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

OKLAHOMA ACADEMY OF FAMILY PHYSICIANS
Date TBD

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Learning Objectives

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
Survey Question 1

How confident are you in your ability to treat migraine?
A. Fully confident
B. Very confident
C. Confident
D. Somewhat confident
E. Not at all confident

Survey Question 2

How often do you currently apply established criteria to make differential diagnoses for migraine headache?
A. Always
B. Very often
C. Sometimes
D. Rarely
E. Never

Survey Question 3

How often do you currently review new treatment options for acute management of migraine with patients?
A. Always
B. Very often
C. Sometimes
D. Rarely
E. Never
### Pre-Test Question 1

Which of the following statements is correct regarding patients who present in a primary care practice with complaints of headache?

- **A.** Migraines and tension-type headaches are approximately equivalent in prevalence.
- **B.** Migraine prevalence is about 15% higher in women than in men.
- **C.** Migraine is the most common headache seen in primary care.
- **D.** Patients with complaints suggesting migraine should be referred to a headache specialist to confirm the diagnosis.

### Pre-Test Question 2

Which of the following is a "red flag" that should prompt imaging or laboratory testing to rule out a secondary headache?

- **A.** Headache onset in adolescence or early adulthood
- **B.** Systemic symptoms and signs such as fever or unintentional weight loss
- **C.** Heightened sensitivity to light and/or sound during a headache
- **D.** Increasing frequency of migraine

### Pre-Test Question 3

Which of the following statements is correct regarding medications for the acute treatment of migraine?

- **A.** Triptans remain the gold standard largely because of their broad efficacy and lack of medication overuse headache.
- **B.** The cardiovascular contraindications to triptans do not apply to rimegepant, ubrogepant, and lasmiditan.
- **C.** Oral calcitonin gene-related peptide (CGRP) antagonists are indicated both for migraine prophylaxis and acute treatment of migraine
- **D.** Rimegepant, ubrogepant, and lasmiditan are indicated to treat only migraines without aura.
Pre-Test Question 4
Which of the following statements is correct regarding stratified vs stepped care for acute management of migraines?
A. Stratified care, in which the patient selects treatment based on severity of and disability associated with a migraine, is more likely to result in medication overuse.
B. In stepped care, treatment is accelerated at specified intervals according to an evidence-based treatment algorithm.
C. There is a limited role for newer medications for the acute treatment of migraine in stratified care.
D. Results of a randomized controlled trial demonstrate that compared with stepped care, stratified care is associated with better treatment response and reduced disability time.

Pre-Test Question 5
Which of the following statements is correct regarding episodic and chronic migraine?
A. Unsuccessful acute treatment of migraine is associated with progression from episodic to chronic migraine.
B. Patients inevitably advance from episodic to a chronic migraine over time regardless of how their migraines are managed.
C. Chronic migraine refers to a pattern in which patients experience migraine on a daily basis for 4 or more consecutive days at least once per month.
D. Chronic migraine is more common in men while episodic migraine is more common in women.

Epidemiology
- Affects ≈37 million Americans (15% of population)¹
- Episodic migraine (EM): <15 days/month²⁻⁴
  - 18% women vs 6% men
- Chronic migraine (CM): ≥15 days/month²⁻⁴
  - Overall prevalence of CM: 1% to 3%
  - 3 times more common in women than men
  - Prevalence peaks during midlife (~10 years later than EM)²⁻⁵

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

- >37% of women in a primary care waiting room have migraine
- 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

Migraine Is the Most Common Headache Seen in Primary Care

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

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

Migraine Consequences

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

References:
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 Without Aura


Diagnosis of Migraine With Aura

At least 3 of the following:
1. At least 1 aura symptom spreads gradually over 25 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

ID Migraine™

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: mean migraine 93% of the time
Yes to 3/3 questions: mean 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

Vascular

Infectious

Inflammatory, Neoplastic

Primary Headache

Secondary Headache Disorders

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. A different oral triptan and lower dose of sumatriptan injectable
B. Ubrogepants (an oral gepant)
C. Lasmiditan (a ditan)
D. New nasal-delivery sumatriptan
E. All of the above are options

Guideline Recommendations for 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 (e.g., ED visits)
- Minimal or no adverse effects
Poor Acute Treatment Associated With Chronic Migraine Risk

- 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</th>
<th>Patients Who Progressed to Chronic Migraine [%]</th>
</tr>
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<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>
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</table>

Stepped Care vs Stratified Care

<table>
<thead>
<tr>
<th>Stepped Care</th>
<th>Stratified Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Strategy</td>
<td>Patient selects treatment based on severity and disability of migraine attack</td>
</tr>
<tr>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>Non-specific agent may work</td>
<td>May require a more expensive agent initially</td>
</tr>
<tr>
<td>Potential cost savings</td>
<td>Higher patient satisfaction</td>
</tr>
<tr>
<td>Chasing the pain after central sensitization occurs is futile and more costly in the long run</td>
<td></td>
</tr>
<tr>
<td>Medication overuse is common</td>
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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**
  - 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!
- Rapid onset, well-tolerated, and good sustained pain-free results in clinical studies
- FDA approval October 2019 for use in adults
- Dosage: 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
The Role of Serotonin (5-HT) in Migraine Pathophysiology


Cortex
Thalamus
Trigeminal ganglion
5-HT1D receptors
Trigeminal inhibition
5-HT1B receptors
Vasoconstriction
Decreased pain signal transmission
5-HT1F receptors
Decreased central integration

Lasmiditan
- Presumed mechanism of action: peripheral and central activation of 5-HT1 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)

CGRP
- Triptans and sumatriptan prevent CGRP release andGG protein coupling
- CGRP-mediated vasoconstriction
- induces vasodilation and prevents CGRP release
- CGRP receptor antagonists (gepants):
  - rimegepant
  - ubrogepant
  - atogepant
  - zavegepant
- Anti-CGRP ligand mAbs:
  - fremanezumab
  - galcanezumab
  - eptinezumab
- Anti-CGRP mAb:
  - erenumab

CGRP
- Neurogenic inflammation,
**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 Uburogepant**

- Approved for acute treatment of migraine with or without aura in adults
  - Uburogepant: 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: Uburogepant and Rimegepant**

<table>
<thead>
<tr>
<th></th>
<th>Uburogepant</th>
<th>Rimegepant</th>
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<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>50 mg, 100 mg</td>
<td>75 mg</td>
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<td></td>
<td>Maximum daily dose: 200 mg</td>
<td>Maximum daily dose: 75 mg</td>
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<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Half-life: 5-7 hours</td>
<td>11 hours</td>
</tr>
<tr>
<td></td>
<td>T_max: 5.5 hours</td>
<td>5.5 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, rated from most bothersome symptom (MBS)</strong></td>
<td>20% achieved pain freedom at 2 hours</td>
<td>20% achieved pain freedom at 2 hours</td>
</tr>
<tr>
<td></td>
<td>10% achieved freedom from MBS at 2 hours</td>
<td>10% 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>
Ubrogepant

- RCTs: ACHIEVE-I and ACHIEVE-II:
  - Pain relief separated from placebo at 1 hour
  - Absence of MBS achieved 1.5 hours
  - Pain freedom achieved at 2 hours
- Optional second dose at 2 hours post-initial dose demonstrated a higher rate of pain freedom vs placebo
- Safety and efficacy results of 1-year extension trial comparable to results of ACHIEVE-I and II
- Efficacy unaffected whether or not patients used concomitant preventive medication

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 Ditans and Gepants at 2 to 8 Hours Post Dose

therapeutic gain (%) vs time post dose (h)
therapy dose (mg)

- Lasmiditan 100 mg
- Lasmiditan 200 mg
- Uburogepant 50 mg
- Uburogepant 100 mg
- Uburogepant 200 mg
- Rimegepant 75 mg

Therapeutic gain (%) vs time post dose (h)

therapeutic dose (mg)

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- Uburogepant 100 mg
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- Lasmiditan 200 mg
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- Uburogepant 100 mg
- Uburogepant 200 mg
- Rimegepant 75 mg
New Acute Treatment Options for Linda

- Oral ubrogepant
- Oral rimegepant
- Oral lasmiditan
- Trial of a different triptan
- Combination treatment (e.g., 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

Post-Test Question 1

Which of the following statements is correct regarding patients who present in a primary care practice with complaints of headache?

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Question & Answer

Thank you

Please remember to complete the program evaluation. This will be used to process your CME certificate.