Unmet Needs and the Evolving Landscape in Acute Treatment of Migraine: Primary Care Professionals on the Front Line

South Carolina Academy of Family Physicians
June 13, 2021
Myrtle Beach, South Carolina

Provided by
In Collaboration With
Supported by an educational grant from Allergan
Presented by:
Stewart J. Tepper, MD, FAHS
Professor of Neurology
Geisel School of Medicine at Dartmouth
Director, Dartmouth Headache Center
Dartmouth-Hitchcock Medical Center
Lebanon, NH
Faculty Co-Chairs

Susan Hutchinson, MD
Director
Orange County Migraine and Headache Center
Irvine, California

Stewart J. Tepper, MD, FAHS
Professor of Neurology
Geisel School of Medicine at Dartmouth
Hanover, New Hampshire
Director, Dartmouth Headache Center
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire
After taking part in this educational activity, clinicians should be better able to:

- Appreciate the prevalence of migraine in a primary care setting
- Utilize established criteria to make differential the diagnosis for migraine headache and to distinguish episodic from chronic migraine
- Assess the evidence regarding the potential benefits and risks of new and emerging acute migraine treatments
Epidemiology

- Affects ≈37 million Americans (15% of population)\(^1\)
- Episodic migraine (EM): <15 days/month\(^2-4\)
  - 18% women vs 6% men
- Chronic migraine (CM): ≥15 days/month\(^2-4\)
  - Overall prevalence of CM: 1% to 3%
    - 3 times more common in women than men
  - Prevalence peaks during midlife (≈10 years later than EM)\(^1-5\)

They’re Here... (in my waiting room, that is)

- Approximately 37% of women in a primary care waiting room have migraine.¹

- Other primary headache disorders appear infrequently in a primary care office.

- Migraine is a chronic condition, so patients need a lifetime of care from a good primary care physician.  
  - The United States has only 590 headache specialists certified by the United Council for Neurologic Subspecialties.²

---

Migraine Is the Most Common Headache Seen in Primary Care

N = 377 patients with an International Headache Society diagnosis, based on diary review

94% Migraine type
3% Episodic tension type
3% Unclassifiable

Migraine Consequences

- Economic burden in US: up to $28 billion per year\(^1\)
- A leading cause of outpatient and emergency department (ED) visits\(^2\)
  - 4th leading cause of ED visits (adults)—2.8% of all visits\(^3\)
- Important public health problem—especially among reproductive-aged women\(^2\)
- Significant effect on physical, social, and occupational functioning
- Quality of life significantly more impaired in patients with chronic (\(\geq 15\) headache days/month) vs episodic (<15 headache days/month) migraine\(^4\)
- Acute treatment management gaps greater for people with chronic than with episodic migraine\(^5\)

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

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

During the headache, at least 1 of the following:

1. Nausea and/or vomiting
2. Photophobia and phonophobia

And:

• Not better accounted for by another International Classification of Headache Disorders (ICHD)-3 diagnosis.

Diagnosis of 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 aura symptoms occur in succession
3. Each aura symptom lasts 5 to 60 minutes
4. At least 1 aura symptom is unilateral
5. At least 1 aura symptom is positive
6. Aura is accompanied or followed by headache within 60 minutes

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

1. You felt nauseated or sick to your stomach
   - Yes ☐  No ☐

2. Light bothered you (a lot more than when you don’t have headaches)
   - Yes ☐  No ☐

3. Your headaches limited your ability to work, study, or do what you needed to do
   - Yes ☐  No ☐

Yes to 2/3 questions: means migraine 93% of the time
Yes to 3/3 questions: means migraine 98% of the time

SNOOP4: Ruling Out Secondary Causes of Headache in Migraine

Systemic symptoms and signs
Neurologic symptoms or signs
Onset: peak at onset or ≤1 minute
Older: after age 50 years
Previous headache: pattern change
Postural, positional aggravation
Precipitated by coughing, straining, other Valsalva maneuver
Papilledema

Not Missing a Secondary Headache

- Key point: migraine patients can have or develop a secondary headache
- Red flag: “Worst headache ever”
- SNOOP mnemonic
- Choosing wisely; blood work and brain imaging are not routinely required in the absence of red flags and the presence of a stable headache pattern and normal exam
Headache Pattern Recognition

- Minutes
  - Vascular

- Hours/Days
  - Infectious

- Weeks/Months
  - Inflammatory, Neoplastic

- Months/Years
  - Primary Headache

Secondary Headache Disorders

Courtesy of Roger Cady, MD.
Case Study: Linda

- 28-year-old female with 10-year history of migraine without aura
- Triggers include menses, stress, lack of sleep, and skipped meals
- Oral sumatriptan works for her nonhormonal migraines if taken early in attack
  - Does not terminate her menstrual migraines, which can be severe, prolonged, and are associated with nausea and vomiting
Linda’s Migraines

- Tried sumatriptan 6-mg injection
  - Caused chest tightness and pain with injection
- Tried sumatriptan nasal spray
  - Caused bad taste and did not work well
- Delays taking her oral sumatriptan if nauseated
- Sumatriptan also makes her tired
  - Often waits until she gets home to take it
What Would You Offer Linda?

- A different oral triptan and lower dose of sumatriptan injectable
- Ubrogepant (an oral gepant)
- Lasmiditan (a ditan)
- New nasal-delivery sumatriptan
- All of the above are options
Goals of Acute Migraine Treatment

- Rapid and consistent freedom from pain and associated symptoms without recurrence
- Restored ability to function
- Minimal need for repeat dosing or rescue medications
- Optimal self-care and reduced subsequent use of resources (eg, ED visits)
- Minimal or no adverse effects

American Migraine Prevalence and Prevention, a longitudinal, population-based study (N=5681 with EM)

Overall, 3.1% progressed to CM in within 1 year

More effective treatment = better outcomes, lower risk of new-onset CM

<table>
<thead>
<tr>
<th>Treatment Efficacy (assessed by the 4-question Migraine Treatment Optimization Questionnaire)</th>
<th>Patients Who Progressed to Chronic Migraine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>1.9</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.7</td>
</tr>
<tr>
<td>Poor</td>
<td>4.4</td>
</tr>
<tr>
<td>Very poor</td>
<td>6.8</td>
</tr>
</tbody>
</table>

### Stepped Care vs Stratified Care

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Stepped Care</th>
<th>Stratified Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start with nonspecific agent</td>
<td>Patient selects treatment based on severity and disability of migraine attack</td>
</tr>
<tr>
<td></td>
<td>Escalate treatment (increase level of potency or specificity) only if response is suboptimal</td>
<td></td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Nonspecific agent may work</td>
<td>More likely to abort the attack early</td>
</tr>
<tr>
<td></td>
<td>Potential cost savings</td>
<td>Higher patient satisfaction</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Chasing the pain after central sensitization occurs is futile and more costly in the long run</td>
<td>May require a more expensive agent initially</td>
</tr>
<tr>
<td></td>
<td>Medication overuse is common</td>
<td></td>
</tr>
</tbody>
</table>

- Stratified care matches patient and attack characteristics to treatment
- Randomized controlled trial results: “Stratified care provides significantly better clinical outcomes than step care strategies within or across attacks as measured by headache response and disability time.”

Current and New Acute Migraine Treatment Options

- Triptans
- Ergots/dihydroergotamine (DHE)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Nonspecific options (analgesics, combination analgesics)
- Noninvasive devices
- Oral CGRP antagonists (ubrogepant, rimegepant)
- Oral ditan (lasmiditan)

CGRP, calcitonin gene-related peptide.
# Safety Concerns Associated With Acute Migraine Treatments

| Triptans and Ergots/Dihydroergotamine (DHE) | Contraindicated in patients with coronary artery disease, peripheral vascular disease, and uncontrolled hypertension, and in those at high risk of cardiac disease  
Eletriptan and DHE have a CYP3A4 interaction |
|----------------|---------------------------------------------------------------------------------------------------|
| NSAIDs         | Contraindicated in patients with gastrointestinal (GI) issues, at risk for GI bleeding, and with renal dysfunction  
May worsen hypertension  
Risk of medication overuse |
| Lasmiditan     | Patients should not drive or operate machinery for 8 hours after taking lasmiditan  
Schedule V medication  
Avoid concomitant use with drugs that are P-gp or BCRP substrates |
| Gepants        | CYP3A4 interaction |
| Narcotics and Butalbital | Nonspecific in treatment of acute migraine  
Can lead to medication overuse, overdose, sedation, abuse, and a myriad of bad patient outcomes  
Can reduce efficacy of both preventive and other acute medications  
**Should not be used ever in acute treatment of migraine!** |
Triptans—What Is New?

- Sumatriptan comes in oral, injectable, nasal, and breath-powered formulations, plus a combination tablet with naproxen sodium

- Newest formulations
  - 3-mg injectable sumatriptan in an auto-injector
    - Key features: tolerability and ease of use
    - May repeat subcutaneous injection at 1 hour; max is 12 mg in 24 hours

- Breath-powered nasal delivery of sumatriptan powder to posterior nasal cavity
  - Dosage 22 mg (11 mg delivered in each nostril)
  - May repeat at 2 hours; max is 44 mg in 24 hours

- Nasal spray with permeation enhancer
  - 10-mg dose
Newest Sumatriptan Nasal Spray

- Nasal sumatriptan 10 mg combined with an absorption-enhancement agent to increase bioavailability, speed of onset, and tolerability\(^1\)

- Rapid onset, well-tolerated, and good sustained pain-free results in clinical studies

- FDA approval October 2019 for use in adults

- Dosage is 1 spray (10 mg) in 1 nostril, may repeat; max 3 sprays in 24 hours for acute migraine
  - Efficacy equivalent to sumatriptan 4-mg injectable

FDA, US Food and Drug Administration.
The Role of Serotonin (5-HT) in Migraine Pathophysiology

1+2+3+4 = Relief from headache pain and associated symptoms

1 Vasoconstriction
2 Trigeminal inhibition
3 Decreased pain signal transmission
4 Decreased central integration

Lasmiditan

- Presumed mechanism of action: peripheral and central activation of 5-HT$_{1F}$ receptors
- Lacks vasoconstrictive activity
- 2-hour pain freedom:
  - 100 mg, 28.2% to 31.4%
  - 200 mg, 32.2% to 38.8%
  - Placebo, 15.3% to 21.3%
- Most common adverse events (AEs): dizziness, paresthesia, and somnolence
- Schedule V (controlled medication, same category as pregabalin)
  - Patients advised not to drive/operate machinery for 8 hours after dosing even if no central nervous system AEs (somnolence, dizziness)

Calcitonin Gene-Related Peptide (CGRP)

Anti-CGRP receptor mAb: erenumab

5-HT_{1D}, 5-HT_{1F}

Triptans and lasmiditan prevent CGRP release and contract CGRP-dilated vessels

OnabotulinumtoxinA prevents CGRP release

CGRP receptor antagonists (gepants):
- rimegepant
- ubrogepant
- atogepant
- zavegepant

Anti-CGRP ligand mAbs: fremanezumab, galcanezumab, eptinezumab

CGRP receptor

Cerebrovascular smooth-muscle cell

Gα

cAMP, adenosine 3',5'-cyclic monophosphate; mAb, monoclonal antibody.

CGRP: Vasodilator in Cerebral Arteries, Released in Response to Trigeminal Activation

- CGRP is released during the headache phase of a migraine attack
- CGRP is involved in:
  - Vasodilation
  - Neurogenic inflammation
  - Heightened peripheral sensitivity to pain
  - Heightened central sensitization to sensory input

Oral CGRP Antagonists: Rimegepant and Ubrogepant

- Approved for acute treatment of migraine with or without aura in adults
  - Ubrogepant: December 2019
  - Rimegepant: February 2020
- No apparent vasoconstriction/cardiac contraindications
- May be good options when triptans are contraindicated, not tolerated, or not effective
# Approved CGRP Inhibitors for Acute Treatment of Migraine: Ubrogepant and Rimegepant

<table>
<thead>
<tr>
<th></th>
<th>Ubrogepant</th>
<th>Rimegepant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>50 mg, 100 mg Maximum daily dose: 200 mg</td>
<td>75 mg Maximum daily dose: 75 mg</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Half-life 5-7 hours</td>
<td>11 hours</td>
</tr>
<tr>
<td></td>
<td>T-max 1.5 hours</td>
<td>1.5 hours</td>
</tr>
<tr>
<td><strong>Pain relief</strong></td>
<td>Achieved at 1 hour</td>
<td>Achieved at 2 hours</td>
</tr>
<tr>
<td><strong>Pain freedom, relief from most bothersome symptom (MBS)</strong></td>
<td>≈20% achieved pain freedom at 2 hours 39% achieved freedom from MBS at 2 hours</td>
<td>≈20% achieved pain freedom at 2 hours 36% achieved freedom from MBS at 2 hours</td>
</tr>
<tr>
<td><strong>Most common adverse events</strong></td>
<td>Very low rates of nausea, somnolence, dry mouth</td>
<td>Very low rates of nausea, dizziness, urinary tract infection</td>
</tr>
</tbody>
</table>
RCTs ACHIEVE-1 and ACHIEVE-II:

- Pain relief separated from placebo at 1 hour\(^1\)
- Absence of MBS achieved 1.5 hours\(^1\)
- Pain freedom achieved at 2 hours\(^1\)

Optional second dose at 2 hours post-initial dose demonstrated a higher rate of pain freedom vs placebo\(^2\)

Safety and efficacy results of 1-year extension trial comparable to results of ACHIEVE-I and II\(^3\)

Efficacy unaffected whether or not patients used concomitant preventive medication\(^4\)

---

Rimegepant

- 75 mg orally dissolving tablet (ODT) dosed 1 time in 24 hours for acute migraine treatment
- T-max is 1.5 hours with ODT vs 2 hours with standard oral tablet
- Substantial decreases from baseline in migraine days per month with rimegepant 75 mg as needed, suggesting preventive effect and, perhaps, no risk for transformation to medication overuse headache
- Safety, tolerability comparable to placebo
  - Co-administration with sumatriptan also safe, well-tolerated
- No serious adverse events
- Long-term multiple-dose use was well tolerated

Efficacy of Ditan and Gepants at 2 to 8 Hours Post Dose

Therapeutic gain = percent of patients pain-free in active treatment group minus percent pain-free in placebo group, estimated from Kaplan-Meier analyses.

Patient data censored post 2 hours if patient took a second dose of study drug or other rescue medication.

New Acute Treatment Options for Linda

- Oral ubrogepant
- Oral rimegepant
- Oral lasmiditan
- Trial of a different triptan
- Combination treatment (eg, add NSAID)
- Alternative nonoral formulations
- Noninvasive neuromodulation device
Summary

Primary care is at the forefront of treating patients with migraine

Goals of acute treatment include headache freedom at 2 hours and relief of MBS at 2 hours

Awareness and incorporation of new acute migraine treatment options can address the unmet needs of our patients with migraine
Question & Answer
Thank you

Please remember to complete and return your program evaluation as you exit the room. This will be used to process your CME certificate.
Unmet Needs and the Evolving Landscape in Acute Treatment of Migraine: Primary Care Professionals on the Front Line

South Carolina Academy of Family Physicians
June 13, 2021
Myrtle Beach, South Carolina

Supported by an educational grant from Allergan