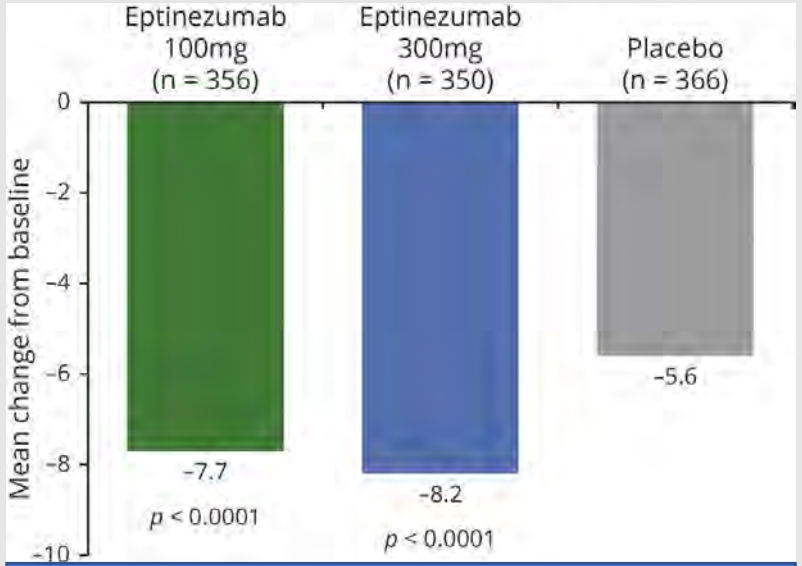
≥1 (67.9%)

≥2 (49.0%)

≥3 (34.8%)prior preventives

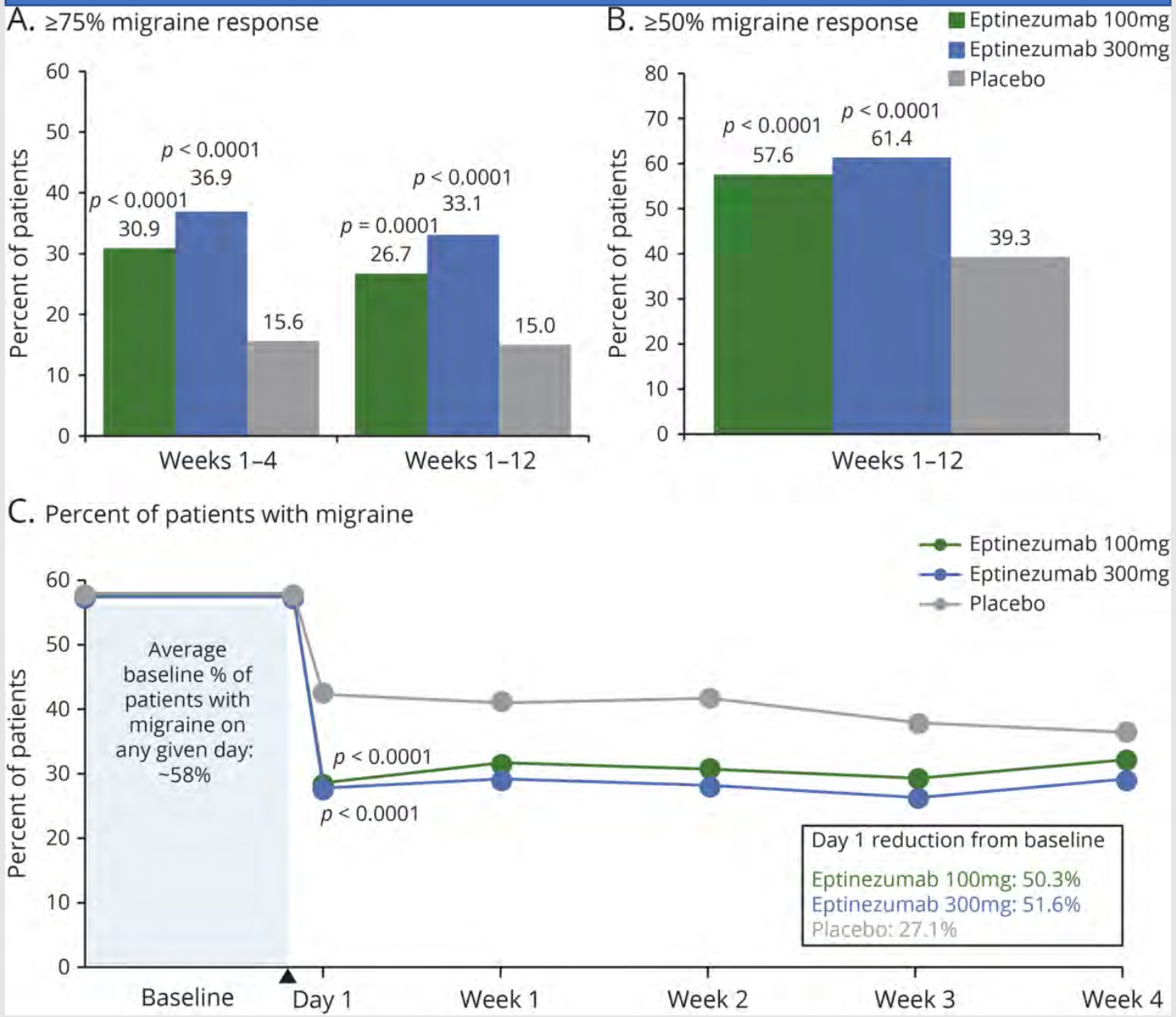
Ashina M et al. Cephalalgia 2018;38:1611-21

Eptinezumab CM Phase 3



Primary Outcome: Change in Monthly Migraine Days Over Weeks 1-12

Secondary Outcomes

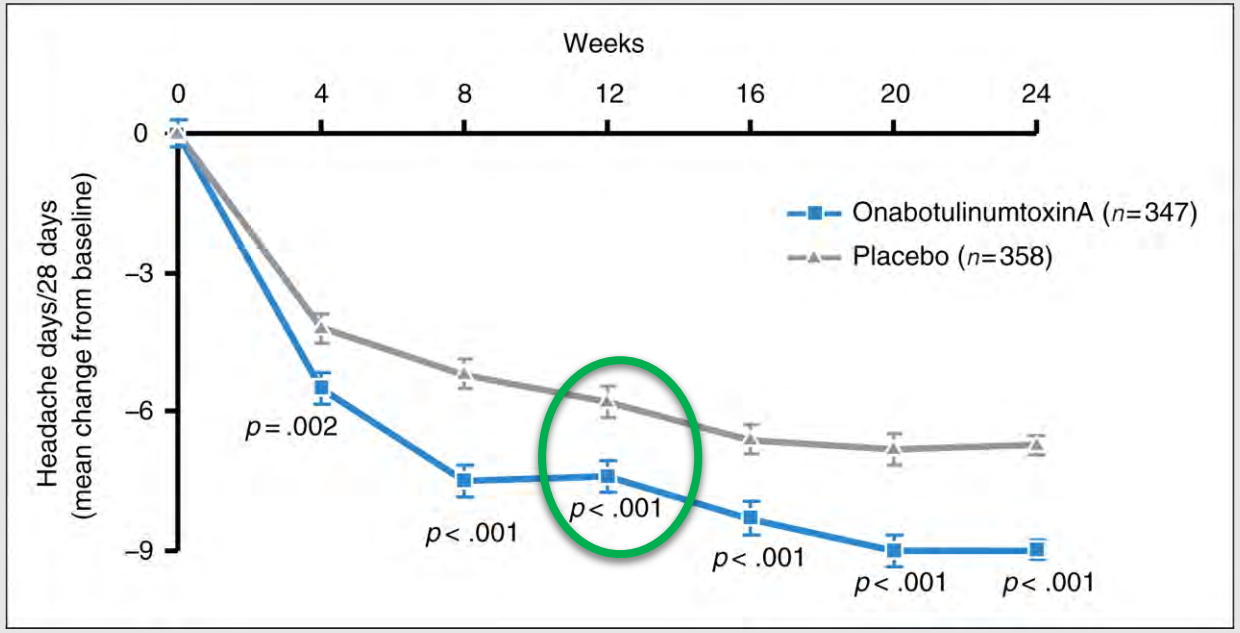


Lipton RB et al. Neurology 2020;94:e1365-77

Comparison to Current Treatments

OnabotulinumtoxinA for CM

PREEMPT 2 primary endpoint: mean change from baseline in headache day frequency



Hmm, these graphs all look kind of the same…

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Cephalalgia

Diener HC et al. Cephalalgia 2010;30:804-814

Topiramate for CM (up to 100 mg daily)

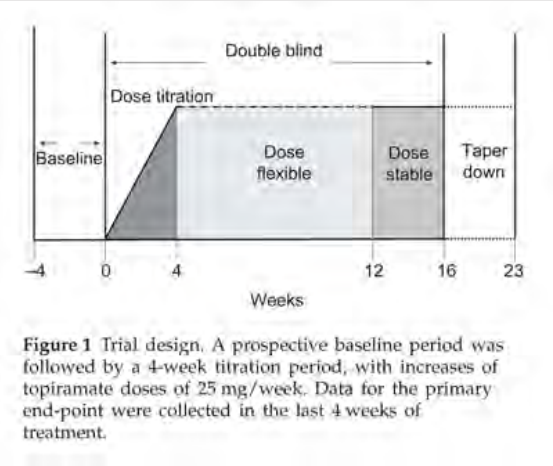


Figure 1 Trial design. A prospective baseline period was followed by a 4-week titration period, with increases of topiramate doses of 25 mg/week. Data for the primary end-point were collected in the last 4 weeks of treatment.

Responder Rate	Topiramate	Placebo
50%	~46%	22%
75%	~26%	12%
100%	5.8%	1.9%

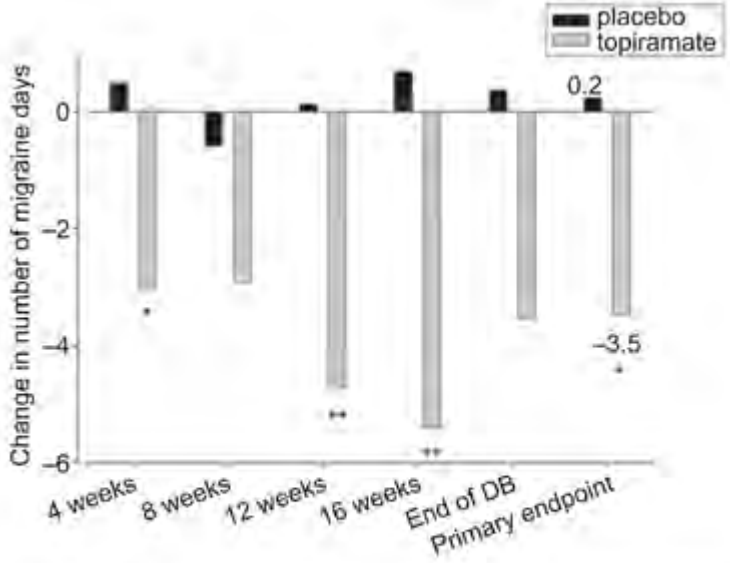


Figure 3 Mean change from baseline to monthly migraine days, intent-to-treat population. ■, Placebo; □, topiramate. $^{*}P < 0.05$; $^{**}P < 0.01$ vs. placebo.

Diener H-C et al. Cephalalgia 2007;27:814-23

Pros and Cons vs. Current Preventive Therapy

Monoclonal Ab

- Injection (SC or IV)
- No titration
- May have rapid onset in some
- “Super-responders” (75-100%)
- Low incidence of side effects
- Not eliminated by the liver or kidney
- Potential for increased adherence
- Indicated for EM and CM
- High cost and inconsistent insurance coverage (prior treatment failure)
- Prior treatment failures required
- Pre-authorization

Oral Preventives

- Oral
- Requires gradual dose increase
- 2 months of adequate dose to asses effectiveness
- Treatment limited by side effects and other medical conditions
- Eliminated by liver and kidney
- Poor adherence
- None FDA-approved for CM
- Most generic, covered by insurance
- No pre-authorization for most

OnabotulinumtoxinA

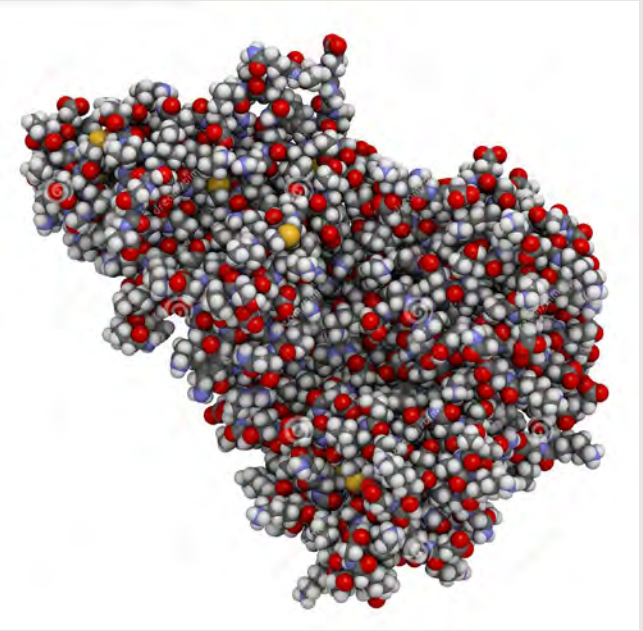
- Injections (31 SC)
- Adherence > orals
- Indication: Chronic migraine
- Good option for patients with multiple medical problems
- Low incidence of side effects
- 2-3 treatments required to assess effectiveness (24-36 weeks)
- Requires pre-authorization and failed oral treatment by most insurers
- Office procedure

CGRP Small Molecules For Preventive Treatment

Atogepant (Submitted to FDA)

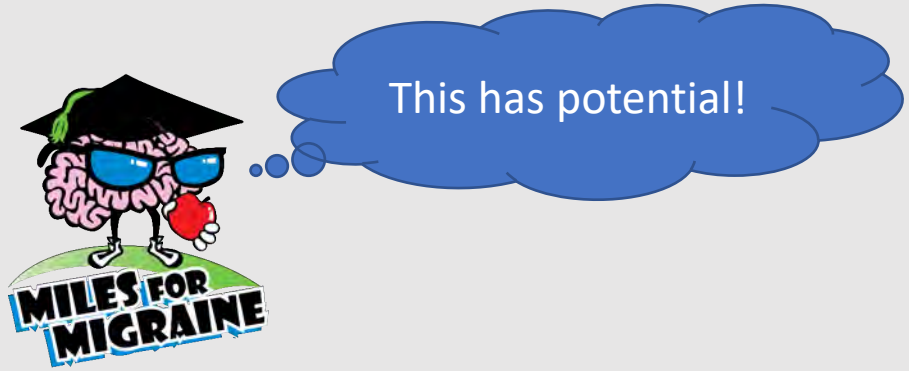
Rimegepant ODT (Submitted to FDA)

Vizegepant* (Phase 2/3 clinical trials)
*possible injection, oral, inhalation



PACAP: Another possible target

- Pituitary adenylate cyclase-activating polypeptide
- Present in sensory trigeminal neurons
- Selectively activates PAC_1 receptor, modulates pain
- PACAP38 given IV produces marked dilation of arteries in the head and delayed migraine-like attacks in migraine patients
- PCACP38 is elevated during cluster and migraine attacks
- Anti-PACAP38 ligand monoclonal antibody in development
- An anti-PAC_1 receptor monoclonal antibody is a therapeutic target under investigation



Tuka B et al. J Headache Pain 2016:17:69
Tatji J et al . Neuropeptides 2015;19-30
Burio-Beltrán E et al. J Headache Pain 2018

Neuromodulation (FDA-cleared)

Non-invasive vagus nerve stimulation
(episodic cluster, cluster prevention, migraine acute)
gammaCore™

Trigeminal and Occipital Nerve Stimulation
(migraine acute)
(Relivion®®)

Supraorbital transcutaneous stimulation
(migraine acute and prevention)
Cefaly™

I'm buzzing with excitement!

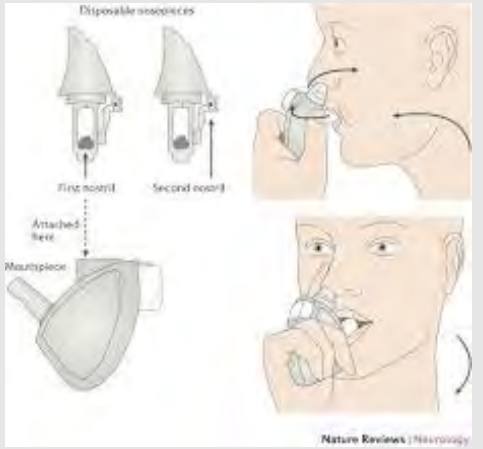
Transcranial magnetic stimulation
(migraine acute and prevention)
SpringTMS™

Remote non-painful electrical stimulation
(migraine acute)
Nerivio™

MILES FOR MIGRAINE

Old Dogs, New Tricks

New Non-Oral Triptan Formulations



- Useful for:
  - Rapid escalation of migraine
  - Migraine is of maximal intensity at onset
  - Migraines that are present upon awakening
  - Migraines that awaken patients from sleep
  - Migraines associated with severe nausea and vomit
  - Oral triptans don't work well (gastric stasis)
- Sumatriptan 3 mg SC (Zembrace™)
- Sumatriptan 22 mg nasal powder (Onzetra™)
- Sumatriptan 10 mg nasal spray (Tosymra™)

MILES FOR MIGRAINE

In Development / Clinical Trials

- Transdermal zolmitriptan (Phase 3 completed)
- Oral liquid celecoxib
- DHE nasal spray
- DHE nasal powder
- Oral meloxicam – rizatriptan combination (MoSEIC™ technology*)
- Promethazine – sumatriptan combination capsule (Phase 2)
- DaxibotulinumtoxinA

*Molecular Solubility Enhanced Inclusion Complex (modified pH to enhance GI absorption)

Summary

- This is an exciting time in the field of headache medicine!
- Preventives designed specifically for migraine treatment
- Potential for acute treatments that can be used in patients with vascular risk factors
- One size will not fit all – will still have to use multiple therapies in some patients
- New options are better tolerated and may improve adherence
- Gepants used for acute and preventive treatment
- Uses for other headache conditions will likely follow

Thank You!

Every Step Counts!