Navigating the Intersection of Migraine and OUD

Part 1: Assessment and Non-Opioid Pharmacologic Treatment

<table>
<thead>
<tr>
<th>Meredith Barad, MD</th>
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</thead>
<tbody>
<tr>
<td>Clinical Associate Professor of Anesthesia (Pain Medicine) and Neurology &amp; Neurological Sciences</td>
</tr>
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<tr>
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<td>Director, Comprehensive Pain Center</td>
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<tr>
<td>Director, Pain Management Fellowship</td>
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<tr>
<td>Albany Medical Center</td>
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<td>Albany, NY</td>
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<table>
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<tr>
<th>Jennifer Robblee, MD</th>
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<tr>
<td>Neurologist</td>
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<tr>
<td>Jan and Tom Lewis Migraine Treatment Program</td>
</tr>
<tr>
<td>Assistant Professor</td>
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<tr>
<td>Department of Neurology</td>
</tr>
<tr>
<td>Barrow Neurological Institute</td>
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<tr>
<td>Phoenix, AZ</td>
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Accreditation and Credit Designation

**Accreditation:**
- The American Academy of Pain Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

**Credit Designation:**
- The American Academy of Pain Medicine designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
### Speaker, Reviewer, and Planner Disclosures

<table>
<thead>
<tr>
<th>Speakers</th>
<th>Reviewer</th>
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<tbody>
<tr>
<td><strong>Meredith Barad, MD</strong></td>
<td><strong>David A. Edwards, MD, PhD</strong></td>
</tr>
<tr>
<td>Honoraria: Sprint Therapeutics</td>
<td>Vanderbilt University Medical Center</td>
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<tr>
<td><strong>Charles E. Argoff, MD</strong></td>
<td>Chair, AAPM Education and CME Oversight Committee</td>
</tr>
<tr>
<td>Research: AbbVie, Amgen, Lilly, Teva</td>
<td>No relevant financial relationships</td>
</tr>
<tr>
<td>Honoraria: AbbVie, Amgen, Averitas, Collegium, Grunenthal, Lilly, Lundbeck, Teva</td>
<td><strong>Planners</strong></td>
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<tr>
<td>Consulting fee: Averitas, Grunenthal, Lilly, Lundbeck, MK Life Sciences, Neumentum, Tremeau, Vertex</td>
<td>Dana E. Boyte</td>
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<tr>
<td>Royalties: Elsevier</td>
<td>AAPM Executive Director</td>
</tr>
<tr>
<td><strong>Jennifer Robblee, MD</strong></td>
<td>No relevant financial relationships</td>
</tr>
<tr>
<td>Site investigator: Eli Lilly, AbbVie</td>
<td>Angela Casey and Stephanie Lee</td>
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<tr>
<td>Grant: Barrow Neuro Foundation</td>
<td>PharmaCom Group</td>
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<tr>
<td>Paid editorial: MedLink Neurology, Neurodiem</td>
<td>No relevant financial relationships</td>
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</table>

### Target Audience

- The overarching goal of PCSS is to train healthcare professionals in evidence-based practices for the prevention and treatment of opioid use disorders, particularly in prescribing medications, as well for the prevention and treatment of substance use disorders.
Educational Objectives

At the conclusion of this activity participants should be able to:

- Describe the intersection between opioid use disorder (OUD) and migraine, particularly in the setting of medication-overuse headache (MOH)
- Employ diagnostic approaches to migraine based on underlying pathophysiologic mechanisms
- Apply non-opioid pharmacologic treatments for migraine in patients with comorbid OUD

Migraine and Opioid Use Disorder (OUD)

Meredith Barad, MD
Clinical Assistant Professor of Anesthesia (Pain Medicine) and Neurology & Neurological Sciences
Stanford Hospital and Clinics
Redwood City, CA

Navigating the Intersection of Migraine and OUD
Part 1: Assessment and Non-Opioid Pharmacologic Treatment

January 11, 2022
**Is There Good Evidence for Use of Opioids for Migraine?**

**Rescue vs Prevention**

**AAN 2000 Guideline: Treatment of Acute Migraine**
(Based on Agency for Health Care Policy and Research 1999 Technical Review)

<table>
<thead>
<tr>
<th>Group 1*</th>
<th>Group 2†</th>
<th>Group 3‡</th>
<th>Group 4§</th>
<th>Group 5¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific:</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>▪ Naratriptan PO</td>
<td>▪ APAP/codeine PO</td>
<td>▪ Butalbital/aspirin/caffeine/codeine PO</td>
<td>▪ APAP PO</td>
<td>▪ Dexamethasone IV</td>
</tr>
<tr>
<td>▪ Rizatriptan PO</td>
<td>▪ Butorphanol IM</td>
<td>▪ Butorphanol IM</td>
<td>▪ Chlorpromazine IM</td>
<td>▪ Hydrocortisone IV</td>
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<tr>
<td>▪ Sumatriptan SC, IN, PO</td>
<td>▪ Butalbital/aspirin/caffeine/codeine PO</td>
<td>▪ Butalbital/aspirin/caffeine/codeine PO</td>
<td>▪ Ergotamine PO</td>
<td></td>
</tr>
<tr>
<td>▪ Zolmitriptan PO</td>
<td>▪ Butorphanol IM</td>
<td>▪ Butalbital/aspirin/caffeine/codeine PO</td>
<td>▪ Ergotamine PO</td>
<td></td>
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<tr>
<td>▪ DHE SC, IM, IV, IN</td>
<td>▪ Butorphanol IM</td>
<td>▪ Ergotamine PO</td>
<td>▪ Ergotamine PO</td>
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<tr>
<td>▪ DHE IV * antiemetic</td>
<td>▪ Butorphanol IM</td>
<td>▪ Metoclopramide IM</td>
<td>▪ Metoclopramide IM</td>
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<tr>
<td><strong>Non-specific:</strong></td>
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<tr>
<td>▪ APAP/aspirin/caffeine PO</td>
<td>▪ Butalbital/aspirin/caffeine PO</td>
<td>▪ Butalbital/aspirin/caffeine PO</td>
<td>▪ APAP PO</td>
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<tr>
<td>▪ Aspirin PO</td>
<td>▪ Butalbital/aspirin/caffeine PO</td>
<td>▪ Metoclopramide IM</td>
<td>▪ Chlorpromazine IM</td>
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<tr>
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<td>▪ Butalbital/aspirin/caffeine PO</td>
<td>▪ Granisetron IV</td>
<td>▪ Lidocaine IV</td>
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<td>▪ Ibuprofen PO</td>
<td>▪ Butalbital/aspirin/caffeine PO</td>
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<tr>
<td>▪ Naproxen sodium PO</td>
<td>▪ Butalbital/aspirin/caffeine PO</td>
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<tr>
<td>▪ Procyclidine IV</td>
<td>▪ Butalbital/aspirin/caffeine PO</td>
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</table>

*Proven, pronounced statistical & clinical benefit (≥2 double-blind, placebo-controlled studies & clinical impression of effect); †Moderate statistical & clinical benefit (1 double-blind, placebo-controlled study & clinical impression of effect); ‡Statistically but not proven clinically or clinically but not proven statistically effective (conflicting or inconsistent evidence); §Proven statistically or clinically ineffective (failed efficacy vs placebo); ¶Clinical & statistical benefits unknown (insufficient evidence)
Subsequent Evidence for Tramadol Rescue

- 2005 double-blind Class I study
  - Tramadol/acetaminophen 75 mg/650 mg vs placebo for acute migraine pain
  - 2 h after dosing, tramadol/APAP was:
    - Superior to placebo for:
      - Headache relief: 55.8% vs 33.8% (P<0.01)
      - Pain intensity mild
      - Headache free: 22.1% vs 9.3% (P<0.01)
      - Pain intensity none
      - Photophobia: 65.4% vs 47.8% none/mild (P=0.003)
      - Phonophobia: 65.7% vs 55.1% none/mild (P=0.008)
    - Not superior for migraine-related nausea: 63.5% vs 70.6% none/mild (P=0.681)

- 2007 single-blind Class II study
  - IV tramadol 100 mg vs placebo for acute migraine pain in the emergency department (ED)
  - 1 h after dosing, IV tramadol was:
    - Superior to placebo for pain response: 70.6% vs 35.3% (P=0.04)
    - Primary endpoint: decrease of pain intensity to <50% of pretreatment value
    - Not superior for pain-free response: 29.4% vs 11.8% (P=0.398)
    - Defined as no pain

**Acute Treatment of Migraine: 2015 AHS Evidence**

<table>
<thead>
<tr>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
<th>Level U</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAs: *Aspirin PO</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>*Rizatriptan PO Sumatriptan PO, *IN, patch, *SC Zolmitriptan IN, PO Combinations: *APAP/aspirin/caffeine PO Sumatriptan/naproxen</td>
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*Based on 2000 AAN evidence review. Level A: Effective based on available evidence; Level B: Probably effective based on available evidence; Level C: Possibly effective based on available evidence; Level U: Evidence is conflicting or inadequate to support or refute efficacy; Level B negative: Probably ineffective; Level C negative: Possibly ineffective

Medication Overuse Headache (MOH)

- Good evidence suggests that using opioids for migraine promotes worsening of headache and development of MOH.
- ICHD-3 defines MOH as:
  - Headache occurring on ≥15 d/month in a patient with a pre-existing primary headache AND
  - Developing as a consequence of regular overuse of acute or symptomatic headache medication (on ≥10 or ≥15 d/month, depending on medication) for >3 months
    - Opioid-overuse headache: regular intake of ≥1 opioids on ≥10 d/month
- MAST study found MOH was associated with higher:
  - Migraine symptom severity: 17.8 ± 2.7 vs 16.4 ± 3.0 (0-21 scale)
  - Pain intensity scores: 7.4 ± 1.6 vs 6.5 ± 1.6 (0-10 scale)
  - Rates of cutaneous allodynia: 53.7% vs 37.5%

ICHD-3-The International Classification of Headache Disorders, 3rd ed; MAST=Migraine in America Symptoms and Treatment

Risk Factors Associated With MOH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio (95% CI)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>5.3 (1.6-24.6)</td>
<td>Obesity is most important risk factor</td>
</tr>
<tr>
<td>Regular tranquilizer use</td>
<td>5.2 (3.0-9.0)</td>
<td>Avoid or withdraw tranquilizers</td>
</tr>
<tr>
<td>Anxiety disorder or depression</td>
<td>4.7 (2.4-9.0)</td>
<td>Screening advised</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>2.7 (1.2-6.3)</td>
<td>Recommend exercise</td>
</tr>
<tr>
<td>Opioid use &gt;10 d/month</td>
<td>2.3 (1.3-3.9)</td>
<td>Might lead to addiction</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.9 (1.4-2.5)</td>
<td>-</td>
</tr>
<tr>
<td>Low educational level</td>
<td>1.9 (1.2-3.0)</td>
<td>-</td>
</tr>
<tr>
<td>Chronic musculoskeletal disease</td>
<td>1.9 (1.4-2.7)</td>
<td>-</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.8 (1.2-2.5)</td>
<td>Smoking cessation education advised</td>
</tr>
<tr>
<td>Age &lt;50 years</td>
<td>1.8 (1.3-2.4)</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>1.6 (1.1-2.2)</td>
<td>-</td>
</tr>
<tr>
<td>Intensity of headache</td>
<td>1.5 (1.0-2.1)</td>
<td>-</td>
</tr>
<tr>
<td>Aspirin use &gt;15 d/month</td>
<td>0.5 (0.3-0.9)</td>
<td>Protective effect</td>
</tr>
<tr>
<td>Ibuprofen use &gt;15 d/month</td>
<td>0.7 (0.5-1.0)</td>
<td>Protective effect</td>
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Navigating the Intersection of Migraine and OUD

Part 1: Assessment and Non-Opioid Pharmacologic Treatment

January 11, 2022
Acute Migraine Treatment By Outpatient Clinicians

- Retrospective cohort analysis of US administrative claims data from 2005-2014
  - Commercial and Medicare databases

Acute migraine treatments received during entire follow-up period

- Triptan: 59.9%
- NSAID: 66.6%
- Strong or weak opioid: 77.4%


Acute Migraine Treatment By Outpatient Clinicians

- Retrospective cohort analysis of US administrative claims data from 2005-2014

  - <1% of patients had an opioid abuse diagnosis over 5 years of follow up
    - Incidence increased with increasing number of days' supply of opioids
    - After adjusting for baseline demographic and clinical characteristics, compared to patients with 1-45 d opioid supply, the risk of opioid abuse was:
      - 3X higher with 46-180 d supply
      - 8X higher with 181-365 d supply
      - 23X higher with >365 d supply

They Get Opioids for Another Pain Condition

- US-based survey of patients with chronic headache
  - 17.7% of patients used opioids to treat not only headache, but also other pain conditions
- Two Danish surveys of patients with chronic headache
  1. Chronic headache was associated with back pain, osteoarthritis, and rheumatoid arthritis
  2. MOH patients used analgesics for:
     - Other pain conditions: 23.9%
     - Muscle/joint pain: 22.6%
     - Back pain: 21.5%


What's the Plan?

Reduce intake of acute medication

Start a preventive drug therapy

Relapse

- Systematic review of treatment for MOH
  - Relapse to overuse of acute medications after discontinuation varied between 0% and 45%
    - The majority of studies showed a relapse rate between 25% and 35%
  - Predictors of relapse:
    - Overuse of opioids vs triptans
    - Comorbid psychiatric disorders
      - Depression was an important predictor of relapse


Assessment and Proposed Pathophysiology of Migraine Headache

Charles E. Argoff, MD
Professor of Neurology
Albany Medical College
Director, Comprehensive Pain Center
Director, Pain Management Fellowship
Albany Medical Center
Albany, New York
An inherited neurological disorder characterized by neurological, sensory, autonomic, vestibular, cognitive, and gastrointestinal symptoms


Making the Migraine Diagnosis: It Is More Than Just a Headache

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<th>Diagnostic Criteria for Migraine (ICHD-3)</th>
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<td>- Pulsating quality</td>
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<tr>
<td>- Moderate or severe pain intensity</td>
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<td>- Aggravated by, or causing avoidance of, routine physical activity</td>
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</table>

Would You Prefer a Simpler Way to Diagnose Migraine? ID Migraine

The 3-item ID Migraine screener is a validated tool to assist in rapidly making the migraine diagnosis:

1. Has a headache limited your activities for a day or more in the last 3 months?
2. Are you nauseated or sick to your stomach when you have a headache?
3. Does light bother you when you have a headache?

Answering yes to:

- 2/3 indicated a migraine diagnosis is likely

  - Sensitivity of 0.81 (95% CI 0.77-0.85)

- 3/3 over 90% sensitive


Migraine Can Be Different For Every Patient

Different phases of migraine

- Premonitory hours-days
- Interictal
- Headache 4-72 h
- Postdrome hours-days
- Aura <1 h

- Hypersensitivity to light, sound, and touch
- Headache
- Anxiety
- Nausea
- Cognitive dysfunction
- Fatigue
- Depression
- Nausea
- Photophobia
- Yawning
- Fatigue
- Nausea
- Mood changes
- Neck stiffness
- Food cravings
- Scintillating scotoma
- Visual distortion
- Pins and needles
- Throbbing headache
- Nausea
- Vomiting
- Photophobia
- Phonophobia
- Cognitive dysfunction
- Congestion
- Alldynia


Navigating the Intersection of Migraine and OUD

Part 1: Assessment and Non-Opioid Pharmacologic Treatment

January 11, 2022
Headache Consultation…
Is It a Migraine?

Classification of Headaches

- Primary “benign” headaches
  - Episodic migraine without aura
  - Episodic migraine with aura
  - Tension-type headache
  - Cluster headaches and variants
  - Chronic daily headache
    - Chronic migraine
    - MOH

- Secondary headaches
  - “Benign vs serious”
STEP # 1

- Differentiate between a primary recurring headache from a secondary headache
  - Take a complete history including a psych assessment
  - Perform an examination

Taking the HISTORY

- Timing
  - Why consult now?
  - How frequent and duration?

- Character
  - Intensity, nature, site, associated symptoms
HISTORY continued

- **Response**
  - Activity during headache
  - Medication / supplements tried

- **Comorbid states**
  - Depression, anxiety, chronic pain, insomnia, obesity

- **Potential causes**
  - Family history
  - Aggravating or relieving factors
  - Triggers

---

**Individual Triggers Occurring At Least Occasionally**

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>79.7</td>
</tr>
<tr>
<td>Hormone*</td>
<td>65.1</td>
</tr>
<tr>
<td>Not eating</td>
<td>57.3</td>
</tr>
<tr>
<td>Weather</td>
<td>53.2</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>49.8</td>
</tr>
<tr>
<td>Perfume / odor</td>
<td>43.7</td>
</tr>
<tr>
<td>Neck pain</td>
<td>38.4</td>
</tr>
<tr>
<td>Lights</td>
<td>38.1</td>
</tr>
<tr>
<td>Alcohol</td>
<td>37.8</td>
</tr>
<tr>
<td>Smoke</td>
<td>35.7</td>
</tr>
<tr>
<td>Sleeping late</td>
<td>32.0</td>
</tr>
<tr>
<td>Heat</td>
<td>30.3</td>
</tr>
<tr>
<td>Food</td>
<td>26.9</td>
</tr>
<tr>
<td>Exercise</td>
<td>22.1</td>
</tr>
<tr>
<td>Sexual activity</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*Women only

Kelman L. The triggers or precipitants of the acute migraine attack. Cephalalgia 2007;27:394-402. doi.org/10.1111/j.1468-2982.2007.01303.x
**Examination Basics for Headache**

- Observation
- Vital Signs
- Eye exam
- Motor / Gait
- Musculoskeletal exam
- Skin

**STEP # 2**
Identify Red Flags

**“SNOOP” 4**

- **S**ystemic
- **N**eurologic
- **O**nset Sudden
- **O**nset after age 50 (pathological diagnosis 3.3 x more likely)
- **P4** Pattern change
  - Progression
  - Precipitation by Valsalva maneuver
  - Postural aggravation
  - Papilledema

STEP # 3

- Necessary workup
  - Choice of testing depends upon the headache type that is suspected
  - No panel or collection of tests should be performed in every case

Is It a Migraine?
Patients Presenting to PCPs with Episodic Headache Most Likely Have Migraine

- Migraine / migrainous is common: 94%
- Tension headache is rare

n=377 patients who returned diaries

Newman et al. Poster presented at: The Diamond Headache Clinical Research and Educational Foundation Meeting; July 16-20, 2002; Lake Buena Vista, FL.

Migraine Prevalence Peaks at 25-55 Years of Age

Adjusted age-specific prevalence of migraine


Navigating the Intersection of Migraine and OUD
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### Making the Migraine Diagnosis: It Is More Than Just a Headache

#### Diagnostic Criteria for Migraine (ICHD-3)

<table>
<thead>
<tr>
<th>Pain features</th>
<th>Non-pain features</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Migraine without aura:</strong> History of ≥5 headache attacks that last 4-72 h, with ≥2 of:</td>
<td><strong>Migraine without aura:</strong> During headache, ≥1 of:</td>
<td><strong>Chronic migraine:</strong> Headache on ≥15 d/month for ≥3 months &amp; Features of migraine on ≥8 d/month</td>
</tr>
<tr>
<td>- Unilateral location</td>
<td>- Nausea and/or vomiting</td>
<td></td>
</tr>
<tr>
<td>- Pulsating quality</td>
<td>- Phonophobia and photophobia</td>
<td></td>
</tr>
<tr>
<td>- Moderate or severe pain intensity</td>
<td>- History of ≥2 attacks with ≥1 fully reversible aura symptom (eg, visual, sensory, speech/language, or motor), with or without headache</td>
<td></td>
</tr>
<tr>
<td>- Aggravated by, or causing avoidance of, routine physical activity</td>
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</table>

#### Tension-Type Headache

<table>
<thead>
<tr>
<th>A. Lasting 30 min to 7 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Steady, pressing quality</td>
</tr>
<tr>
<td>- Bilateral location</td>
</tr>
<tr>
<td>- Mild to moderate intensity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. No aggravation by routine physical activity</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>C. No associated symptoms (mild nausea allowed)</th>
</tr>
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<thead>
<tr>
<th>D. At least 5 attacks fulfilling the 3 bullet points above</th>
</tr>
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<table>
<thead>
<tr>
<th>E. No evidence of organic disease</th>
</tr>
</thead>
</table>
Migraine Pearl

- When patients report “I have migraine headaches” and less severe “non-migraine”, “tension-type headaches”...

- They are probably all migraines !!!

The Anatomy of Migraine Headache

1. Peripheral trigeminal ganglion afferents innervate the meninges and large cerebral arteries

2. Afferents from skin and muscles of neck converge on neurons in the TCC together with afferents arriving from the meninges and cerebral vasculature

3. Ascending connections from the TCC transmit signals to multiple brainstem, thalamic, hypothalamic, and basal ganglia nuclei

4. Multiple cortical areas process inputs from the TCC leading to phenotypic expression of migraine pain and its associated symptoms

The Anatomy of Migraine Headache

Pathways Mediating Migraine Symptoms

Symptoms associated with migraine are mediated by trigeminovascular neurons that project to multiple brainstem, thalamic, hypothalamic, and cortical areas.

- **Thalamocortical projections** mediate photophobia, phonophobia, osmophobia, motor clumsiness, aphasia, and transient decline in cognitive functions.
- **Spinal projections to brainstem, thalamic, and hypothalamic nuclei** mediate irritability, anxiety, low energy, depression, yawning, frequent urination, teary eyes, loss of appetite, nausea, and sleep disturbances.

Exposure to light during migraine can bombard many cortical areas with many signals, which also causes a variety of migraine-associated symptoms.
Pathways Mediating Migraine Chronification

Chronic migraine: a never-ending migraine attack

Chromically hyperexcitable cortex mediates interictal hypersensitivity to light, sound, smell, and touch.

Chromically sensitized thalamus mediates extra-cephalic allodynia and lowers the threshold for the next migraine attack.

Chromically sensitized spinal trigeminal nucleus mediates the ongoing headache and cephalic allodynia.

CGRP Is Found in the Central and Peripheral Nervous Systems

- CGRP is widely distributed in the central and peripheral nervous systems
- CGRP-containing nerve fibers innervate organ systems
- The clinical relevance of CGRP beyond migraine and the nervous system has not been clearly demonstrated

CGRP is expressed within nervous tissue

CGRP is contained in perivascular nerves, and CGRP receptors are found on vascular smooth muscle cells
Evidence for the Role of CGRP in Migraine: CGRP Infusion Can Induce an Attack


- Lines represent individual headache scores following CGRP infusion in patients who have migraine
- CGRP caused moderate to severe headaches in all subjects

Role of CGRP May Involve Multiple Central and Peripheral Processes


Research has yet to determine which of these processes play a causal role, or if they occur as a result of, or in parallel with, migraine
CGRP Receptors: Present in Multiple Central and Peripheral Locations

- Located on both sides of the blood-brain barrier
- Found in multiple areas:
  - Trigeminal ganglion
  - Dura vasculature
  - Brainstem, eg, TNC
  - Brain, eg, thalamus
- Expressed on numerous cell types:
  - Neurons
  - Glial cells
  - Mast cells
  - Vascular smooth muscle cells


Interaction of CGRP with the CGRP Receptor: Role in Migraine Pathophysiology

- Peripherally:
  - Release of CGRP from trigeminal nerve endings is thought to trigger multiple responses induced by CGRP receptor binding, which eventually lead to the sensitization of nociceptor trigeminal neurons
  - Stimulation of nociceptive trigeminal neurons is hypothesized to relay migraine pain signal through the brainstem into the brain, ultimately leading to experience of migraine pain
- Centrally:
  - CGRP binding to receptors within the CNS might have numerous effects, including central sensitization and activation
  - Other central processes (eg, feedback from a sensitized brain) may also contribute to the experience of migraine pain
Conclusion

1. Migraine headache is common

2. Simple to use validated tools can be utilized to assist and expedite the diagnosis of migraine headache in general and when evaluating the person diagnosed with OUD

3. Advances in our understanding the mechanisms of migraine headache has led to new targets for treatment
Challenges and Advances in the Treatment of Migraine

Jennifer Robblee, MD
Neurologist
Jan and Tom Lewis Migraine Treatment Program
Assistant Professor
Department of Neurology
Barrow Neurological Institute
Phoenix, Arizona

Who Needs Treatment?
Patient Selection
When to Start a Preventive Treatment?

- 4 to 6 headaches d/month
- Patient preference
- Disabling attacks
- Acute treatment side effects
- MOH risk


How Do I Know If It Is Working?

- Goal = 50% response
- 3-month trial or adverse effects (AEs)

Non-Specific Oral Preventive Medications

<table>
<thead>
<tr>
<th>Established efficacy*</th>
<th>Probably effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Divalproex</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Memantine</td>
</tr>
<tr>
<td>Timolol</td>
<td>Nadolol</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Venlafaxine</td>
</tr>
</tbody>
</table>

*Frovatriptan for menstrual migraine

Other Non-Specific Preventive Medications*

- Acetazolamide
- Cyproheptadine
- Duloxetine
- Gabapentin
- Nortriptyline
- Pregabalin
- Zonisamide

*Limited evidence ➔ consider for refractory patients not responding to first-line options

CGRP Monoclonal Antibodies

50% responder rates of ~60%  
CGRP=calcitonin gene-related peptide

<table>
<thead>
<tr>
<th>CGRP receptor antibody</th>
<th>Dosage</th>
<th>Main AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab</td>
<td>70-140 mg SC injection qMo</td>
<td>Injection site reactions, Constipation, Hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CGRP ligand antibody</th>
<th>Dosage</th>
<th>Main AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eptinezumab</td>
<td>100-300 mg as 30-min IV infusion q3mo</td>
<td>Nasopharyngitis, Hypersensitivity</td>
</tr>
</tbody>
</table>

| Fremanezumab         | 225 mg SC injection qMo OR 675 mg (3 consecutive 225 mg SC injections) q3mo | Injection site reactions |

| Galcanezumab         | Month 1 loading dose: 240 mg (2 consecutive 120 mg SC injections) Subsequent months: 120 mg SC injection qMo | Injection site reactions |

### Gepants as Preventive
(small-molecule CGRP receptor antagonists)

<table>
<thead>
<tr>
<th>Rimegepant ODT</th>
<th>Atogepant tablets</th>
<th>Zavegepant capsules</th>
</tr>
</thead>
</table>
| - FDA approval:  
  - Episodic migraine  
  - Pending for chronic migraine  
  - 75 mg ODT q2d  
  - Migraine days: -4.3 | - FDA approval:  
  - Episodic migraine  
  - Pending for chronic migraine  
  - 10 mg, 30 mg, 60 mg PO qd  
  - Migraine days: -3.7, -3.9, -4.2 | - Phase 2/3 in progress  
  - 100 mg, 200 mg PO |

Gepants are small-molecule CGRP receptor antagonists used for the prevention of migraine. The table above outlines the key features of three gepants: Rimegepant ODT, Atogepant tablets, and Zavegepant capsules.

- **Rimegepant ODT**
  - FDA approval:  
    - Episodic migraine  
    - Pending for chronic migraine  
  - 75 mg ODT q2d  
  - Migraine days: -4.3

- **Atogepant tablets**
  - FDA approval:  
    - Episodic migraine  
    - Pending for chronic migraine  
  - 10 mg, 30 mg, 60 mg PO qd  
  - Migraine days: -3.7, -3.9, -4.2

- **Zavegepant capsules**
  - Phase 2/3 in progress  
  - 100 mg, 200 mg PO

**CGRP** = calcitonin gene-related peptide;  
**CLR** = calcitonin receptor-like receptor;  
**Gαs** = α-subunit of the GS protein;  
**RAMP1** = receptor activity-modifying protein;  
**RCP** = receptor coupling protein.


Phase 2/3 randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of oral zavegepant in migraine prevention. clinicaltrials.gov/ct2/show/NCT04804033

---

### Acute Treatment

### Migraine Management
# Triptans

<table>
<thead>
<tr>
<th>Triptan</th>
<th>Dosage</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sumatriptan</strong></td>
<td>PO: 25, 50, 100 mg</td>
<td>Oldest</td>
</tr>
<tr>
<td></td>
<td>IN: 5, 10, 20 mg (nasal spray); 11 mg (nasal powder)</td>
<td>High A/E rate</td>
</tr>
<tr>
<td></td>
<td>SC: 3 mg (auto-injector); 4, 6 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Almotriptan</strong></td>
<td>6.25-12.5 mg PO</td>
<td>Fast, low A/E</td>
</tr>
<tr>
<td><strong>Eletriptan</strong></td>
<td>20-40 mg PO</td>
<td>Fast, mod A/E</td>
</tr>
<tr>
<td><strong>Frovatriptan</strong></td>
<td>2.5 mg PO</td>
<td>Long, low A/E</td>
</tr>
<tr>
<td><strong>Naratriptan</strong></td>
<td>1-2.5 mg PO</td>
<td>Long, low A/E</td>
</tr>
<tr>
<td><strong>Rizatriptan</strong></td>
<td>5-10 mg PO/ODT</td>
<td>Fast, mod A/E</td>
</tr>
<tr>
<td><strong>Zolmitriptan</strong></td>
<td>2.5-5 mg PO/OD/IN</td>
<td>Fast, mod A/E</td>
</tr>
<tr>
<td><strong>Sumatriptan + Naproxen</strong></td>
<td>Sumatriptan 85 mg + Naproxen 500 mg</td>
<td>Combo med</td>
</tr>
<tr>
<td><strong>Rizatriptan + Meloxicam</strong></td>
<td>Pending: AXS-07</td>
<td>New &amp; faster</td>
</tr>
</tbody>
</table>


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# NSAIDs

**NSAIDs**

Combo with triptans = 60-80% 2 h headache relief

- **Naproxen**
  - 500 mg prn
- **Indomethacin**
  - 25-75 mg prn
- **Diclofenac PO or powdered for oral solution**
  - 50 mg prn
- **Ketorolac**
  - 10 mg PO; 15.75 mg IN; 30-60 mg IM
### Dihydroergotamine (DHE) 

~40% 2 h pain freedom

- **Nasal**
  - Old nasal spray: 2 mg
    - Administer 1 metered spray (0.5 mg) in each nostril, followed 15 min later by an additional 1 spray (0.5 mg) in each nostril
  - New POD device FDA approved: 1.45 mg
    - Administer 1 metered spray of 0.725 mg into each nostril
    - Can repeat after 1 h
  - Drug levels similar to IV

- **Parenteral**
  - 1 mg SC/IM
    - Can repeat at 1 h intervals (max 3 mg/24 h)
  - 1 mg IV q8h or continuous IV
    - Can repeat after 1 h (max 2 mg/24 h)
  - AE = nausea

**Do NOT use within 24 h of a triptan**

---

### Gepants

~20% 2 h pain freedom*

<table>
<thead>
<tr>
<th>Ubrogepant tablets</th>
<th>Rimegepant ODT†</th>
<th>Zavegepant IN‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-100 mg PO</td>
<td>75 mg ODT</td>
<td>Phase 2/3 in progress</td>
</tr>
<tr>
<td>Can repeat after 2 h</td>
<td>Can repeat after 24 h</td>
<td></td>
</tr>
<tr>
<td>Nausea and somnolence</td>
<td>Nausea and abdominal pain/dyspepsia</td>
<td></td>
</tr>
</tbody>
</table>

Pipeline: FE 205030 SC

---

*Placebo about 11-14%  †Acute and preventive treatment  ‡Oral capsules in clinical trials for prevention
**Lasmiditan tablets**
- 50, 100, or 200 mg PO
  - 50 mg
  - 100 mg
  - 200 mg (100 mg x 2)
- Can repeat after 24 h
- 8 h driving restriction
- Schedule V controlled substance

**Triptans = 5HT\textsubscript{1B/1D} agonist**
- Vasoconstriction due to 1B

**Ditans = 5HT\textsubscript{1F} agonist**
- No vasoconstriction


*Placebo about 20%*

**NOT recommended:**
- Opioids & butalbital
  - Decreased treatment response
  - Risk of chronic daily headache
  - Risk of tolerance, withdrawal, abuse, & overdose
  - Increased sensitization

## Treatment Summary

<table>
<thead>
<tr>
<th>Acute</th>
<th>Preventive</th>
<th>Pipeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>- NSAIDs</td>
<td>- Non-specific orals</td>
<td>- New gepants</td>
</tr>
<tr>
<td>- Triptans</td>
<td>- OnabotulinumtoxinA*</td>
<td>- Zavegepant IN</td>
</tr>
<tr>
<td>- Gepants</td>
<td>- CGRP mAbs</td>
<td>- FE 205030 SC</td>
</tr>
<tr>
<td>- Ditans</td>
<td>- Gepants</td>
<td>- Triptans</td>
</tr>
<tr>
<td>- DHE</td>
<td>- Nerve blocks*</td>
<td>- Zolmitriptan patch</td>
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<tr>
<td>- Devices*</td>
<td>- Devices*</td>
<td>- Rizatriptan + meloxicam</td>
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### References

A Phase 2/3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of oral zavegepant in migraine prevention. [clinicaltrials.gov](https://clinicaltrials.gov)\(\text{ct2/show/NCT04571060}\)


Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol 2018;17:174-82. doi.org/10.1016/s1474-4227(17)30435-0


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### Treatment Acute

- NSAIDs
- Triptans
- Gepants
- Ditans
- DHE
- Devices*

### Treatment Preventive

- Non-specific orals
- OnabotulinumtoxinA*
- CGRP mAbs
- Gepants
- Nerve blocks*
- Devices*
- SEEDS*

### Treatment Pipeline

- New gepants
  - Zavegepant IN
  - FE 205030 SC
- Triptans
  - Zolmitriptan patch
  - Rizatriptan + meloxicam

*Will be addressed in Webinar 2 of series

SEEDS=Sleep, Exercise, Eat & drink, Diary, Stress
PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder.
- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medications for opioid use disorder (MOUD).
- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
- No cost.

For more information visit:
https://pcssNOW.org/mentoring/

PCSS Discussion Forum

Have a clinical question?

Ask a Colleague
A simple and direct way to receive an answer related to medication-assisted treatment. Designed to provide a prompt response to simple practice-related questions.

http://pcss.invisionzone.com/register
PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

<table>
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<tr>
<th>Addiction Technology Transfer Center</th>
<th>American Society of Addiction Medicine</th>
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<td>Association for Multidisciplinary Education and Research in Substance Use and Addiction</td>
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<tr>
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<td>Council on Social Work Education</td>
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<td>Physician Assistant Education Association</td>
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<td>American Psychiatric Nurses Association</td>
<td>Society for Academic Emergency Medicine</td>
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