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**Disclosures**

This session is supported by an independent educational grant from Lilly. For further information concerning Lilly grant funding visit www.lillygrantoffice.com.

The following relationships have been disclosed related to this presentation:

- Sylvia Lucas, MD, PhD: Advisory Board for Amgen Inc.; Lilly USA, LLC; and Teva Pharmaceuticals.
- M. Susan Burke, MD, FACP: No financial relationships to disclose.

**Off-Label/Investigational Discussion**

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
Learning Objectives

1. Describe new advances in pathophysiology of migraine.
2. Develop treatment plans in line with standards of practice for acute and preventive management of migraine.
3. Discuss unmet patient needs and burden of migraine.
4. Analyze safety and efficacy data for new and emerging therapies in acute and preventive treatment of migraine.

CASES IN EPISODIC AND CHRONIC MIGRAINE

MARIA 33 YEARS OLD

- Has been getting throbbing headaches for years, at first 1-2x a month near her menses
- Recently started new job, is now getting them 2-3x/week
- Pain mostly in the back of head and into her neck
- She applies heat but usually has to lie down to make them go away; are occasionally associated with nausea
- Trying to get pregnant so she's never sure why she feels queasy
- Has been using naproxen but doesn't know what she can take if she's pregnant

WHAT DO YOU DO NEXT?

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Basics of the History and Physical Exam: Headache Screening

Timing/ frequency
Exacerbating factors/triggers
  - What medications have been tried
  - Use/abuse of medications
Location
Intensity
Nature of pain
Associated symptoms
  - Visual, motor, sensory, GI


ID Migraine™—A VALIDATED SCREENER
Closing the HA Diagnosis Gap

Choose Yes or No

When you have a HA, do you feel nauseated or sick to your stomach?
When you have a HA, does light bother you (a lot more than when you don’t have a HA)?
During the last 3 months, have your HAs limited your ability to work, study, or do what you needed to do?

2/3 Yes FOR MIGRAINE

Positive predictive value of 93% in primary care setting

Definitions: EM by ICHD Criteria

Migraine Without Aura (1.1)—at least 5 attacks with

At least 2 of the following:
  - Unilateral
  - Pulsating
  - Moderate to severe pain
  - Aggravated by or avoidance of routine physical activity

Migraine With Aura (1.2.1-6)—at least 2 attacks with

At least 1 fully reversible symptom without motor
  - Visual + and/or -
  - Sensory + and/or -
  - Speech or language dysfunction

At least 2 of the following:
  - At least 1 aura symptom develops gradually over ≤5 minutes or different symptoms occur in succession over ≥5 minutes
  - Each symptom lasts ≥5 and ≤60 minutes

No organic disease

75% of patients with migraine experience neck pain

Migraine Misdiagnosis as Sinus Headache^1,3

- 86-88% with self-diagnosis of sinus headache actually have ICHD migraine or probable migraine headache^1,3
- ≤20% report ≥1 cranial autonomic symptom
  - 63% nasal congestion
  - 40% rhinorrhea
  - 38% lacrimation
- ≤50% of patients report their headache is influenced by weather

ID Migraine is intended for the identification of patients with migraine. Symptom duration and frequency are measured by the patient, not by the healthcare provider. Migraine symptoms may be difficult to accurately report. Adapted from: Lipton RB, et al. Neurology. 2003;61:375-382.
Indications for Diagnostic Testing

**Diagnostic tests** indicated if ANY red flags are present (SSNOOP)

- Systemic symptoms: fever, weight loss
- Secondary risk factors: HIV, cancer
- Neurologic symptoms or signs
- Onset: new, sudden, abrupt, or split-second
- Older: especially >50 years
- Pattern change

**Diagnostic tests** NOT indicated if only green flags present

- Stable pattern >6 months
- Long-standing HA history
- Family history of similar HA
- Normal exams
- Consistently triggered by
  - Hormonal cycle
  - Specific sensory input
  - Weather changes

**CHOOSING WISELY**

Don’t perform neuroimaging studies in patients with stable headaches that meet criteria for migraine.

General Approach to Headache Treatment

**EDUCATION**

- ACUTE (ABORTIVE)
  Taken after attack has begun to relieve pain and disability and stop progression

**PREVENTIVE**

- Taken to reduce attack frequency, severity, and duration

**NONPHARMACOLOGIC**

- (behavioral, neuromodulation, complementary/alternative)

Principles of Management for the Patient

- Establish realistic expectations
- Encourage patients to participate in their care
  - Keep a headache diary, identify triggers
  - Accept that some prescription side effects are inevitable; may be few or zero with the monoclonal antibodies (mAbs)
- Optimize behavioral management
- Do not overuse acute meds—not more than 2-3x/week or 9 days/month
- Utilize prevention early to reduce disability and medication overuse
- Regular patient follow-up with dose/drug/combinations/additions as needed

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Behavioral Strategies

• Consistent sleep regimen
• Regular exercise
• Stress management
• Decrease substance use: caffeine, cigarettes
• Diet: fresh, nonprocessed foods

A headache diary can help identify possible triggers.

Acute (Abortive) Migraine Medications

### Nonspecific

- NSAIDs
- Combination analgesics
- Neuroleptics/antiepileptics
- Corticosteroids

### Specific

- Triptans
- Ergotamine/DHE

### New formulations (FDA-approved)

- Breath-powered intranasal sumatriptan dry powder
- New sumatriptan autoinjectors
- Sumatriptan nasal spray with permeation enhancer

### New formulations and classes (in development)

- Microneedle array skin patch (zolmitriptan)
- New DHE intranasal deliveries: HFA propellant, dry powder
- Gepants
- 5-HT1F receptor agonist (lasmiditan)
- New combinations: meloxicam-rizatriptan, promethazine-sumatriptan

When to Start Migraine Prevention Therapy

- Not being offered as often as it should be
- Institute preventive strategies if
  - 2 attacks/month with disability totaling >3 days/month
  - Recurring HA significantly interfering with patient’s daily routine despite acute prescriptions
  - Presence of uncommon migraine conditions: hemiplegic migraine, prolonged aura, migrainous infarction
  - Patient preference, cost considerations, and medication intolerance
  - Acute medications overused >2 days/week, ineffective, intolerable side effects, or contraindicated

Migraine, Conception, and Pregnancy

- Best to discuss medication options before conception
- Most patients with migraine note decreased headache frequency after first trimester
- New-onset migraines in pregnancy warrant workup to rule out secondary causes
- Because of their long half-life, consider stopping mAbs 5-6 months before conception
- Optimize nonpharmacologic treatments
  - Massage, relaxation, exercise, trigger avoidance, neuromodulation device
- Considered relatively safe: acetaminophen, diphenhydramine, caffeine, metoclopramide, triptans, NSAIDs (before third trimester)
- Use medications where benefits > risks
  - Considered relatively safe: nerve blocks, memantine, cyproheptadine (but not when nursing)

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EDUARDO
36 YEARS OLD
Told he had migraines when he was in college
They eased up in his 20s, but in the last few years, his HAs have recurred
Used to get relief with ibuprofen, but he now feels a dull HA most days a week, so he’s taking ibuprofen for a HA or when he’s afraid he may get a HA (4-7 days/week)
Occur bilaterally, not associated with nausea or photophobia
Has a stable job, but, of note, he recently married a woman with 3 young children

EDUARDO’S STORY

Definitions: Chronic Migraine and Medication Overuse Headache

Chronic Migraine
Headache ≥15 days/month AND duration ≥4 hours/day for >3 months
≥8 days/month are migrainous
Not just more episodic migraine
Evolves as complication of episodic migraine (2.5%/year)
More disabling with higher costs
Can be reversed; goal is to revert back to episodic migraine

Medication Overuse Headache
Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder
Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
Not better accounted for by another ICHD-3 diagnosis

DISCUSSION
What treatments should be considered for Eduardo?
• Education/behavioral strategies
• Removal of the overused abortive agent, if possible; prescribe a different abortive
• Nonspecific prevention medications
• OnabotulinumtoxinA
• Anti-CGRP mAb injections
• Neuromodulation devices
• Complementary/alternative agents

Oral Preventive Therapies (Nonspecific) for Episodic Migraine Before mAbs: US Classification/Level of Evidence

<table>
<thead>
<tr>
<th>Level of Evidence/Efficacy</th>
<th>Drug Class/Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEVEL A</strong> Established Efficacy</td>
<td>Antiepileptic drugs: divalproex sodium*, sodium valproate*, topiramate*&lt;br&gt;β blockers: metoprolol, propranolol*, timolol*&lt;br&gt;Triptans: frovatriptan (for menstrual-related migraine)&lt;br&gt;Angiotensin receptor blockers: candesartan (studies now suggest level A efficacy)†</td>
</tr>
<tr>
<td><strong>LEVEL B</strong> Probably Effective</td>
<td>Antidepressants TCA/SNRI: amitriptyline, venlafaxine&lt;br&gt;β blockers: atenolol, nadolol&lt;br&gt;Triptans: naratriptan, zolmitriptan (for menstrual-related migraine)</td>
</tr>
<tr>
<td><strong>LEVEL C</strong> Possibly Effective</td>
<td>ACE inhibitors: lisinopril&lt;br&gt;β blockers: nebivolol, pindolol&lt;br&gt;Alpha agonists: clonidine, guanfacine&lt;br&gt;Antiepileptic drugs: carbamazepine&lt;br&gt;Antihistamines: cyproheptadine</td>
</tr>
</tbody>
</table>

Start low and go slow. Allow 2-3 months for full effect.

*SNot approved. †Not in original paper.
The First Approved Treatment (Specific) for Chronic Migraine

**OnabotulinumtoxinA**
(Specific FDA-approved medication)
- Approved for prophylaxis of chronic migraine (≥15 headache days/month)
- 8-9 fewer headache days/month compared to 6-7 with placebo
- 31 injection sites into head/neck Q3 months
- Boxed warning: possibility for spread causing weakness in distant area/s

**OnabotulinumtoxinA** blocks the presynaptic release of neurotransmitters such as CGRP

---

**Specific Migraine Treatment With Anti-CGRP mAb:**
Effects of Erenumab in Chronic Migraine

*LS=least squares. SE=standard error.*

**Specific Migraine Treatment With Anti-CGRP mAb:**
Effects of Galcanezumab in Chronic Migraine

---

**Specific Migraine Treatment With Anti-CGRP mAb:**
Effects of Fremanezumab in Chronic Migraine

---

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DISCUSSION

When Could a mAb Be Offered to Eduardo?

Complementary and Alternative Considerations

<table>
<thead>
<tr>
<th>Riboflavin</th>
<th>Physical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium</td>
<td>Exercise</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>Massage</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Yoga</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Hypnotherapy</td>
</tr>
<tr>
<td>Spinal/osteopathic manipulation</td>
<td>Cold therapy</td>
</tr>
<tr>
<td>Tai chi</td>
<td></td>
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</table>

Summary

If a patient self-diagnoses their headache, don’t assume they’re correct

Migraine is the most common cause of headache that brings a patient to the clinician

Successful migraine management includes patient education and behavioral/pharmacologic/nonpharmacologic interventions

Initiate nonspecific preventive medications early

Consider safe and effective specific therapies, some targeting CGRP, which greatly enhance the success of migraine management

THE NEW ERA OF MIGRAINE TREATMENT

Sylvia Lucas, MD, PhD, FAHS
Clinical Professor,
Department of Neurology and Neurological Surgery
University of Washington
Harborview Medical Center
Seattle, Washington

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Overview

- Pathophysiology leads to pharmacology and neuromodulation: translational research made real
- New classes of acute medication in development
  - Gepants, lasmiditan
- New classes of preventive medication FDA-approved or in development
  - Anti-CGRP or CGRP receptor mAbs, gepants
- Neuromodulation
  - Noninvasive, FDA-approved: transcutaneous supraorbital neurostimulation (tSNS), single pulse transcranial magnetic stimulation (sTMS), noninvasive vagal nerve stimulation (nVNS), remote electrical neuromodulation (REN)

PATHOPHYSIOLOGY AND NEUROTRANSMITTER TARGETS

- Serotonin
- CGRP

The Role of Serotonin (5-HT) in Migraine Pathophysiology

- Triptans are 5-HT1B/1D agonists
- Lasmiditan is a novel, centrally acting serotonin (5-HT1F) agonist
- Lacks vasooconstrictive activity
- Submitted to the FDA in October 2018

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Phase 3 RCTs of Lasmiditan: SAMURAI and SPARTAN1-3

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lasmiditan 50 mg</th>
<th>Lasmiditan 100 mg</th>
<th>Lasmiditan 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain-Free at 2 Hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of Patients</td>
<td>15.5</td>
<td>26.2</td>
<td>32.2</td>
<td>31.4</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td></td>
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</tr>
</tbody>
</table>

Adverse Events

- **Dizziness + vertigo**
  - 100 mg average 15.5%
  - 200 mg average 16.8%

- **Somnolence + fatigue + lethargy**
  - 100 mg average 10.4%
  - 200 mg average 11%

RCTs=randomized controlled trials.


P<0.001 P<0.001 P<0.001 P<0.001

CGRP AS A MIGRAINE TARGET

Calcitonin Gene-Related Peptide

- First discovered as a potent vasodilator
- Initially considered important in migraine because of its potential peripheral actions
  - Vasodilation
  - Neurogenic inflammation
- Present at all migraine pathogenesis sites

- Belongs to calcitonin family (calcitonin, amylin, adrenomedullin, intermedin) in humans, α-CGRP and β-CGRP isoforms


Migraine Pathophysiology

- Belongs to calcitonin family (calcitonin, amylin, adrenomedullin, intermedin) in humans, α-CGRP and β-CGRP isoforms


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Data Highlighting the Role of CGRP in Patients With Migraine

- When measured from external jugular vein, CGRP concentrations rise during spontaneous migraine attacks.
- After administration of triptans, CGRP serum levels decrease in parallel with symptomatic relief in patients with migraine.
- In patients with migraine, intravenous infusion of CGRP triggers attacks that are indistinguishable from spontaneous attacks.
- Blocking or removing CGRP terminates migraine acutely and prevents migraine.

ACUTE Treatment of Episodic Migraine
- 6 gepants have demonstrated efficacy in acute migraine treatment.
- Early gepants reportedly liver toxic; development halted.
- Ubrogepant and rimegepant have reported positive regulatory results.
- Ubrogepant submitted for acute migraine treatment; rimegepant to be submitted next.
- 2-hour pain freedom for both ≈20%.
- Do not cause blood vessels to constrict; so, unlike triptans, should be safe in people with vascular disease.

PREVENTIVE Treatment of Episodic Migraine
- Atogepant vs placebo reported positive Phase 2; will proceed to Phase 3.
- Rimegepant to be tested for prevention in Phase 2/3.

PREVENTION: MONOCLONAL ANTIBODIES
**mAbs to CGRP or the CGRP Receptor for Migraine Prevention**

**How are they different than our current migraine preventive medications?**

- mAbs for the most part do not cross the blood-brain barrier\(^1\,^2\)
- mAbs are eliminated by the reticuloendothelial system—so far, hepatotoxicity has not been seen\(^1\,^4\)
- Because they work, it is likely that peripheral anti-CGRP action is sufficient to prevent migraine

**Are they an improvement?**\(^3\,^4\) All 4

- Prevent episodic migraine, chronic migraine, medication-overuse headache; galcanezumab also prevents episodic cluster headache
- Have shown quick onset: separate from placebo within 1 week
- Have led to a clinically meaningful response by 1 month
- Have shown unprecedented responder rates of ≥75%
- Have shown safety and tolerability similar to placebo
- Decrease acute medication use days; improve impact, disability, and/or quality of life

**4 Injectable mAbs to CGRP or Its Receptor: 3 Now FDA Approved and Available**

<table>
<thead>
<tr>
<th></th>
<th>Erenumab-aooe (fully human)</th>
<th>Fremanezumab-vfrm (fully humanized)</th>
<th>Galcanezumab-gnlm (humanized)</th>
<th>Eptinezumab (humanized)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studied for</strong></td>
<td>EM, CM</td>
<td>EM, CM, eCH, cCH</td>
<td>EM, CM, eCH, cCH</td>
<td>EM, CM</td>
</tr>
<tr>
<td><strong>Route and dosing</strong></td>
<td>Monthly SC 70, 140 mg</td>
<td>Monthly or quarterly SC, 225 mg monthly, or 675 mg Q3 months</td>
<td>Monthly SC, 240 mg loading dose, then 120 mg SC monthly thereafter</td>
<td>Q3 months IV</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>CGRP receptor</td>
<td>CGRP peptide or ligand</td>
<td>CGRP peptide or ligand</td>
<td>CGRP peptide or ligand</td>
</tr>
<tr>
<td><strong>Regulatory status</strong></td>
<td>FDA-approved 5/17/18 for migraine prevention</td>
<td>FDA-approved 9/14/18 for migraine prevention</td>
<td>FDA-approved 9/26/18 for migraine prevention and 6/4/19 for treatment of eCH</td>
<td>Submitted BLA to FDA 2/22/19 for migraine prevention</td>
</tr>
</tbody>
</table>


**Pivotal Randomized Controlled Trials of the mAbs for Both Episodic and Chronic Migraine Prevention**

- Primary endpoint: all reduce mean monthly migraine days by up to 10 days per month
- Other findings
  - All improve patient reported outcomes
  - The majority with chronic migraine convert to episodic migraine
  - The majority with acute medication overuse convert to non-overuse
  - They work in patients who have had a lack of success with numerous previous preventive medications

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NONINVASIVE NEUROMODULATION: ANOTHER THERAPEUTIC OPTION

4 FDA-Cleared, Noninvasive, Nonsignificant Risk Neurostimulators

- **External Trigeminal Stimulation (eTNS)**
  - FDA-cleared for acute and preventive migraine treatment
  - Purchased online for $550
  - Little or no insurance coverage
  - Preventively: wear nightly for 20 minutes; acutely: use different program for 60 minutes

- **Single Pulse Transcranial Magnetic Stimulation (stimTMS)**
  - FDA-cleared for acute and preventive migraine treatment
  - Little or no insurance coverage
  - 4 pulses twice daily; extra pulses as needed, up to 17 pulses/day

- **Noninvasive Vagal Nerve Stimulation (nVNS)**
  - FDA-cleared for acute treatment of migraine, acute treatment of episodic cluster headache, and adjunctive preventive treatment of cluster headache
  - Being studied for migraine prevention
  - Turn on for 2 minute cycles, up to 3x in a row, up to 3x/day
  - $575/month to recharge

- **Remote Electrical Neuromodulation (REN)**
  - Recently FDA-cleared for acute migraine pain
  - Planned for launch after Q4 2019
  - Attaches to the arm
  - Controlled by smart phone application

**Conclusions**

This is a watershed moment in migraine treatment

- New acute medication classes, devices, formulations, and combinations offer opportunity to match patient needs to treatments
- Older, nonspecific oral medications with adverse events and poor adherence are giving way to new designer medications and neuromodulators
- mAbs are specific for migraine, given monthly or quarterly, and well-tolerated and safe; start to work within 1-4 weeks; and reduce acute medication use while improving quality of life
- The 2019 AHS consensus statement highlights the importance of documenting prescriptions and drug failures so appropriate patients can qualify for these agents

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