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# Migraine Therapeutics Update Q4 2020

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# Disclosures (past year)

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**Bold** = relevant to content

# Case Presentation

CC: “Do you have any suggestions for things I haven’t tried?”

HPI: 57-year-old manager for family business

Migraines since age 16 – occurred every 3 months

Worse in college, required IV fluids at times

- More frequent, occurred with menses
- Took aspirin/caffeine tabs most days
- Headache recurred when medication wore off

Now:

- Migraine present upon awakening, often with nausea at onset. Intensity is 2-10 out of 10
- Gets out of bed and may drink water → vomits
- Photophobia, phonophobia, osmophobia, vomiting “bile”
- Watery diarrhea with vomiting later in the day

Takes symptomatic meds 5 days weekly

Misses activities and work, cancels activities and trips, affects relationships with sisters

## Current meds for Headache:

- CoQ10
- Eletriptan 20-40 mg (8 tabs monthly)
- Ondansetron ODT
- Promethazine suppositories
- ASA/APAP/caffeine (2-3 times weekly)

## Previous headache meds:

- Symptomatic: Sumatriptan 100 mg (wore off), ASA/caffeine
- Preventive: Topiramate 300 mg (helped but lost weight and cognitive dysfunction), amitriptyline 10 mg (sleepy), propranolol 20 mg (low BP), venlafaxine (vivid dreams, ineffective), sodium valproate (weight gain, tremor)
- Procedures: OnabotulimtoxinA X 3 (ineffective)

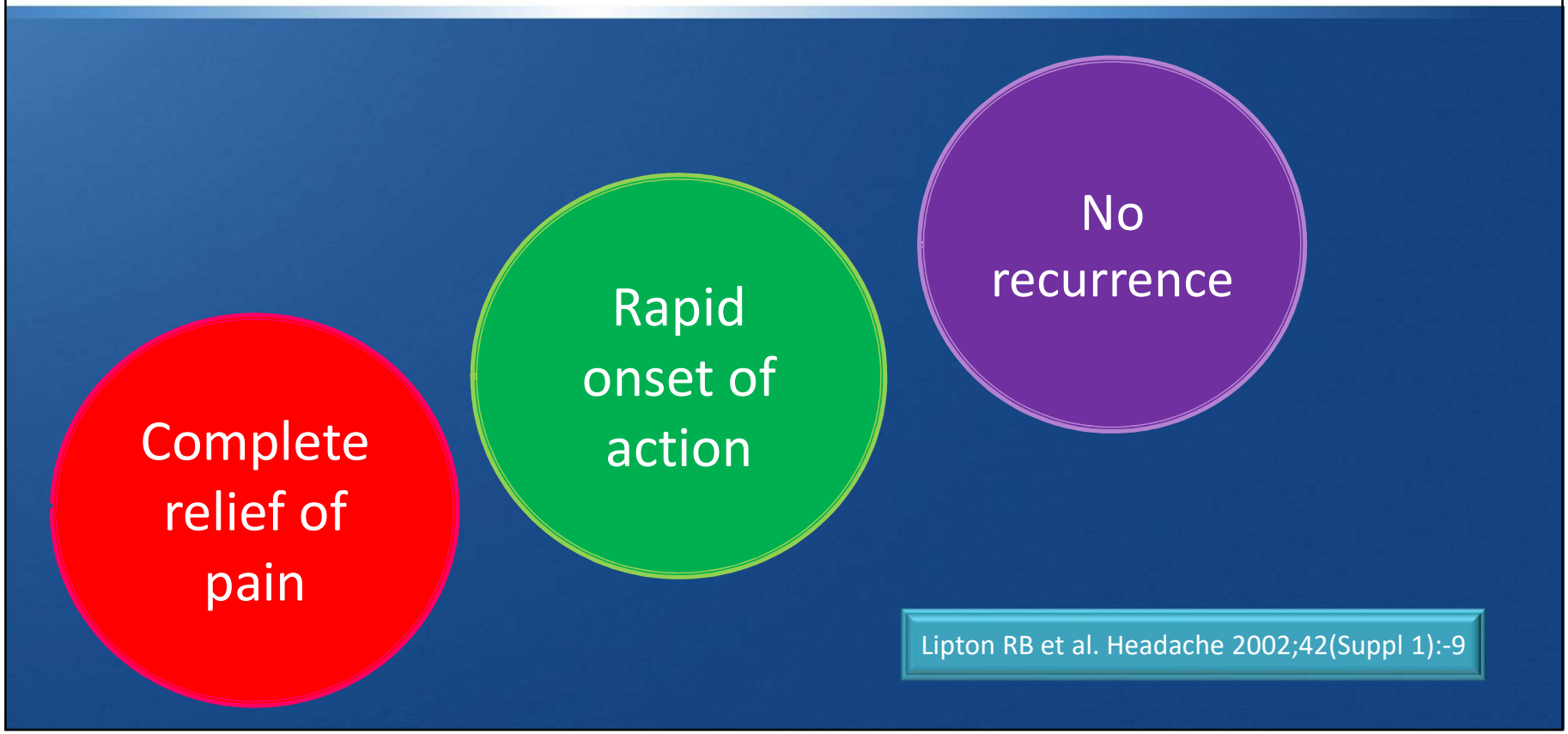
# Case 2

- CC: What can I take for my migraine headaches?
- HPI:
  - 67-year-old woman with episodic migraine with aura since age 13
  - Successfully used triptans in the past but experienced angina 2 years ago and diagnosed with coronary artery disease so they were stopped
  - Tried NSAIDs, OTCs, isometheptene, butalbital without success
  - Allergic to codeine and morphine derivatives
- PMHx: Hypertension, hypercholesterolemia
- FHx: MI and stroke on both sides of the family

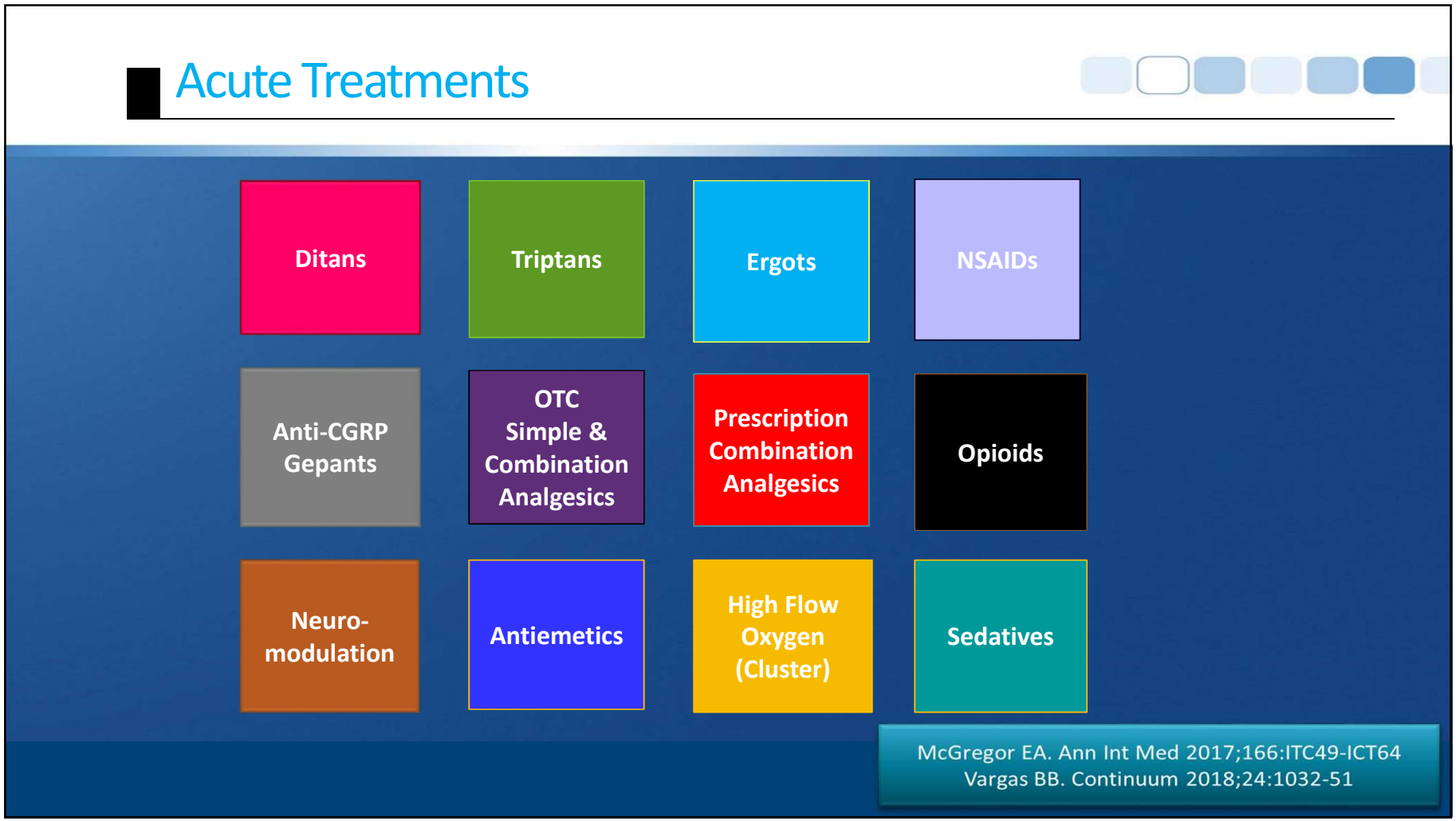
# Learning Objectives

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

# What Do Patients Want From Acute Migraine Treatment?



# Acute Treatments




Acute Treatments
Ditans
Triptans
Ergots
NSAIDs
Anti-CGRP Gepants
OTC Simple & Combination Analgesics
Prescription Combination Analgesics
Opioids
Neuro-modulation
Antiemetics
High Flow Oxygen (Cluster)
Sedatives
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# Acute Treatment

- Should be offered to all patients with migraine
- Discuss treatment strategy
  - Treat early but…
  - Know which headaches to treat and set limits (2 days weekly)
- Start with the treatment that is most likely to work for each attack
  - At the most effective dosage
- Try to use acute medications with a low risk of MO

# Too Much of a Good Thing: Recognizing Medication Overuse Headache

Definition: Headache occurring ≥ 15 days monthly in people with pre-existing headache as a consequence of regular overuse of acute headache treatments (for at least 3 months)

AKA "Transformed migraine", "Rebound headache"

Develops with medications that sensitize the trigeminal system

| ≥ 10 days monthly | ≥ 15 days monthly |
|---|---|
| Triptans | Acetaminophen |
| Opioids | Aspirin |
| Butalbital | NSAIDs |
| Combination analgesics (including caffeine) | |

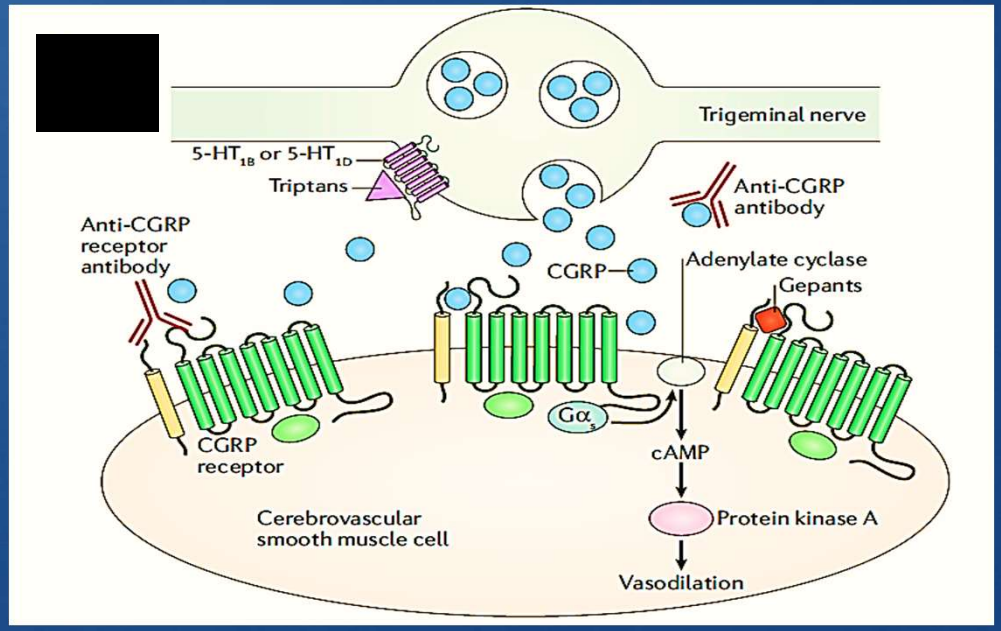
# When to Consider Non-Oral Treatment

- Associated with marked nausea and vomiting
- Migraine present on awaking
- Migraine that awakens the patient from sleep
- Migraines that peak in intensity within 30 minutes of onset
- Poor response to oral treatments (gastric stasis during the attack)

# Limitations of Acute Treatments

- Medical contraindications
  - Triptans
  - Ergots
  - NSAIDs
- Lack of effectiveness or incomplete relief
  - Unacceptable latency of onset
  - Relief may not be sustained
- Side effects
  - Nausea
  - Triptan sensations

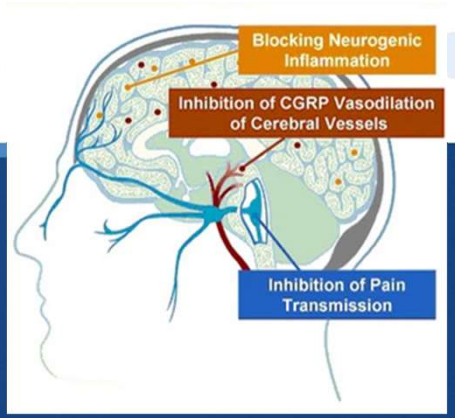
# Treatment Targets




Edvinsson L et al. Rev Neurol 2018;14:338-50

# What's New

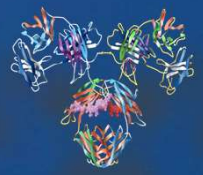
# Gepants: Calcitonin Gene-Related Peptide




- 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

# Small Molecule CGRP Receptor Antagonists vs. Monoclonal Antibodies ("gepants")



| Small Molecules | Monoclonal Antibodies |
|---|---|
| Target specificity lower | Target specificity high |
| Clearance (Liver, kidney) | Clearance RES |
| Size < 1kD | Size ~150kD |
| Oral | Parenteral |
| Many enter cells and cross BBB | Do not enter cells or cross BBB |
| Half-life minutes to hours | Half-life ~4 weeks |
| Immunogenicity (No) | Immunogenicity (yes) |

## For Acute and Preventive Treatment

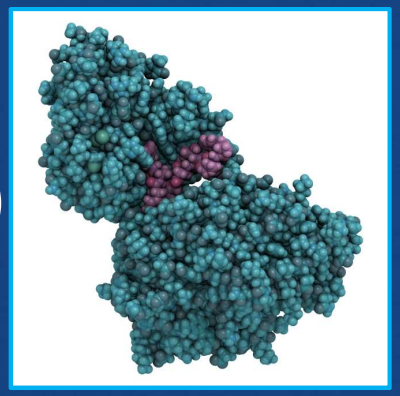
Acute Treatment (all ~20% pain free in 2 hours)

- Rimegepant ODT (Nurtec™ 75 mg ODT)
- Ubrogepant (Ubrelvy™ 50 mg, 100 mg)
- Zavegepant (intranasal*, Phase 3 clinical trials)

Preventive Treatment

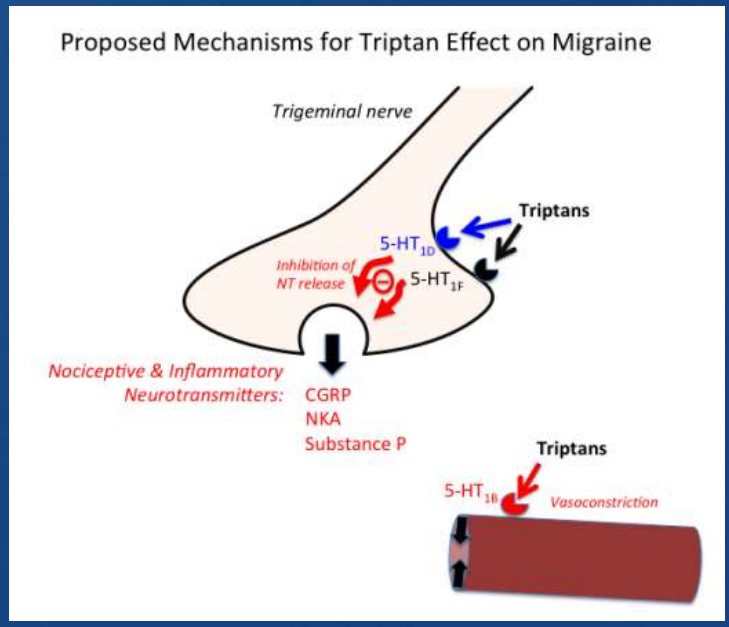
- Atogepant (Phase 3)
- Rimegepant ODT (Submitted to FDA, q o day)
- Zivegepant* (Phase 2/3 clinical trials)

*possible SC, PO, inhalation



# Ditans: 5HT-1F Receptor Antagonists

- No vasoconstrictive effects – option for those in whom triptans (5HT-1B/1D antagonists) are contraindicated
- Permeate the blood-brain barrier
  - CNS effects and side effects
- Block neurogenic inflammation in the dura



# Lasmiditan (5HT-1F receptor agonist)

- Acute oral migraine treatment – Reyvow™
- Met primary and key secondary endpoints in Phase 3 trials (SPARTAN and SAMURAI dose-finding, single attack studies, n=4439)
  - Patients with some vascular risk factors included
  - 2 hour pain free 38.8% (200 mg) vs 21% PBO
  - Statistically significant benefit for pain freedom at 2 hours and relief of most bothersome symptom (48.7% vs 33.5% PBO)
  - No significant cardiovascular AEs (dizziness most common)
  - CV risk factors did not affect outcomes
  - Avoid driving for 8 hours after administration (Schedule V)

Shapiro RE et al. J Headache Pain 2019;20

# Neuromodulation Devices

*FDA Cleared

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

*Transcranial magnetic stimulation
(migraine acute and prevention)
SpringTMS™ - UNAVAILABLE

Supraorbital, supratrochear, GON simulation
(migraine acute)
Relivion™
IN REGULATORY TRIALS

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

*Supraorbital transcutaneous stimulation
(migraine acute and prevention)
Cefaly™
AVAILABLE WITHOUT $R_X$

# Other New Acute Therapies

- Sumatriptan 10 mg nasal spray with permeation enhancer (Tosymra™)
- Celecoxib oral solution (Elyxyb™)

# Old Dogs, New Tricks

# In Development / Clinical Trials

- Transdermal zolmitriptan (Phase 3 completed) (Qtrypta™)
- INP-104: DHE nasal spray (FDA submission pending)
- STS-101: DHE dry nasal formulation (did not meet primary outcome, second trial expected)
- AXS-07: Oral meloxicam 20 mg– rizatriptan 10 mg combination (MoSEIC™ technology*) (Completed phase 2)
- CL-HIT: Promethazine – sumatriptan capsule (completed Phase 2)

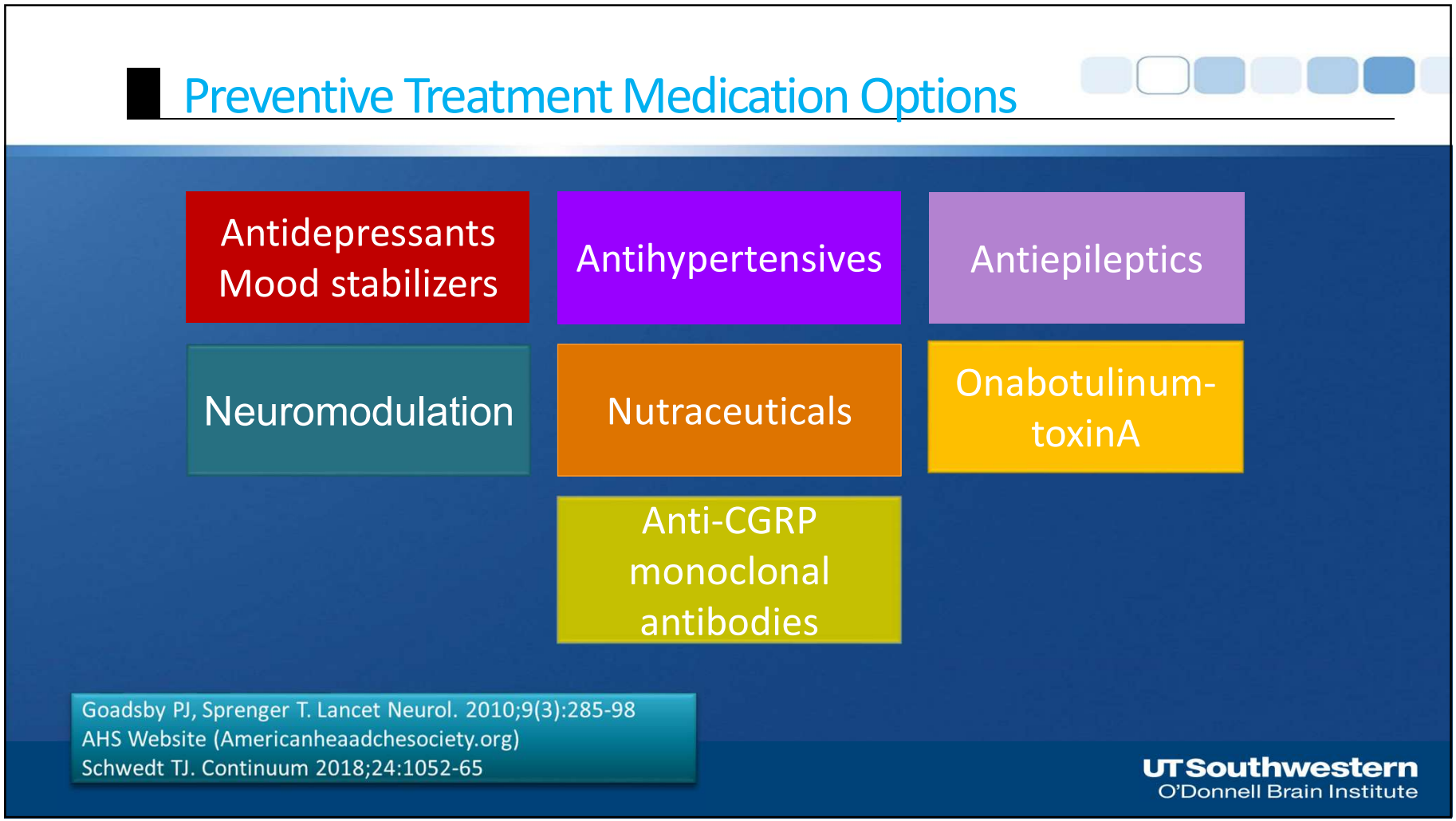
*Molecular Solubility Enhanced Inclusion Complex (modified pH to enhance GI absorption)

# 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 migrainous infarction

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

# Preventive Treatment Medication Options



# 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

# New and Emerging Therapies

- Monoclonal antibodies vs. CGRP (SC, IV)
- Small molecules vs. CGRP
- PACAP-38 receptor antagonist

# Monoclonal Antibodies Against CGRP

Block CGRP, without causing vasoconstriction

CGRP mAbs have very low CNS penetration

Reduce the bioavailability of CGRP; high target specificity

Eliminated through reticuloendothelial system, similarly to endogenous antibodies (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 | Ligand | Ligand | Receptor | Ligand |
| Administration | SC | IV | SC | SC |
| Dosing interval | Q month | Q 3 months | Q month | Q month/Q3 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) |
| Trade name | Emgality™ | Vyepti™ | Aimovig™ | Ajovy™ |

- May have rapid onset of action, sometimes within days (up to 6 months)
- All showed statistical superiority in reducing headache days vs. placebo
- All reduced acute medication usage
- Average therapeutic gain over placebo 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

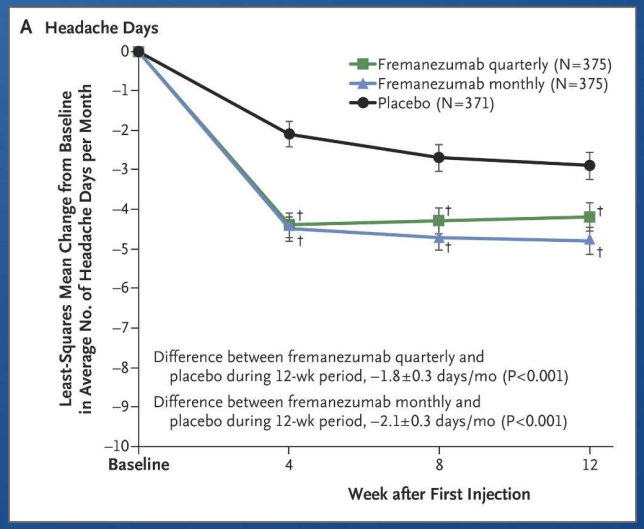
# Common Adverse Events Reported in Clinical Trials with CGRP mAbs

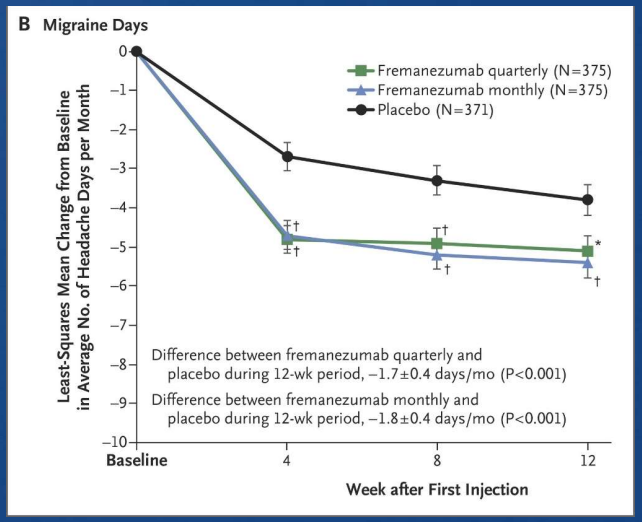
- Injection site pain, erythema
- Constipation (especially erenumab 140 mg → ileus)
- Other treatment-emergent adverse events were not different than those occurring with the placebo injections
  - Upper respiratory tract infection, arthralgia, "flu-like"
  - Nausea
  - UTI
  - Some reports of abdominal pain, back pain, alopecia
- No signal of cardiovascular adv
- erse 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)

# Efficacy Data: Examples from Clinical Trials
# Change in Monthly Migraine Days

## Fremanezumab EM Phase 3

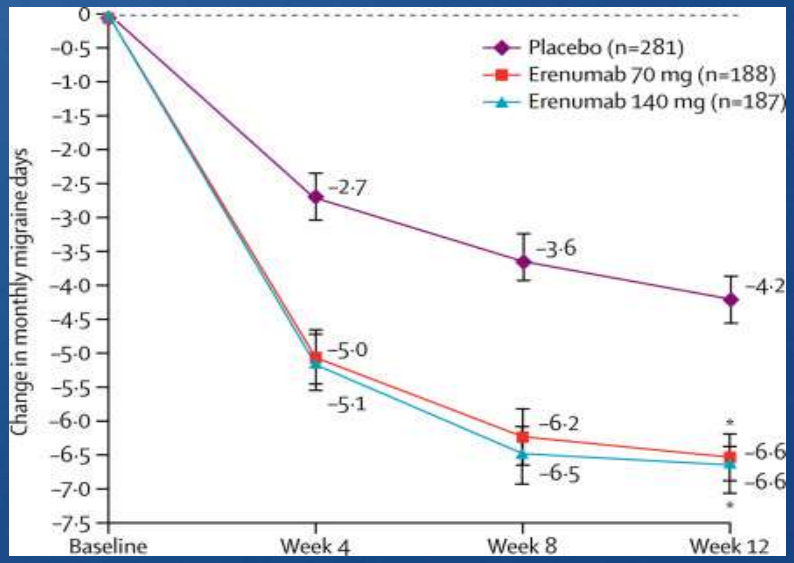



Baseline ~8 migraine days

Silberstein SD et al. NEJM 2017;377:2113-22

# Erenumab CM Phase 2



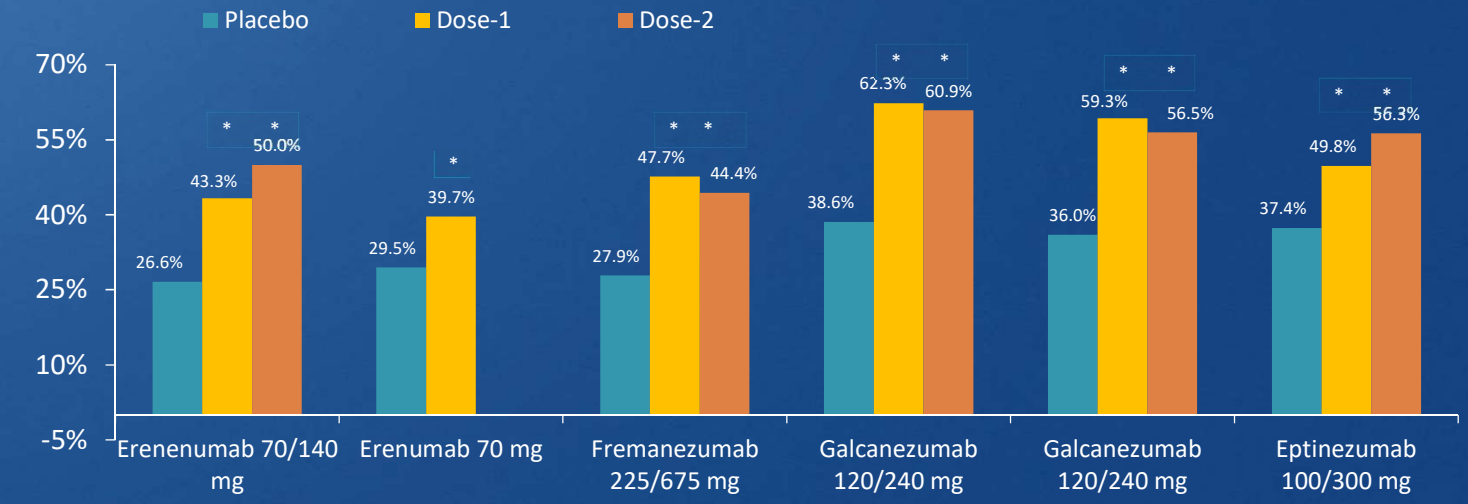

* p<0.05

Baseline ~18 migraine days

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

# 50% Responder Rate: Episodic Migraine

## ≥50% reduction in monthly migraine days

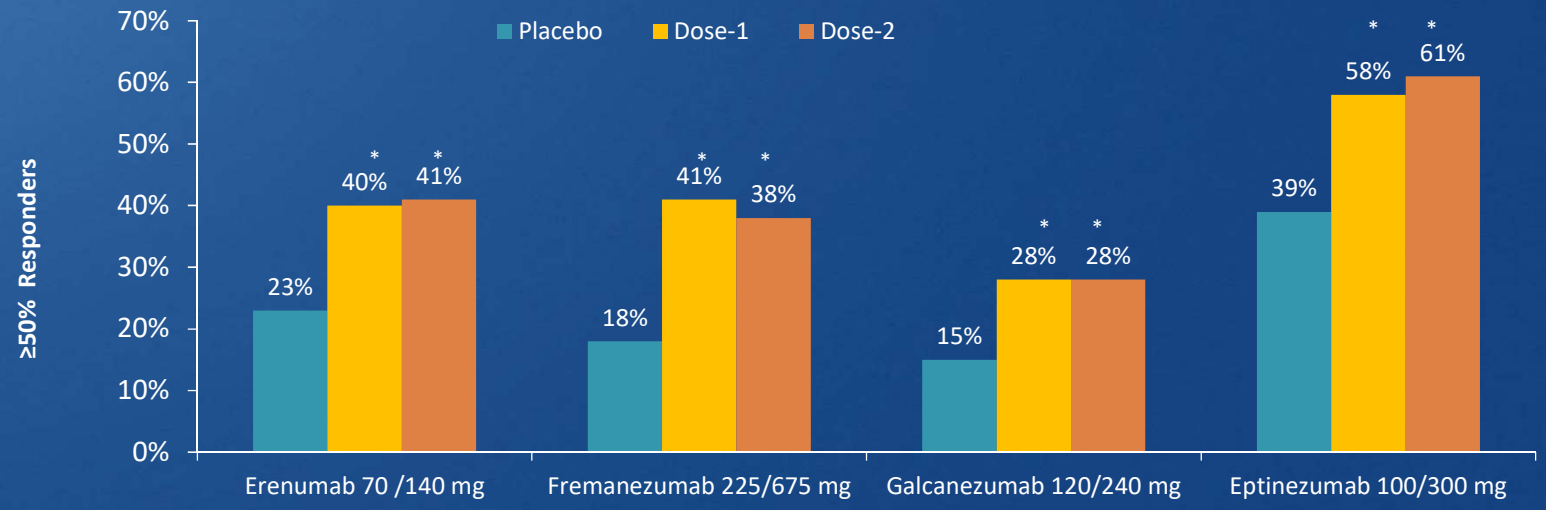



*Statistically significant difference vs placebo

Goadsby PJ et al. N Engl J Med 2017;377:2123-2132
Dodick DW et al Cephalagia 2018;38:1026-1037
Dodick DW et al. JAMA 2018;319:1999-2008
Stauffer VL et al. JAMA Neurol 2018;75:1080-1088
Skljarevski V et al. Cephalalgia 2018;38:1442-1454
Saper R et al. AAN 2018. Abstract S20.001

# 50% Responder Rate: Chronic Migraine

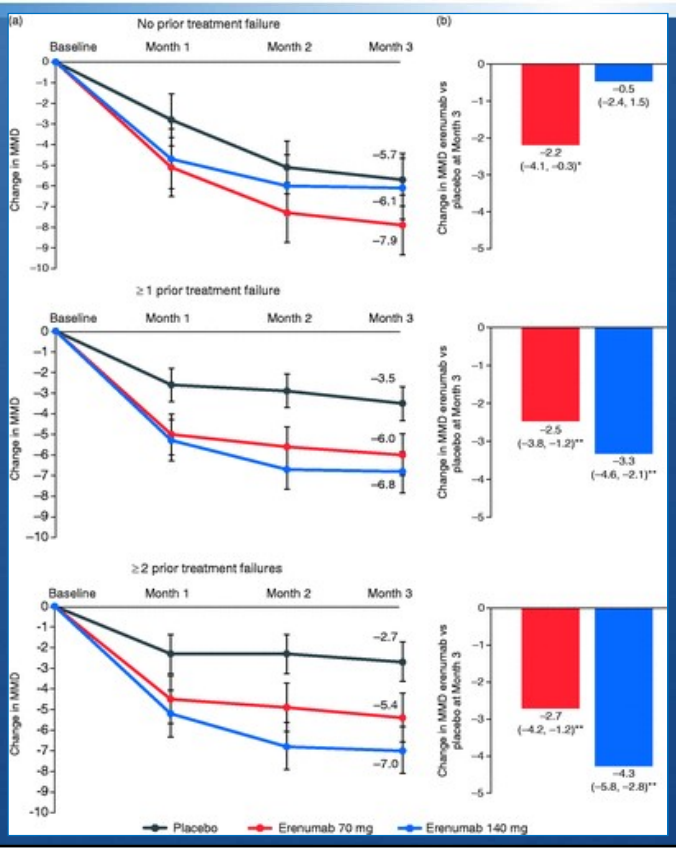
## ≥50% reduction in monthly migraine days




*Statistically significant difference vs placebo

Tepper SJ et al. Lancet Neurol 2017;16:425-434
Silberstein SD et al. N Engl J Med 2017;377:2113-2122
Detke HC et al. Headache 2017;57:1336-1337
Kudrow DB et al. AAN 2018 Abstract P4.470

# 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%)

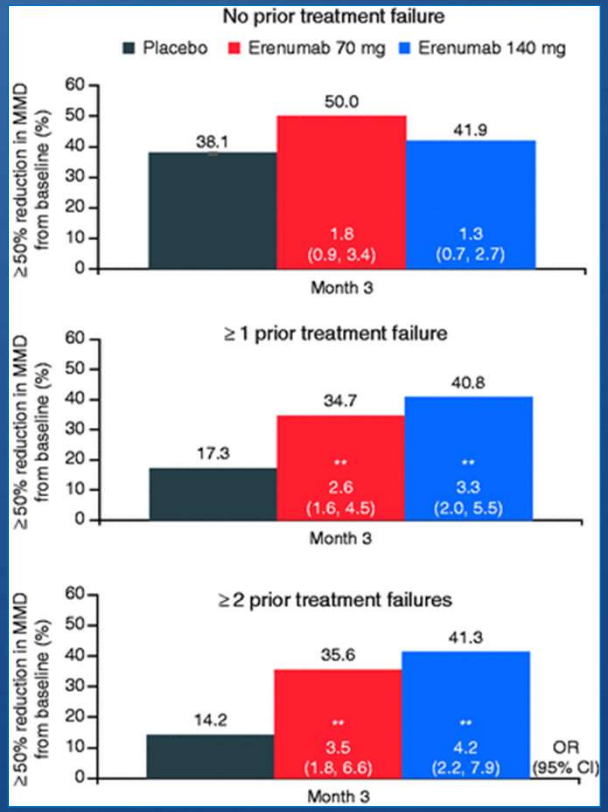
≥1 (67.9%)

≥2 (49.0%)

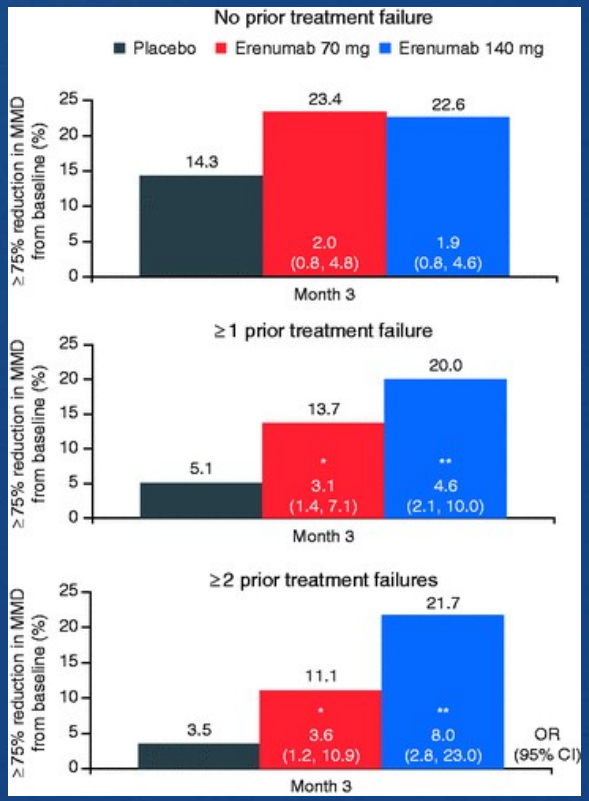
≥3 (34.8%)prior preventives

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

50% responder rate over 3 months




75% responder rate over 3 months



# NNT= Number needed to treat
# NNH = Number needed to harm

Therapeutic gain (TG) = Active response – placebo response

NNT= 1/Therapeutic gain

- For NNT, the lower the value, the better

Therapeutic harm (TH) = Active adverse events (AEs) - placebo AEs

- NNH = 1/Therapeutic harm
  - For NNH, the higher the value the better
- NNH/NNT: the higher the value the better
  - The NNH/NNT ratio describes the value of an intervention as a cost/benefit analysis number

# Number Needed to Treat Versus Harm

## Data from Migraine Prevention RCTs

| Drug | Erenumab 70 mg | Erenumab 140 mg | Topiramate 100 mg | Topiramate 100 mg | OnabotA 155 units | Erenumab 70 mg | Erenumab 140 mg | Topiramate 100 mg | Propranolol 160 mg |
|---|---|---|---|---|---|---|---|---|---|
| **Indication** | CM | CM | CM | CM | CM | EM | EM | EM | EM |
| **NNT** | 7 | 6 | 13 | 4 | 9 | 6 | 6 | 5 | 5 |
| **NNH** | **1000** | 250 | 21 | 13 | 39 | **1000** | **1000** | 8 | 11 |
| **NNH/NNT** | **143** | **42** | 2 | 3 | 4 | **167** | **167** | 2 | 2 |

Slide courtesy of Matthew Robbins, MD, FAHS
Adapted from Vo P et al. Cephalalgia 2019;39:608–616

# Key Challenges to Introduction of CGRP mAbs

- Long biological half-life
  - Risk in patients who experience adverse events
  - Pregnancy (planned and unplanned)
- Uncertainty in patients with atherosclerotic and vasospastic (e.g., Raynaud's) vascular disease, multiple vascular risk factors, hypertension
- Patient access and physician burden related to *step-edits and prior authorization*
- Limited coverage in federal and state programs
- Reserved for onabotulinumtoxinA treatment failures (CM) by some payers (or must stop onabotulinumtoxinA treatment prior to approval)

# PACAP: Another potential target

- Pituitary adenylate cyclase-activating polypeptide
- Present in sensory trigeminal neurons
- Selectively activates $PAC_1$ receptor, modulates nociception
- PACAP38 infusion produces marked dilatation of extracranial arteries 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

IV PACAP27 induces migraine-like attacks in migraine patients

- 55% vs 10% for placebo, n=20 (p=0.022)
- Duration of attack was longer for PACAP27 (p=0.03)

Monoclonal antibody against the ligand in development

Ghanizada H et al. Cephalalgia 2019 PMID 31299857

# 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 will be used for acute and preventive treatment
- Uses for other headache conditions will likely follow

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