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

36 million adults in the US are affected by migraine

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

Ferrari, MD. Lancet Neurology. 2015; 14(1);65-80

Calcitonin Gene Related Peptide (CGRP)
Overview of Possible Targets of Migraine-specific Medications

![Diagram showing targets of migraine medications]

1. **Blockade of CGRP receptor**
   - Monoclonal antibody: Erenumab
   - Gepants: Atogepant, Rimegepant, Ubropitant

2. **Blockade of CGRP**
   - Monoclonal antibody: Eptinezumab, Fremanezumab, Galcanezumab

3. **Stimulation of 5-HT<sub>1B/1D</sub> receptor**
   - Triptans: Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan, Zolmitriptan

4. **Stimulation of 5-HT<sub>1F</sub> receptor**
   - Dihydropyridines: Lasmiditan

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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 great”
# 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
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
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)

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
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?*

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
# Gepants

**Oral small molecule calcitonin gene-related peptide receptor antagonist**

**Available**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ubrogepant</td>
<td>• Ubrelvy</td>
</tr>
<tr>
<td></td>
<td>• Acute</td>
</tr>
<tr>
<td>Rimegepant</td>
<td>• Nurtec ODT</td>
</tr>
<tr>
<td></td>
<td>• Acute (+preventative 2021?)</td>
</tr>
<tr>
<td>Atogepant</td>
<td>• Migraine prevention in daily dose</td>
</tr>
<tr>
<td>Zavegepant</td>
<td>• Nasal spray (10 and 20 mg)</td>
</tr>
<tr>
<td></td>
<td>• Acute treatment</td>
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</tbody>
</table>

**Clinical trials**
<table>
<thead>
<tr>
<th>CLASS</th>
<th>GEPANT</th>
<th>DITAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Name</td>
<td>UBRELVY</td>
<td>NURTEC ODT</td>
</tr>
<tr>
<td>Generic Name</td>
<td>ubrogepant</td>
<td>rimegepant</td>
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<tr>
<td>Manufacturer</td>
<td>Allergan</td>
<td>Biohaven</td>
</tr>
</tbody>
</table>
| 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**
Preventative Treatments for Migraine

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

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Type</th>
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<tbody>
<tr>
<td>Erenumab</td>
<td>CGRP Receptor</td>
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<tr>
<td>Fremanezumab</td>
<td>CGRP Ligand</td>
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<tr>
<td>Galcanezumab*</td>
<td>CGRP Ligand</td>
</tr>
<tr>
<td>Eptinezumab</td>
<td>CGRP Ligand</td>
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*Also for episodic cluster headache*
### CGRP mAbs

#### Migraine Prevention Dosing

<table>
<thead>
<tr>
<th>mAb</th>
<th>Dosing Details</th>
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</table>
| **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
- **Fremanezumab**: monthly or q3 months
- **Galcanezumab**: monthly
- **Eptinezumab**: IV q 3 months
- **Cluster HA dosing**
  - 100 mg + 100 mg + 100 mg
# CGRP mAbs for Migraine Prevention

<table>
<thead>
<tr>
<th></th>
<th>Eptinezumab</th>
<th>Erenumab</th>
<th>Fremanezumab</th>
<th>Galcanezumab</th>
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<tr>
<td><strong>PROMISE-1 in EM:</strong></td>
<td>reduced mean MMD with eptinezumab 30, 100, and 300 mg vs placebo (-4.0, -3.9, -4.3 d, respectively, weeks 1-12; ( P &lt; .0001^{[a]} ))</td>
<td>reduced mean MMD with erenumab 70 mg (-3.2 d) and 140 mg (-3.7 d) vs placebo (-1.8 d); ( P &lt; .001^{[e]} )</td>
<td>reduced mean MMD with fremanezumab quarterly (-3.5 d) or monthly (-3.7 d) vs placebo (-2.4 d) at week 12; ( P &lt; .001^{[g]} )</td>
<td>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 &lt; .001^{[h]} )</td>
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<tr>
<td><strong>PROMISE-2 in CM:</strong></td>
<td>reduced mean MMD with eptinezumab 100 mg and 300 mg vs placebo (-7.7, -8.2, -5.6 d, respectively, weeks 1-12; ( P &lt; .0001^{[b]} ))</td>
<td>reduced mean MMD with erenumab 70 mg (-2.9 d) vs placebo (-1.8 d); ( P &lt; .001^{[d]} )</td>
<td>reduced mean MMD with fremanezumab quarterly (-4.3 d) and monthly (-4.6 d) vs placebo (-2.5 d) at week 12; ( P &lt; .001^{[i]} )</td>
<td>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 &lt; .001^{[i]} )</td>
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<tr>
<td><strong>STRIVE in EM:</strong></td>
<td>In CM: reduced mean MMD with eptinezumab 70 mg (-6.6 d) and 140 mg (-6.6 d) vs placebo (-4.2 d); ( P &lt; .0001^{[e]} )</td>
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<tr>
<td><strong>ARISE in EM:</strong></td>
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<td><strong>HALO CM in CM:</strong></td>
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<td><strong>EVOLVE-1 in EM:</strong></td>
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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
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
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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