Migraine: A New Approach

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Learning Objectives

▪ Review the diagnosis and impact of migraine
▪ Identify current and emerging treatment options for migraine
▪ Recognize how CGRP targeted therapies can modulate treatment
Prevalence and Burden of Migraine

- 13% prevalence in US in any given year
- 18% women; 6-7% men
- One of leading causes of disability world-wide\(^1\)
- High socio-economic burden
- Most common neurologic disease seen in primary care
- Migraine most common type of primary headache seen in a primary care office
- Not enough neurologists or headache specialists to see the 39 million Americans with migraine

Disability of Migraine

- Age group 15-49, TOP leading cause of years lived with disability
- 6th most common disabling illness in the world
- Peaks in ages 22-55 for men and women
- Affects 1 in every 4 households in US

The Prevalence of Migraine in Primary Care

12% → Population
29% → Primary Care Waiting Room
94% → Out-Patient with a Complaint of Headache

Migraine – Most Common Headache in Clinical Practice

- Patients seen in primary care
- IHS diagnosis based on diary review

They’re Here... (In My Waiting Room That Is)

- >37% of women of reproductive age in a physician’s waiting room have migraine
- People with episodic tension headache rarely seek medical advice
- Other primary headache disorders infrequently appear in a primary care office
- Chronic condition – they will need a lifetime of care, they will need a good PCP
  - Only 567 certified headache specialists in the United States

PCP = primary care physician
Diagnosis of Migraine without Aura

At least 5 attacks lasting 4-72 hours with at least 2 of the following:

1. Unilateral location
2. Pulsating quality
3. Moderate to severe pain
4. Aggravation or avoidance of physical activity

During the headache at least one of the following:

1. Nausea and/or vomiting
2. Photophobia and phonophobia
3. Not better accounted for by another ICHD-3 diagnosis

Migraine with Aura

At least 2 attacks with 1 or more of the following fully reversible aura symptoms:
1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal

At least 3 of the following:
1. At least 1 aura symptom spreads gradually over >5 minutes
2. 2 or more occur in succession
3. Each aura symptom lasts 5-60 minutes
4. At least one aura symptom is unilateral
5. At least one aura symptom is positive
6. Aura accompanied or followed by headache within 60 minutes

# ID Migraine

> During the last 3 months, did you have the following with your headaches?

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
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<tbody>
<tr>
<td>You felt nauseated or sick to your stomach?</td>
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<tr>
<td>Light bothered you (a lot more than when you don’t have headaches)?</td>
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<tr>
<td>Your headaches limited your ability to work, study, or do what you needed to do?</td>
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- 2/3 for migraine
- Sensitivity: 0.81
- Specificity: 0.75

Classification of Migraine

- Episodic less than 15 days per month of headache
- Infrequent Episodic <4 headache days/month
- Frequent Episodic 4 to <15 migraine headache days/month
- Chronic 15 or more headache days per month of which 8 or more meet criteria for migraine for at least 3 months
- Migraine may or may not be associated with medication overuse
Evolution of Chronic Migraine (CM) from Episodic Migraine (EM)

- Patients may transition among these 3 migraine states in the direction of increasing and decreasing frequency.
- Transitions occur over weeks to months.
- CM develops in individuals with EM at the rate of 2.5% per year.

Current Theory of Migraine Pathophysiology

**Vascular Theory**

*Pain caused by:*
- Constriction of blood vessels in the cranium
- Rebound vasodilation

**Neurogenic Theory**

*Pain caused by interaction between:*
- Cortical spreading depression (cortex)
- Trigeminal system

**Neurovascular Theory**

*Pain caused by combination of:*
- Cortical spreading depression (cortex)
- Trigeminal system
- Cranial vascular changes brought about by release of neuropeptides and proinflammatory substances

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Migraine Is a Complex Disease With Peripheral and Central Components

Peripheral components¹:
• Trigeminal afferents (CGRP)
• Meningeal vasculature
• Resident immune cells

Central components¹:
• Trigeminal efferent (CGRP)
• Trigeminal cervical complex
• Thalamus
• Cortex

CGRP = calcitonin gene related peptide

1. Ferrari, MD. Lancet Neurology. 2015; 14(1);65-80; Figure Ferrari, MD. Lancet Neurology. 2015; 14(1);65-80.
What is CGRP?

- Calcitonin gene-related peptide – a 37 amino acid polypeptide in neurons and glial cells (universally present)
- Receptors to CGRP are located throughout the trigeminal system and multiple brain regions (as well as other locations throughout the body)
- CGRP is a vasodilator and causes neurogenic inflammation
- CGRP modulates pain signaling
Role of CGRP in Other Selected Systems

**Respiratory system**
- CGRP is abundant in lungs and vasodilates pulmonary arterioles
- CGRP protects against pulmonary hypertension in animal models

**Diabetes and obesity**
- Potential for protective and causative roles for CGRP in diabetes
- CGRP dampens insulin release and CGRP KO mice are resistant to diet-induced obesity
- Possible connection between lower CGRP and impaired wound healing, neuropathy and cardiovascular disease common in diabetes

**Wound healing**
- CGRP produces vasodilation and inflammation in the skin
- Depletion of CGRP, by capsaicin, reduced wound healing in rats
- Impaired wound healing, angiogenesis and enhanced inflammation in CGRP KO mice

**Ischemia**
- CGRP plays a protective role against ischemia in the gut, kidney, brain, and heart
- CGRP KO mice are more susceptible to ischemic injury and have impaired recovery
- Endogenous but not exogenous CGRP protects against myocardial infarction

KO=knockout
CGRP and Migraine: Where is the Evidence?

- CGRP levels elevated during migraine attack (measured external jugular vein)\(^1\)

- Infusion of CGRP in migraine patients can cause migraine\(^2\)

- Infusion of CGRP blocking medication can resolve a migraine attack in a migraine individual\(^3\)

- Development of new targeted CGRP blocking molecules show promise in migraine treatment (including large monoclonal antibodies and small molecule oral medications called “gepants”)

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Role of CGRP in Migraine Pathophysiology

CGRP enhances synaptic excitability
* To date, dural mast cell degranulation has not been observed in humans

CGRP causes vasodilation and mast cell degranulation indirectly activating nociceptors*

Felt as cutaneous allodynia and photophobia

CGRP stimulates cytokine release, thereby stimulating trigeminal neurons

Felt as initial head pain

CGRP enhances synaptic excitability

Felt as throbbing pain and sensitivity to movement

Meet Jasmine

- 38-year-old school teacher with 20 year history of migraine without aura
- Takes oral Sumatriptan 100 mg for acute treatment
- Does not work well if nauseated or wakes up with severe headache as is typical when on her menses
- Tried Sumatriptan 6 mg injection but caused flushing, chest tightness, and headache seemed to get worse before it got better
- Would like other options for acute treatment
- Has no medication allergies
- No cardiac disease
Migraine attacks are now 1-2 times per week
Missing 1 day of work per month due to migraine
Topiramate caused cognitive impairment and fatigue
Amitriptyline caused dry mouth, constipation and weight gain
Anti-hypertensives not ideal due to low blood pressure
Has 2 children, ages 8 and 10
Husband had vasectomy
Asks, “What is new for acute and preventive treatment”
She states, “I want my life back”
Treatment of Migraine
Acute Migraine Treatment Goals

- Rapid relief of headache pain
- Relief of “most bothersome symptoms” (MBS) including nausea, photophobia and phonophobia
- Sustained pain freedom
- No need to rescue or take a 2nd dose
- Return to full function
- Little to no side-effects from acute medication
Current, New and Emerging Acute Migraine Treatment Options

- Triptans (5 HT-1B and 1D receptor agonists)
- Ergots/Dihydroergotamine
- NSAIDS
- Non-specific options (Analgesics, Butalbital, Narcotics)
- Non-invasive devices
- Oral CGRP receptor antagonists
- Ditan (Lasmiditan - selective 5 HT-1F receptor agonist)
**Triptans – What is New?**

- Seven triptans (Sumatriptan, Rizatriptan, Zolmitriptan, Almotriptan, Eletriptan, Naratriptan, Frovatriptan)

- Sumatriptan has oral, injectable, nasal, breath-powered formulations

- New: 3 mg injectable Sumatriptan in auto-injector (Zembrace)
  Key feature: Tolerability and ease of use, dose is 3 mg subcutaneous injection may repeat 1 hour; max is 12 mg in 24 hours

- Breath-powered nasal delivery of Sumatriptan powder to posterior nasal cavity-Onztra Xsail 1 nosepiece each nostril 11 mg per nosepiece, total dosage 22 mg; may repeat 2 hours; max 44 mg in 24 hours

- DFN-02 (Nasal Sumatriptan 10 mg combined with an absorption enhancement agent to increase bioavailability)¹ (Tosymra)

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<tr>
<th>Safety Concerns of Acute Migraine Prescription Treatment Options</th>
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<tbody>
<tr>
<td>▪ Triptans and Ergots/Dihydroergotamine are all contraindicated in patients with coronary artery disease, peripheral vascular disease, uncontrolled high blood pressure and those at high risk of cardiac disease</td>
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<tr>
<td>▪ Triptans and Ergots/Dihydroergotamine should not be taken in the same 24-hour period due to risk of vasoconstriction</td>
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<tr>
<td>▪ Risk of medication overuse with triptans</td>
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<tr>
<td>▪ Narcotics and Butalbital are non-specific in treatment of acute migraine, can lead to medication overuse, overdose, sedation, abuse, and can cause preventives to be less effective</td>
</tr>
<tr>
<td>▪ NSAIDs contraindicated in many patients due to GI issues or those at risk for GI bleeding and those with certain kidney conditions</td>
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Oral CGRP Receptor Antagonists "Gepants"
Ubrogepant

- FDA approval December 2019
- Oral tablet 50 & 100 mg may be repeated in 2 hrs; max daily dose 200 mg
- Approved for acute treatment of migraine with or without aura in adults
- No cardiac contraindications
- Concomitant use of CYP3A4 inhibitors contraindicated; caution with CYP3A4 inducers
Clinical Trials Ubrogepant

- Limitations of current acute migraine treatment include those who can’t take triptans due to contraindications or side-effects or ineffectiveness
- CGRP oral medications appear to be free of vasoconstriction and have similar efficacy to triptans for acute migraine
- Ubrogepant 5-7 hours half-life; T max is 1.5 hours
- Two pivotal phase 3 clinical trials:
  - ACHIEVE I - 1327 adults, single migraine attack treatment for moderate to severe migraine looking at 50 and 100 mg dose Ubrogepant vs placebo. Statistically significant difference in pain-freedom vs placebo as well as absence of most bothersome symptom (MBS) and most common MBS photophobia.
  - ACHIEVE II - 1686 patients ages 18-75 and looked at 25 and 50 mg dose Ubrogepant vs placebo. Both doses superior to placebo for pain-freedom. The 50 mg dose superior in relief of MBS vs placebo
- Most common side-effects were nausea and dizziness in less than 2.5% of patients enrolled in the clinical trials. Four cases of abnormal liver enzymes reported but none felt to be related to the study drug

Rimegepant

- FDA approved February 2020
- Available as an orally dissolving 75 mg tablet
- Tmax 30 minutes sooner with ODT vs standard oral tablet (1.5 hrs vs 2 hrs)
- Approved for acute treatment of migraine with and without aura in adults
- Dose is 75 mg in 24 hour period
Clinical Trials Rimegepant

- Rimegepant is an oral CGRP receptor antagonist
- Half-life is 10 hours
- Dosage in phase 3 trials is 75 mg
- Primary end-points of pain-freedom and relief of most bothersome symptom (MBS)
  - Study 301 - 1084 adults
    - 19.2% pain-free at 2 hours vs 14.2% placebo
    - 36.6% relief of MBS vs 27.7% placebo
    - 2-24 hours sustained pain relief 38.9% vs 27.9% placebo
  - Study 302 - 1072 patients
    - 19.6% pain-free at 2 hours vs 12.0% placebo
    - 37.6% relief of MBS vs 25.2% placebo
    - 2-24 hour sustained pain relief was 42.6% active drug vs 26.5% placebo
- Well-tolerated with 1.4% nausea compared to 1.1% placebo. No “triptan” like side-effects

Lasmiditan

- FDA approved October 2019, DEA scheduled January 2020
- Available as a 50 & 100 mg tablet
- Dose is 50 or 100 or 200 mg taken as a single dose in a 24 hour period
- FDA approved for acute treatment of migraine with or without aura in adults
- No driving for 8 hours
- Schedule V controlled medication
Clinical Trials Lasmiditan

- Oral serotonin receptor agonist that targets 5-HT 1F receptor (unlike triptans which target 5-HT 1B/1D receptors)
- No vasoconstrictive effects
- Could be useful for patients with cardiovascular disease for whom triptans contraindicated
- Samurai and Spartan: phase 3 randomized, DB, PC studies
- At 2 hours, with Lasmiditan 200mg: 32-39% pain FREE vs 15-21% placebo, MBS free 41-49% vs 30-34% with placebo, 60-65% had pain RELIEF vs 40% with placebo
- With 200mg dose separation from placebo noted for pain FREE as early as 1 hour. 100mg and 200mg separated from placebo for MBS at 0.5 hours
- Some CNS side-effects including dizziness, paresthesia, somnolence, and fatigue
- On going open-label multi-dose safety trial – GLADIATOR
- Driving precautions . . . .no driving for 8 hours after dosing
- FDA approved 10/2019; Schedule V controlled medication

Impaired Driving Evaluation

November 2017 Publication
US Depart of Health and Human Services, FDA, Center for Drug Evaluation and Research

“Evaluating Drug Effects on the Ability to Operate a Motor Vehicle” (Guidance for Industry)

“Recommended” for all drugs that may result in impairment (particularly CNS penetrant and psychoactive drugs but may apply elsewhere as well)

Lasmiditan: 2 Randomized Controlled Crossover Studies in Healthy Subjects, simulating driving comparing baseline to: active control (50mg diphenhydramine or 1mg alprazolam) vs Lasmiditan (50mg, 100mg, or 200mg) or placebo

100km flat meandering road, steady lane position and constant rate of speed. SDLP (standard deviation of lateral position) measured. Non-inferiority criterion (4.4cm) = mean change in SDLP with a 0.05% blood alcohol concentration vs placebo

Lasmiditan showed dose-related increase in SLDP at 1.5 hours; non-inferior to placebo at 8 hours, as well as at 12 and 24 hours

Literature shows that subjects are poor judges of their perception to drive safely!!

New and Emerging Preventive Migraine Treatments
Current Preventive Landscape

- Anti-depressants
- Anti-epileptics
- Anti-hypertensives
- Onabotulinum Toxin A
- Non-invasive neurostimulators
- Herbal Preventives
- Hormonal Approaches
FDA Approved Oral Medications for Prevention of Episodic Migraine

- Divalproex sodium
- Topiramate
- Timolol
- Propanolol

Note: Others commonly used but not FDA approved include Amitriptyline, Venlafaxine, Metoprolol, Naldolol, Atenolol, Nortriptyline, Duloxetine, Verapamil, Gabapentin, Candesartan, Fluoxetine, Escitalopram, Cyproheptadine

Short-term prevention menstrual migraine: Frovatriptan, Naratriptan, Sumatriptan, Zolmitriptan, Rizatriptan. All have shown efficacy in clinical trials but not FDA approved for prevention.
Non-Pharmacologic Treatment Options

- Herbal treatments
  - Magnesium 500mg (may cause diarrhea)
  - Riboflavin (vitamin B2) – dietary: 1.6-3.8 mg, supplement: 400mg
  - Co Q 10 150mg
  - Butterbur 75mg
- Acupuncture
- Biofeedback, CBT*, stress-reduction
- Psychological counseling
- Yoga, exercise, meditation
- Non-invasive nerve stimulators (both acute and preventative – require Rx)
- Class IV Laser (photobiomodulation – “aka cold laser”) – not FDA approved for migraine but has been shown to reduce inflammation and pain in musculoskeletal and peripheral neurologic conditions – safe, non-invasive…


*CBT = cognitive behavioral therapy
Onabotulinum Toxin A (Botox)

- FDA approved for chronic migraine only (not EM)
- Approved protocol is 155 units injected in 31 individual sites every 12 weeks
- Sites include procerus, corrugators, frontalis, temporalis, occipitalis, upper paracervicals, and upper trapezius
- FDA approved for chronic migraine in 2010
- MOA includes inhibition of release of neuropeptides including CGRP from peripheral nervous system
Anti-CGRP Monoclonal Antibodies

Specifically designed to target migraine prevention
Anti-CGRP Monoclonal Antibodies for Migraine Prevention

- Target specific preventive treatment to block the activity of CGRP either by binding directly to the CGRP ligand or by blocking the CGRP receptor in the peripheral nervous system

- Net effect is to block CGRP activity, lessen the migraine cascade of inflammatory activity, and prevent transmission of pain signals to travel to higher order neurons

- All Anti-CGRP monoclonal antibodies work on the peripheral nervous system (PNS) and do not work directly on the central nervous system (CNS)

- Anti-CGRP mABs are large monoclonal antibodies and cannot cross the blood-brain barrier to any significant degree
<table>
<thead>
<tr>
<th>Key Features Anti-CGRP mAB’s</th>
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<tbody>
<tr>
<td>Work on peripheral nervous system (PNS)</td>
</tr>
<tr>
<td>No central nervous system side-effects (CNS)</td>
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<tr>
<td>No effect on liver or kidney</td>
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<tr>
<td>No drug to drug interactions</td>
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<tr>
<td>Degraded by enzymatic proteolysis</td>
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<tr>
<td>Favorable side-effect profile in clinical trials</td>
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<tr>
<td>Approved for migraine prevention in adults</td>
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<tr>
<td>No data in pregnancy and breastfeeding</td>
</tr>
<tr>
<td>Not available in oral tablet</td>
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<tr>
<td>Expensive to make (grown in cell cultures)</td>
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<tr>
<td>CV patients – no red flags but excluded from trials</td>
</tr>
<tr>
<td>Immunogenicity is possible – impact unclear</td>
</tr>
<tr>
<td>More similar than different</td>
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Erenumab-aooe

- FDA approved May 2018 for the preventive treatment of migraine in adults
- Fully humanized immunoglobulin (IgG2) selectively targets and blocks the CGRP receptor
- Competes with the binding of CGRP and inhibits its function at the CGRP receptor site
- Half-life is 28 days
- Dose is 70 or 140 mg monthly subcutaneous injection into upper arm, abdomen or thigh with auto-injector
- Brand name Aimovig (Amgen/Novartis)
Clinical Study Highlights

- STRIVE-multi-center, PC, DB, 24-week study erenumab vs placebo in EM
  - Mean Migraine Frequency Baseline 8 MMD; 3.7 reduction in 140 mg-arm erenumab, 3.2 reduction in 70-mg arm; 1.8 reduction in placebo arm; statistically significant (months 4-6 compared to baseline)

- Exploratory analysis 22% in 140 mg-arm, 20.8% in 70 mg-arm, and 7.9% in placebo arm 75% or greater reduction MMD

- CM study multi-center, PC, DB, 12-week study in CM reduction in MMD by 6.6 compared to 4.2 placebo group

- Post-hoc analysis 21% (140 mg-arm), 17% (70 mg-arm), 8% (placebo arm) 75% or greater reduction in MMD

MMD = monthly migraine days
Safety Concerns

- Erenumab has been evaluated in 2,537 patients with migraine who received at least 1 dose of Erenumab. Among this population, 2,057 were exposed to Erenumab (70 or 140 mg monthly) for 6 or more months.

- The most common adverse reactions (incidence >3%) were injection site reactions and constipation. Injection site reactions were 3% in the placebo group, 6% in the 70 mg group, 5% in the 140 mg group. Constipation occurred in 1% of the placebo group, 1% in the 70 mg group, 3% in the 140 mg group.

- Potential for immunogenicity. In studies with Erenumab, 6.2% of patients receiving 70 mg monthly developed anti-erenumab antibodies, 2.6% of patients receiving 140 mg monthly developed anti-erenumab antibodies. No impact on efficacy or safety was noted in these patients but data too limited to make a definitive conclusion.

- Updated label USPI October 8, 2019 – revised warning and precautions to include language on constipation with serious complications.

- Updated label USPI April 30, 2020 – postmarketing reports of new or worsening hypertension – most occurred within 7 days and after first dose. There were cases requiring pharmacological treatment and, in some cases, hospitalization.
Fremanezumab-vfrm

- FDA approved 9/14/18 for the prevention of migraine in adults
- Fully humanized immunoglobulin (IgG2a) binds to the CGRP ligand
- Half-life is 31 days
- Dose is 225 mg monthly or three 225 mg subcutaneous injections quarterly
- Available in a pre-filled syringe (1.5 ml) or an autoinjector
- May be injected in upper arm, abdomen, or thigh
- Brand name Ajovy (Teva)

Ajovy (Fremanezumab-vfrm) prescribing information. 2018. Teva.
Clinical Study Highlights

- In the Halo-EM Phase 3 Trial, 875 patients randomized to 225 mg monthly dose of Fremanezumab, a single dose of 675 mg followed by placebo, or placebo for 12 weeks. Mean monthly migraine days (MMD) decreased from 8.9 to 4.9 in monthly dosing group, decreased from 9.2 to 5.3 in the single-higher dose group, and 9.1 to 6.5 in placebo group. Statistically significant 1.3-1.5 reduction in mean MMD compared to placebo.

- In the Halo-CM Phase 3 Trial, 1130 patients randomized to Fremanezumab quarterly dosing, monthly dosing, or placebo in a 23-week study. Primary endpoint was mean change in number of headache days from baseline. Reduction was 4.3 in quarterly dosing group, 4.6 with monthly dosing group, and 2.5 with placebo group. Patients with at least 50% reduction in headache days per month was 38% in quarterly group, 41% in monthly group, and 18% in placebo group. 20-22% of patients continued on current preventive medication but had to be off Onabotulinum Toxin A for at least 4 months before screening.

Safety Concerns

- Fremanezumab was studied in 2512 patients who received at least one dose of Fremanezumab. Most common adverse reactions seen in the clinical trials (incidence at least 5% and greater than placebo) were injection site reactions including injection site pain, induration, and erythema. Injection site reactions occurred in 43% of the 225 mg monthly dose group, 45% of the 675 mg quarterly group, and 38% in placebo group. Total of 1% discontinued in the clinical trial.

- Fremanezumab contraindicated in patients with serious hypersensitivity to Fremanezumab or to any of the excipients (EDTA, L-histidine, polysorbate, sucrose).

- Hypersensitivity reactions (rash, pruritus, urticaria) were mild to moderate in most cases and were reported from hours to 1 month after administration in the clinical trials. A few cases required corticosteroid treatment. No cases of anaphylaxis were reported.

- Potential for immunogenicity. In 3 month placebo-controlled studies, development of anti-fremanezumab antibodies as observed in .4% of treated patients. No conclusions can be made on any impact of ADA on safety of efficacy.

ADA = anti-drug antibodies
Fremanezumab-vfrm prescribing information. 2018. Teva Pharmaceuticals USA.
Galcanezumab-gnlm

- FDA approval 9/27/18 for the prevention of migraine in adults
- FDA approval June 2019 for treatment of Episodic Cluster Headache at 300mg (given as 3 100mg SC injections) monthly until the end of the cluster period
- Fully humanized immunoglobulin (IgG4) binds to the CGRP ligand
- IgG4 less innate immune response compared to IgG2
- Half-life is 27 days
- Two cases urticaria in clinical trials seen - was not immediate nor after 1st injection
- Approved dose is loading dose of 240 mg subcutaneous injection (given as two 120 mg auto-injectors or prefilled syringe) followed by monthly 120 mg injection
- Brand name Emgality (Lilly) (available as autoinjector or syringe)
Clinical Study Highlights

- Galcanezumab was studied for EM in EVOLVE-1 and EVOLVE-2 DB, PC, 6-month clinical trials with 120 mg dose (after the 240mg loading dose) vs placebo. Primary objective was change in monthly migraine days. Reduction of 4.7 MMD vs 2.8 placebo in EVOLVE-1 trial and reduction of 4.3 vs 2.3 placebo in EVOLVE-2. Baseline was 9 MMD in these EM trials. Responders in at least 1 out of 6 months: 59-62% at least 50% reduction vs 36-39% placebo. 34-39% at least 75% reduction vs 18-19% placebo, 12-16% achieved 100% reduction vs 6% in placebo.

- REGAIN was a 3 month DB, PC, 3 month study for CM. Propanolol or Topiramate was continued in 15% of study participants. The 240 mg dose was not superior to the 120 mg in this study. Baseline MMHD was 20. In the active group 4.3 fewer MMHD vs 2.7 reduction in placebo group.

- Open label-extension study with 240 mg loading dose Galcanezumab followed by 120 mg monthly injection (80% EM, 20% CM) demonstrated 6.4 fewer MMHD from baseline of 10 at 12 months.

Safety Concerns

- Galcanezumab has been studied in over 2500 patients in clinical trials. Most common adverse reaction greater than placebo was injection site reactions seen in 18% of patients receiving Galcanezumab compared to 13% in placebo group. Rash, urticaria and dyspnea were reported.

- Galcanezumab is contraindicated in patients with hypersensitivity to Galcanezumab or any of its excipients. (L-histidine, polysorbate)

- Hypersensitivity reactions occurred in the clinical trials. Post marketing reports of angioedema and anaphylaxis

- Potential for immunogenicity. In the 3-6 month trials, 4.8% of patients developed antibodies to Galcanezumab. In the 12 month trial, up to 12.5% developed ADA. No affect was seen on pharmacokinetics. No conclusions can be made on any impact of ADA on safety of efficacy

ADA = anti-drug antibodies

Emgality Prescribing Information. 2018. Data on File Lilly, USA.
Eptinezumab

- Promise-2 trial results presented at AAN 2018. 1072 patients with CM ages 18-65 enrolled and received either 100 or 300 mg Eptinezumab or placebo. Reduction of 7.7 to 8.2 MMDs vs 5.6 in placebo group over week 1-12. About 1/3 of patients achieved 75% or greater reduction in MMDs in week 1-12 vs 15% in placebo group

- Anti-CGRP mAB given intravenously; FDA approved February 2020

- Fully humanized immunoglobulin

- Quarterly dosing

- Features include quick onset of action and high bioavailability. Reduction in migraine seen first 24 hours post-infusion in Promise-2 Study

- Drawback is the need for access for Infusion and added cost of infusion

- Brand name Vyepti (Lundbeck Pharmaceutical)
Important Points About Anti-CGRP mAB’s

- No head to head comparator trials
- Onabotulinum Toxin A had to be stopped 4 months or more before Anti-CGRP trial entry so safety of having patients on both preventives not known
- Long-term safety not known (could there be a downside of long-term CGRP suppression)
- Insufficient data on safety during pregnancy and lactation
- All companies forming Pregnancy Registries
- Only FDA approved for 18 and over in US
Who is a Candidate for an Anti-CGRP mAB?

- Adults with migraine who have 4 or more monthly migraine headache days
- Migraines are disabling
- Current or past standard preventives have either not been tolerated or have been ineffective (most insurance companies will require trial of 2 preventives prior to approval of CGRP mAB)
- If adult has chronic migraine, insurance company may require failure of 6 month trial with Onabotulinum Toxin A
Atogepant

- Oral CGRP Receptor Antagonist in clinical development for prevention of migraine
- Phase 2b/3a study looked at daily dosing ranging from 10 mg daily up to 60 mg bid compared to placebo in 834 subjects. All treatment groups showed statistical significance over placebo in primary efficacy end-point of reduction from baseline in mean migraine/probable migraine days per month
- Side-effects included nausea, fatigue, constipation, nasopharyngitis, and UTI in a small number of participants. No sign of hepatotoxicity in this 12 week trial
- Has a 10 hour half-life
- Potential option for patients who prefer oral daily preventive for migraine as opposed to injection or IV administration of a anti-CGRP mAB

Summary of Treatment Options

- CGRP is a neuropeptide that plays a key role in migraine pathogenesis.
- Anti-CGRP Monoclonal Antibodies represent a new category for migraine prevention for adults in the US and 4 Anti-CGRP mAB’s are now FDA approved.
- New and emerging acute migraine treatment options include new formulations for Sumatriptan and an oral 5-HT 1F agonist.
- Oral CGRP receptor antagonists show promise for both acute and preventive treatment of migraine.
- Knowledge of how to incorporate new acute and preventive migraine treatments in our migraine patients can reduce the burden of migraine in our patients lives.
Back to Jasmine

- 38-year-old school teacher with 20 year history of migraine without aura
- Takes oral Sumatriptan 100 mg for acute treatment
- Does not work well if nauseated or wakes up with severe headache as is typical when on her menses
- Tried Sumatriptan 6 mg injection but caused flushing, chest tightness, and headache seemed to get worse before it got better
- Would like other options for acute treatment
- Has no medication allergies
- No cardiac disease
Prevention for Jasmine

- Migraine attacks are now 1-2 times per week
- Missing 1 day of work per month due to migraine
- Topiramate caused cognitive impairment and fatigue
- Amitriptyline caused dry mouth, constipation and weight gain
- Anti-hypertensives not ideal due to low blood pressure
- Has 2 children, ages 8 and 10
- Husband had vasectomy
- Asks, “What is new for preventive treatment”
- She states, “I want my life back”
Treatment Options – Jasmine

- Acute non-oral options include Sumatriptan 3 and 4 mg injection for potentially less side-effects she had with the 6 mg dose and/or a nasal formulation of a triptan and/or nasal dihydroergotamine (DHE)

- Non-invasive Cefaly device

- Prevention with one of the Anti-CGRP Monoclonal Antibodies based on tolerability issues with 2 standard oral preventives tried in the past (Topiramate and Amitriptyline)

- Onabotulinum ToxinA an option if she transforms to CM (her current pattern is 1-2 migraine headache days per week)

- Non-pharmacologic treatment including exercise, healthy eating, adequate sleep, stress-reduction, keeping a headache diary, and close follow-up