Diagnosing and Managing Primary Headache Disorders in the Primary Care Setting: Challenges and Opportunities

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Disclosures

- **Dawn Buse, PhD** has received consulting fees from Amgen, Allergan, Biohaven, Dr. Reddy's, Lilly, and Teva, and research grant support from Amgen, Allergan, Dr. Reddy's, and Lilly.
- **Andrew Charles, MD** is a consultant for Alder, Amgen, Biohaven, Eli Lilly, and eNeura. He has conducted research for Takeda Pharmaceuticals.

During the course of this lecture, the faculty will mention the use of medications for both FDA-approved and non-approved indications

This activity is supported by an educational grant from Lilly.

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Pre-Test Question 1

1. A 32-year-old woman complains of painful headaches at least 2 times a day for the past two weeks, occurring on the right side near her temple. They have sudden onset and usually resolve within an hour. She reports right-sided tearing and nasal congestion and feels restless during the headaches. Which headache type is most likely?

a. Chronic migraine
b. Episodic tension-type headache
c. Cluster headache
d. Headache due to secondary cause

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Pre-Test Question 2

Which of these facts support the role of inhibiting CGRP for headache prevention?

a. CGRP is a neuropeptide with vasodilation properties

b. CGRP levels increase during migraines; experimental injection of CGRP mimics the symptoms of a migraine

c. CGRP modulates acetylcholine and glutamate release

d. CGRP antibodies cross the blood brain barrier

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Pre-Test Question 3

Which of the following classes is used for acute headache treatment?

a. CGRP inhibitors
b. Botulinum toxin
c. Beta-blockers
d. Gepants

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Pre-Test Question 4

A 24-year-old married female with a 5-year migraine history presents to your office and you are interested in providing preventive migraine therapy to her. She is actively trying to get pregnant. Which of the following would you start with?

a. Begin with a dosage of preventive therapy slightly higher than abortive therapy
b. Start a preventive agent, then taper/stop after 3 months if well-controlled.
c. Discuss medication considerations in pregnancy
d. Recommend daily NSAID or ergotamine use to start

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Agenda

- Discuss best practices for timely and accurate diagnosis of primary headache disorders
- Identify the mechanisms of action and clinical profiles of new and emerging agents
- Design evidence-based treatment plans for patients with primary headache disorders
- Use patient-specific factors to select therapies for primary headache disorders
- Improve communication with patients for better outcomes

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Headache Impact

Dawn C. Buse, PhD

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Migraine Impact

- One in five US adults has migraine[1]
- Ranks #5 for emergency department (ED) visits, annually[1]
  - Most common primary headache reason to visit an ED[2]
  - 5 million headache annual visits to US EDs[2]
  - Mean cost of migraine-related ED visit = $775[2]
- Diagnosis in the ED:
  - Increase in neuroimaging, such as CT scans, by 50% between 1992–2001[3]
  - > ½ of migraine patients who presented to an urban ED in 2008 received head CT

1. Saguil A, Lax JW. *Am Fam Physician.* 2014;89:742-744. 2. Minen MT et al. *Headache.* 2014;54:1131-1145. 3. Minen MT et al. *Headache.* 2014;54:1131-1145.

Migraine Impact
(continued)

- Moderate-to-severe pain in 90% of migraineurs[1]
  - 75% report impaired function in daily life
  - 33% require bed rest to recover
- Absenteeism: missed work days due to sickness or injury[2]
  - Estimated 1–2 days/year/worker; increases with additional risk factors and/or chronic diseases
  - Annual estimated costs to employer $16–286 per employee

1. Becker WJ et al. *Can Fam Physician.* 2015;61:670-679. 2. Asay GR et al. www.cdc.gov/pcd/issues/2016/15_0503.htm. Accessed on 3/14/2017

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Diagnosis

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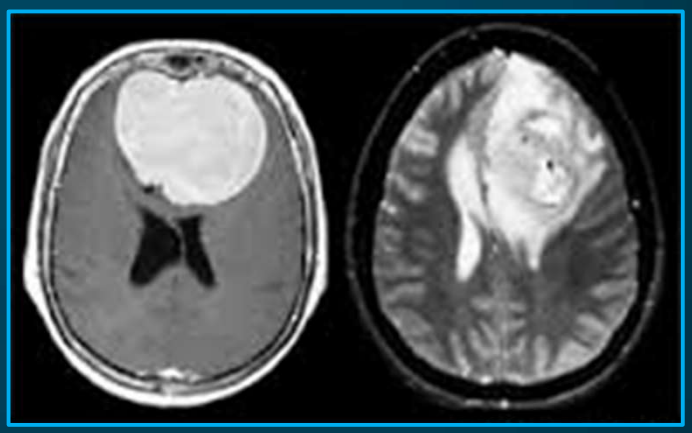
Headache

- Can be primary headache, such as migraine
- Can be secondary headache, that is due to a different cause:
  - Head injury
  - SAH
  - Brain tumor



SAH = subarachnoid hemorrhage.

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Headache History: Useful Questions

- *When did your headaches first start?*
- *How often do you get headaches that, if untreated, are so severe you find it difficult to function?*
- *What is the pain like and how long does it last?*
- *How quickly does it build to maximum?*
- *Do you have other symptoms besides head pain with these headaches?*
- *What makes your headaches better or worse?*
- *How often do you take something for your headaches? What do you take?*
- *Does anyone else in your family have similar headaches?*
- *Do you get other kinds of headache?*
- *Has there been any recent change in your headaches?*

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Headache Screening: Standard Examination

- Observe the patient walking
- Assess symmetry of cranial nerves, motor, sensory, coordination, DTRs
- Observe patient's body language (eye contact, mood)
- Palpate head, arteries, trigger points
- Examine neck for stiffness and ROM
- Perform funduscopic exam
- Examine oral cavity/TMJ

CN = cranial nerve; DTR = deep tendon reflex; ROM = range of motion; TMJ = temporomandibular joint.

Diagnosis and Treatment of Headache. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI); 2009.

Headache Decision Aid 1
(Types of Primary Headache)

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Headache Type: Decision Aid Part 1

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Migraine Headache

ETTH

Decision Aid: Pt. 2

Cluster Headache

The tool below will help guide you through a series of questions to determine the type of headache your patient may have.

Is your patient's headache:

PLEASE CLICK ON ONE OF THE FOLLOWING:

Primary or **Secondary**

Primary: headaches that are not the result of another medical condition

Secondary: headaches due to an underlying medical condition such as neck injury or sinus infection

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Cluster Headache

Number and duration of attacks per month:

PLEASE CLICK ONE OF THE FOLLOWING:

≥5 lasting 4-72 hrs | ≥10 lasting 30 min – 7 days | Other

Symptoms:

PLEASE CLICK ALL OF THE SYMPTOMS THAT APPLY:

Unilateral	or	Bilateral
Pulsating	or	Not pulsating
Moderate to Severe	or	Mild to Moderate
Aggravation by routine physical activity	or	Not aggravated by routine physical activity

CLICK TO RETURN TO PRIMARY/SECONDARY

◀ Back

HELP

Other Symptoms:

PLEASE CLICK ALL OF THE SYMPTOMS THAT APPLY:

Nausea/Vomiting | Photophobia

Phonophobia | Other symptoms not listed here

Attributable to any other disorder?

PLEASE CLICK ONE OF THE FOLLOWING:

No | Yes

CLICK HERE TO Reset

PLEASE CLICK TO Submit

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Headache Type: Decision Aid Part 1

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Cluster Headache

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- Photophobia
- Phonophobia
- Other symptoms not listed here

Attributable to any other disorder?

PLEASE CLICK ONE OF THE FOLLOWING:

- No
- Yes

CLICK HERE TO: Reset

PLEASE CLICK TO: Submit

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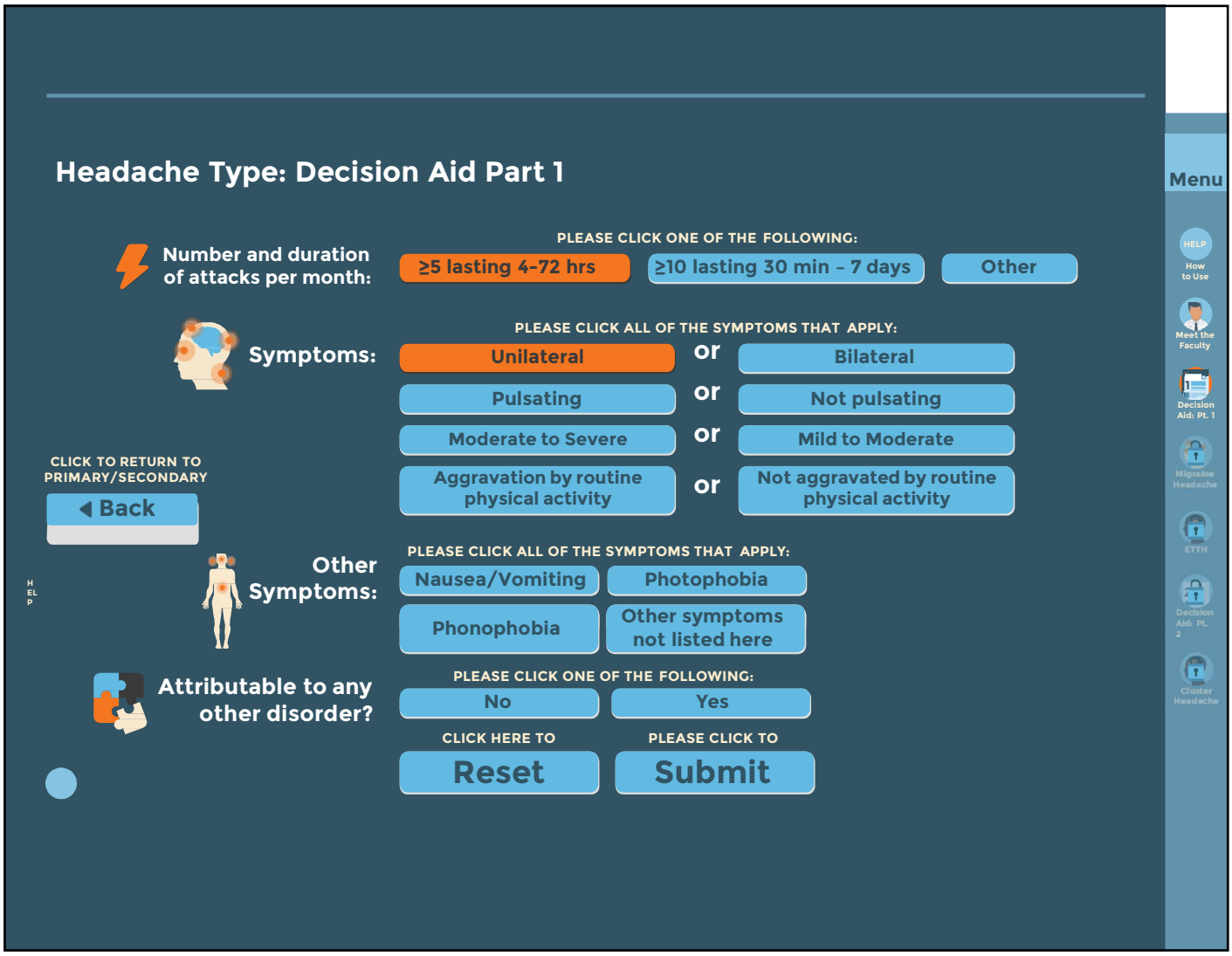
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Cluster Headache
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≥5 lasting 4-72 hrs
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Other
Symptoms:
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Unilateral
or
Bilateral
Pulsating
or
Not pulsating
Moderate to Severe
or
Mild to Moderate
Aggravation by routine physical activity
or
Not aggravated by routine physical activity
CLICK TO RETURN TO PRIMARY/SECONDARY
Back
HELP
Other Symptoms:
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Nausea/Vomiting
Photophobia
Phonophobia
Other symptoms not listed here
Attributable to any other disorder?
PLEASE CLICK ONE OF THE FOLLOWING:
No
Yes
CLICK HERE TO
Reset
PLEASE CLICK TO
Submit

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Cluster Headache

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◀ Back

HELP

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Nausea/Vomiting | Photophobia

Phonophobia | Other symptoms not listed here

Attributable to any other disorder?

PLEASE CLICK ONE OF THE FOLLOWING:

No | Yes

CLICK HERE TO Reset

PLEASE CLICK TO Submit

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Cluster Headache

Number and duration of attacks per month:

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- ≥5 lasting 4-72 hrs
- ≥10 lasting 30 min – 7 days
- Other

Symptoms:

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Unilateral	or	Bilateral
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CLICK TO RETURN TO PRIMARY/SECONDARY

◀ Back

HELP

Other Symptoms:

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- Nausea/Vomiting
- Photophobia
- Phonophobia
- Other symptoms not listed here

Attributable to any other disorder?

PLEASE CLICK ONE OF THE FOLLOWING:

- No
- Yes

CLICK HERE TO: Reset

PLEASE CLICK TO: Submit

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Cluster Headache

Number and duration of attacks per month:

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Symptoms:

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CLICK TO RETURN TO PRIMARY/SECONDARY

◀ Back

HELP

Other Symptoms:

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- Nausea/Vomiting
- Photophobia
- Phonophobia
- Other symptoms not listed here

Attributable to any other disorder?

PLEASE CLICK ONE OF THE FOLLOWING:

- No
- Yes

CLICK HERE TO Reset

PLEASE CLICK TO Submit

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Cluster Headache

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CLICK TO RETURN TO PRIMARY/SECONDARY

◀ Back

HELP

Other Symptoms:

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- Nausea/Vomiting
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- Phonophobia
- Other symptoms not listed here

Attributable to any other disorder?

PLEASE CLICK ONE OF THE FOLLOWING:

- No
- Yes

CLICK HERE TO Reset

PLEASE CLICK TO Submit

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Cluster Headache

Number and duration of attacks per month:

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- ≥5 lasting 4-72 hrs
- ≥10 lasting 30 min – 7 days
- Other

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- Unilateral or Bilateral
- Pulsating or Not pulsating
- Moderate to Severe or Mild to Moderate
- Aggravation by routine physical activity or Not aggravated by routine physical activity

CLICK TO RETURN TO PRIMARY/SECONDARY

◀ Back

HELP

Other Symptoms:

PLEASE CLICK ALL OF THE SYMPTOMS THAT APPLY:

- Nausea/Vomiting
- Photophobia
- Phonophobia
- Other symptoms not listed here

Attributable to any other disorder?

PLEASE CLICK ONE OF THE FOLLOWING:

- No
- Yes

CLICK HERE TO Reset

PLEASE CLICK TO Submit

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Cluster Headache
CLICK BACK TO EXPLORE MORE OPTIONS
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Based on your choices your patient's headache could be a migraine
≥5 attacks lasting 4-72 hrs
≥2 of the following features:
Unilateral
Pulsating
Moderate or severe intensity
Aggravation by routine physical activity
≥1 of the following symptoms:
Nausea and/or vomiting
Photophobia and Phonophobia
Not attributable to another disorder
CLICK HERE FOR MORE INFORMATION ON
Migraine
OR CLICK THE BACK BUTTON TO EXPLORE MORE OPTIONS
HELP

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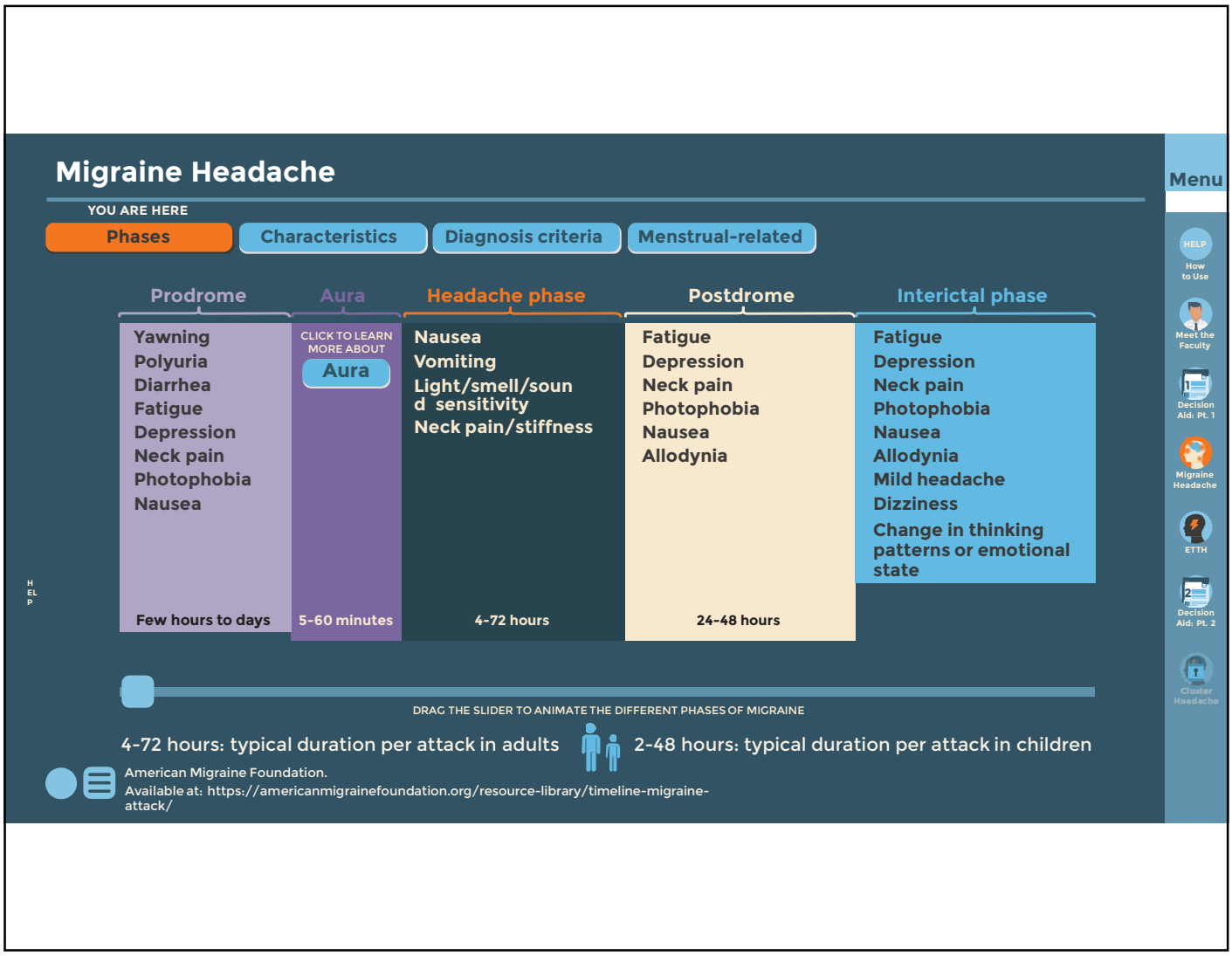
Migraine Headache
YOU ARE HERE
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Cluster Headache
Prodrome
Yawning
Polyuria
Diarrhea
Fatigue
Depression
Neck pain
Photophobia
Nausea
Few hours to days
Aura
CLICK TO LEARN MORE ABOUT
Aura
5-60 minutes
Headache phase
Nausea
Vomiting
Light/smell/sound sensitivity
Neck pain/stiffness
4-72 hours
Postdrome
Fatigue
Depression
Neck pain
Photophobia
Nausea
Allodynia
24-48 hours
Interictal phase
Fatigue
Depression
Neck pain
Photophobia
Nausea
Allodynia
Mild headache
Dizziness
Change in thinking patterns or emotional state
HELP
DRAG THE SLIDER TO ANIMATE THE DIFFERENT PHASES OF MIGRAINE
4-72 hours: typical duration per attack in adults
2-48 hours: typical duration per attack in children
American Migraine Foundation.
Available at: https://americanmigrainefoundation.org/resource-library/timeline-migraine-attack/

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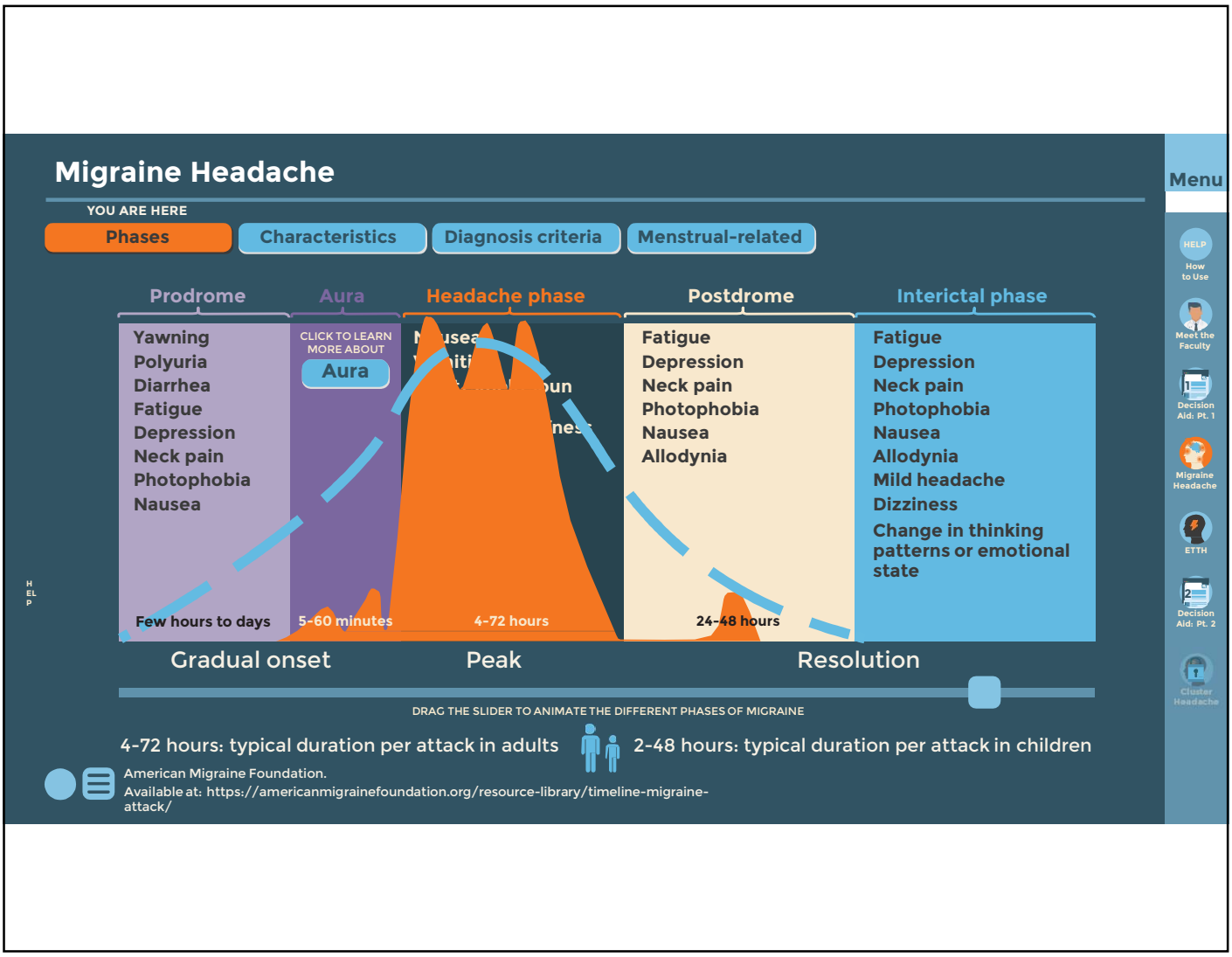
Migraine Headache
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Photophobia
Nausea
CLICK TO LEARN MORE ABOUT
Aura
Fatigue
Depression
Neck pain
Photophobia
Nausea
Allodynia
Fatigue
Depression
Neck pain
Photophobia
Nausea
Allodynia
Mild headache
Dizziness
Change in thinking patterns or emotional state
Few hours to days
5-60 minutes
4-72 hours
24-48 hours
Gradual onset
Peak
Resolution
DRAG THE SLIDER TO ANIMATE THE DIFFERENT PHASES OF MIGRAINE
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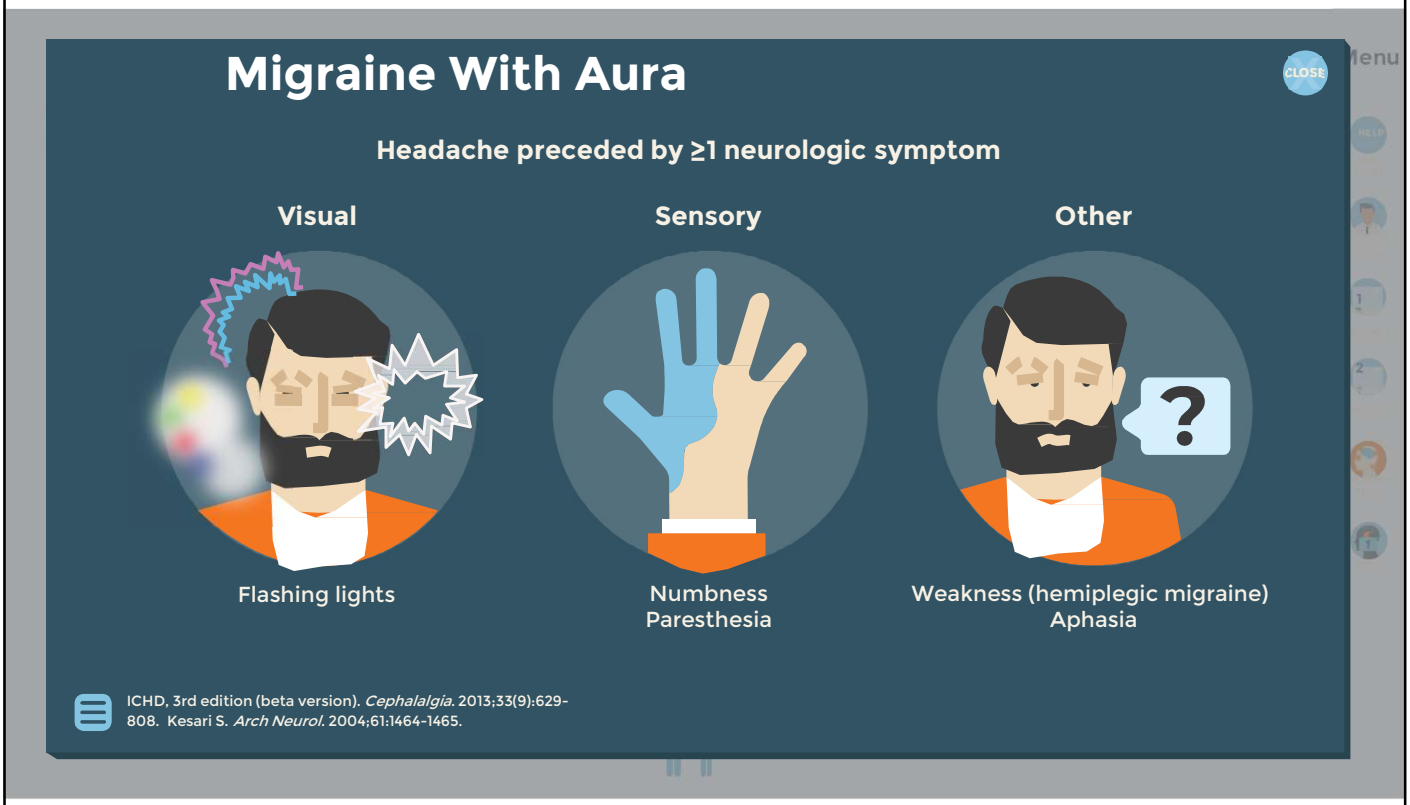
Migraine With Aura
CLOSE
Headache preceded by ≥1 neurologic symptom
Visual
Sensory
Other
Flashing lights
Numbness
Paresthesia
Weakness (hemiplegic migraine)
Aphasia
ICHD, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808. Kesari S. Arch Neurol. 2004;61:1464-1465.

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Migraine Attack

YOU ARE HERE

Phases | Characteristics | Diagnosis criteria | Menstrual-related

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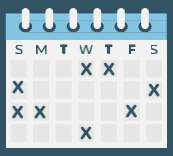
Cluster Headache

Time

Occur any time of day

Frequency



1–10 per month; average 1.5 per month

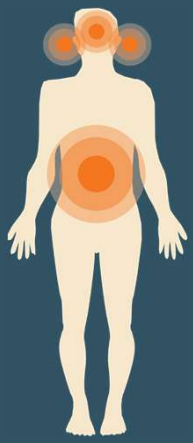
Location

60% unilateral; 20% always same side
40% bilateral; neck pain very common

Pain

Moderate to severe; 50% pulsating; aggravated by movement

Associated Symptoms



CNS:
Photophobia
Phonophobia
Osmophobia

Gastrointestinal:
Anorexia (common)
Nausea (frequent)
Vomiting (common)
Diarrhea (occasional)

Headache. *Cephalalgia*. 2013;33:629-808.

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Simplified Diagnostic Criteria: ID Migraine

- Symptoms in the last 3 months:
  - Light sensitivity
  - Nausea with headache
  - Decreased ability to function with headache
- Any 2 or 3 of above symptoms = migraine

Lipton RB et al. *Neurology.* 2003;12:375-382.

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IHS Classification: Migraine vs Tension-type HA

Migraine

- ≥5 attacks lasting 4–72 hours
- ≥2 of the following:
  - Unilateral
  - Pulsating
  - Moderate or severe intensity
  - Aggravation by routine physical activity
- ≥1 of the following
  - Nausea and/or vomiting
  - Photophobia and phonophobia
- Not attributable to another disorder

Tension-type

- ≥10 attacks lasting 30 min–7 days
- ≥2 of the following:
  - Bilateral
  - Not pulsating
  - Mild or moderate intensity
  - Not aggravated by routine physical activity
- No nausea or vomiting
- One or neither photophobia or phonophobia
- Not attributable to another disorder

HA = headache.

IHS Classification ICHD-3 beta (www.ichd-3.org/1-migraine/). Headache Classification Committee of IHS. *Cephalalgia.* 2013;33:629-808.

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Cluster Headache Diagnostic Criteria

At least five attacks fulfilling criteria:

- **Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min** (when untreated)
- Either or both of the following:

  1. At least one of the following symptoms or signs, ipsilateral to the headache:

  a) conjunctival injection and/or lacrimation
  b) nasal congestion and/or rhinorrhea
  c) eyelid edema
  d) forehead and facial sweating
  e) forehead and facial flushing
  f) sensation of fullness in the ear
  g) miosis and/or ptosis

  2. Sense of restlessness or agitation
- Attacks have frequency between 1 every other day to 8 per day for more than half of the time when the disorder is active
- Not better accounted for by another ICHD-3 diagnosis

ICHD, 3rd edition (beta version). *Cephalalgia.* 2013;33(9):629-808.

Migraine Headache

Characteristics of Migraine Headache	
Attacks	Occur any time of day
Frequency	1–10 per month; average 1.5 per month
Onset	Gradual onset, peak, then subsidence
Duration	4–72 hours in adults; 2–48 hours in children
Location	60% unilateral; 20% always same side; 40% bilateral; neck pain very common
Pain	Moderate to severe; 50% pulsating; aggravated by movement
Associated symptoms	GI: anorexia (common); nausea (frequent); vomiting (common); diarrhea (16%). CNS: photophobia; phonophobia; osmophobia

Headache. *Cephalalgia.* 2013;33:629-808.

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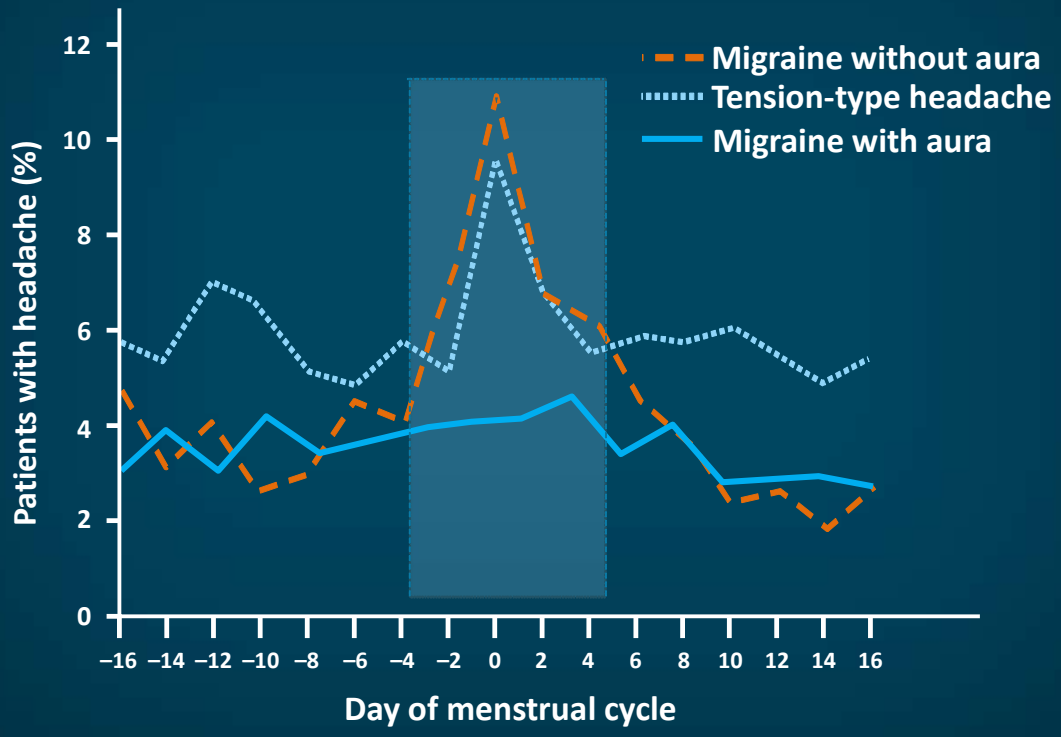
Episodic Tension-Type Headache (ETTH)

- ETTH was previously known as:
  - Tension headache
  - Muscle-contraction headache
  - Psychogenic headache
  - Stress headache
- Most common headache type
  - Can occur at any age
  - Most people with ETTH self-medicate with OTC analgesics

ICHD, 3rd edition (beta version). *Cephalalgia.* 2013;33(9):629-808.

Menstrual-Related Migraine



Stewart WF et al. *Neurology.* 2000;55:1517-1523.

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Certain Situations Make Migraine Treatment More Problematic

- Severe attacks that awaken a patient from sleep
- Migraine with menses (35–54% of women)
  - Longer duration and greater recurrence
  - Increased association with disability
  - Increased resistance to treatment
- The patient reports side effects with medications for acute migraine
- Nausea is present early in the course of the attack
- Medical mythology issues ("*I can't prescribe triptans because…*")
  - Patient had chest tightness with a triptan
  - Patient is taking SSRIs or SNRIs
  - Patient is pregnant
  - Patient is breastfeeding

SSRI = selective serotonin-reuptake inhibitor; SNRI = serotonin and norepinephrine-reuptake inhibitor.

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Excluding Secondary Causes of Headache: the Role of Brain Imaging

- Indicated when secondary cause of headache is suspected
- CT and MRI overused in assessment of migraine sufferers (particularly in the emergency department)
- CHOOSING WISELY: Don't perform neuroimaging studies in patients with stable headaches that meet criteria for migraine

CT = computed tomography. MRI = magnetic resonance imaging.

Ropper A, Brown R, eds. *Adams and Victor's Principles of Neurology*. Eighth ed. New York, NY: McGraw-Hill; 2005:16-21 Minen MT et al. *Headache.* 2014;54:1131-1145. Chosing Wisely. (www.choosingwisely.org/as-part-of-choosing-wisely-campaign-american-headache-society-releases-list-of-commonly-used-tests-and-treatments-to-question/). Accessed on 8/10/17.

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Excluding Secondary Causes of Headache: the Role of Brain Imaging (continued)

- Guidelines recommend head imaging:
  - For new-onset severe headache
  - New type of headache after age 50
  - New abnormal physical signs on neurological examination
  - If immunosuppressed (ED Guidelines)[1]
  - Not be performed in migraine sufferers who have a stable headache that meets the criteria for migraine (American Headache Society)[2]
  - Not be performed for an uncomplicated headache (American College of Radiology)[3]

1.Minen MT et al. *Headache*. 2014;54:1131-1145. 2. Loder E et al. *Headache*. 2013;53:1651-1659. 3. American College of Radiology (ACR); 2012. Choosing Wisely. (www.choosingwisely.org/as-part-of-choosing-wisely-campaign-american-headache-society-releases-list-of-commonly-used-tests-and-treatments-to-question/). Accessed 8/7/17.

Chronic Migraine

ICHD-3 beta criteria[1]

- Headache on ≥15 days/month ≥3 months with ≥5 prior migraine attacks
- On ≥8 days/month, headache fulfills criteria for migraine
- Not attributed to another causative disorder
- Medication-overuse headache (MOH) is classified separately as a secondary chronic daily headache

FDA-approved simplified diagnosis for chronic migraine (phenotype approach)[2]

- Headache ≥15 days/month

  AND

- Duration of ≥4 hours/day

1. HCC of IHS. *Cephalalgia.* 2013;33:629-808. 2. OnabotulinumtoxinA [Botox®] prescribing information (www.allergan.com/assets/pdf/botox_pi.pdf). Accessed 10-30-17.

39

Chronic Migraine

- Episodic migraine (EM) occurs in 12% of the population, CM in 1%
- CM evolves as a complication of EM (2.5%/year) and is much more disabling
- Risk factors for development of CM include:
  - Headache features (attack frequency, cutaneous allodynia)
  - Headache-related disability
  - Comorbidities (anxiety, depression, obesity)
  - Iatrogenic factors (medication type and frequency of use)

40

Initial Treatment Considerations

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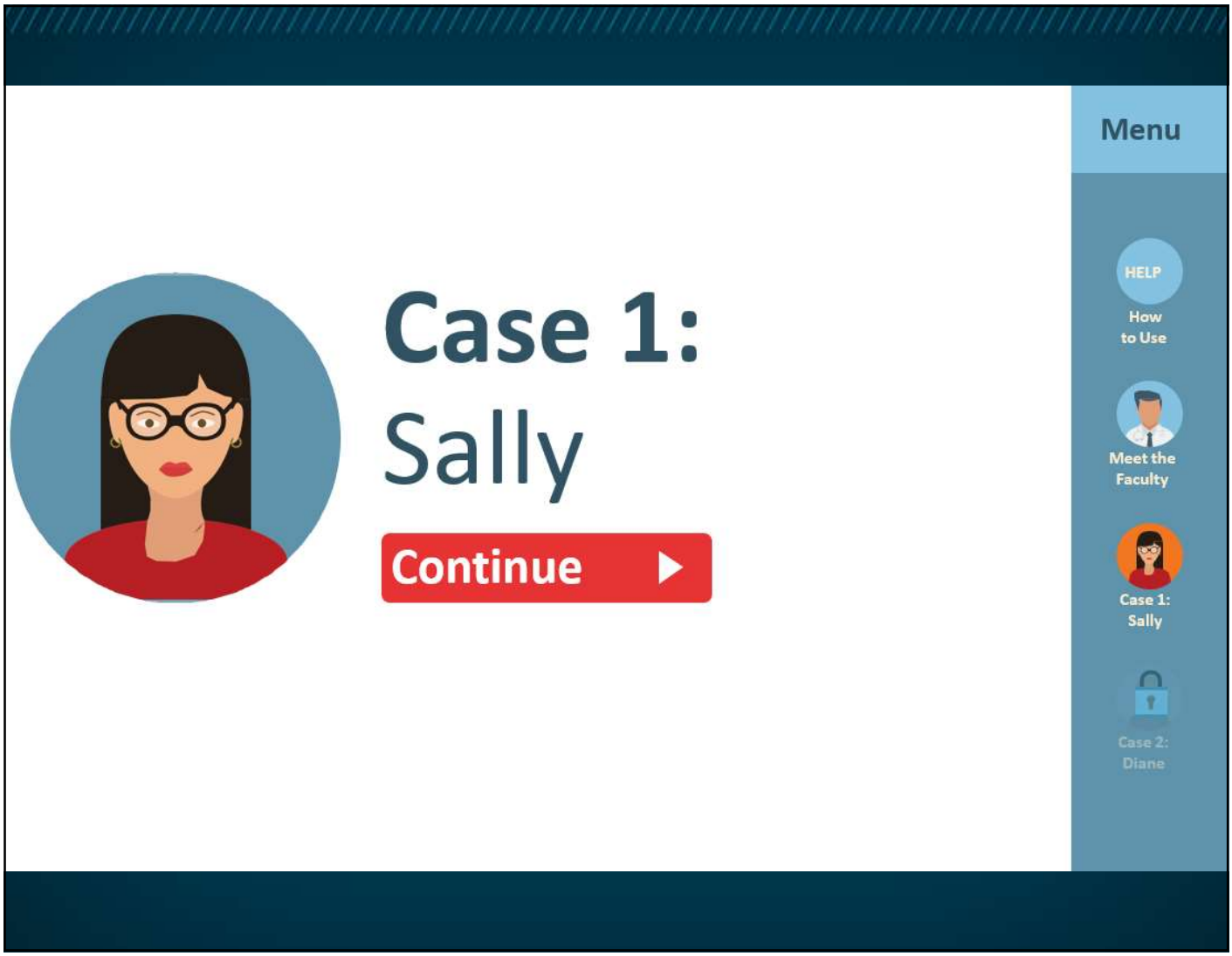
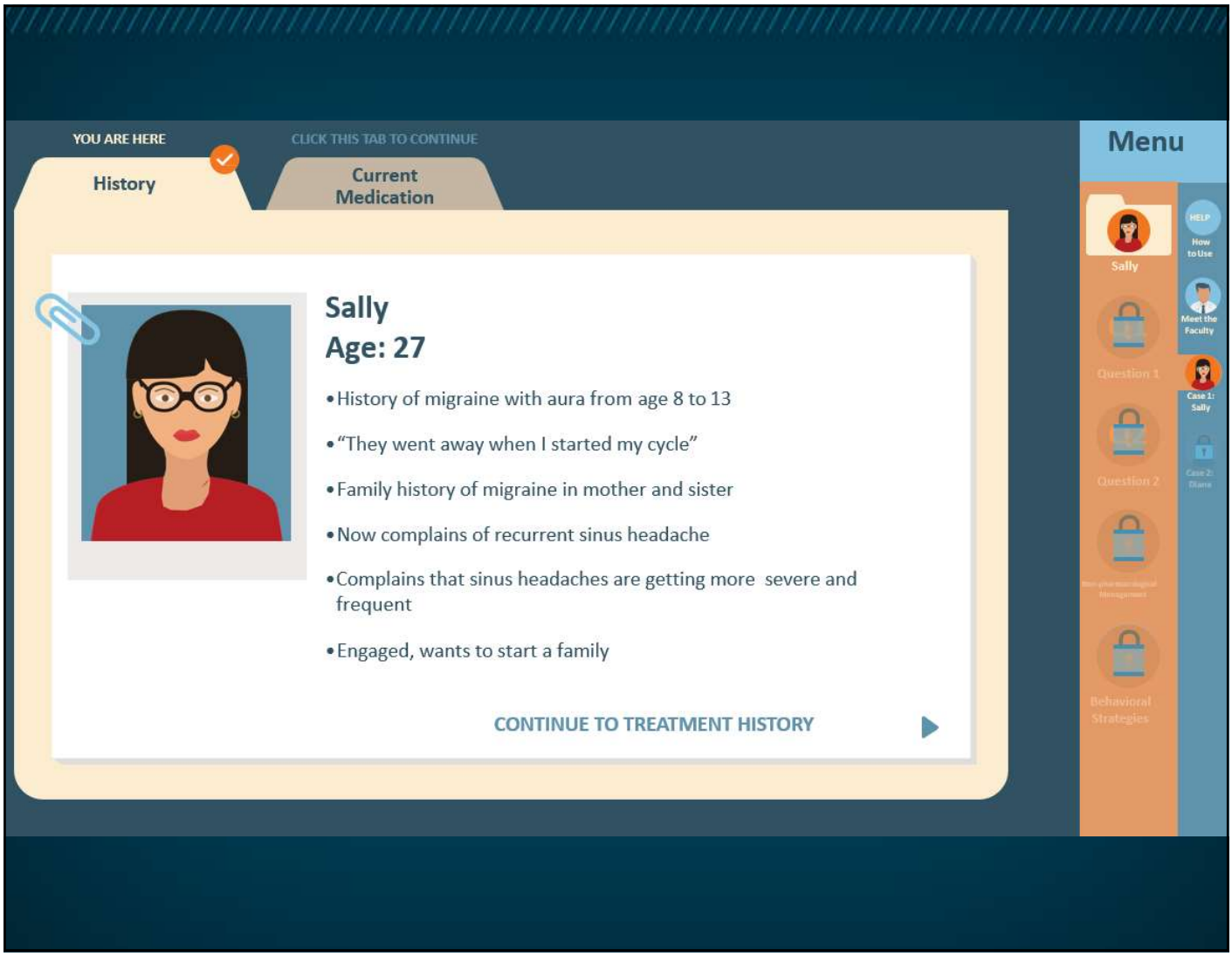
Headache Decision Aid 2 (Patient Case)


Menu
HELP
How to Use
Meet the Faculty
Case 1: Sally
Case 2: Diane
Case 1:
Sally
Continue

43


YOU ARE HERE
CLICK THIS TAB TO CONTINUE
History
Current Medication
Sally
Age: 27
•History of migraine with aura from age 8 to 13
•"They went away when I started my cycle"
•Family history of migraine in mother and sister
•Now complains of recurrent sinus headache
•Complains that sinus headaches are getting more severe and frequent
•Engaged, wants to start a family
CONTINUE TO TREATMENT HISTORY
Menu
Sally
Question 1
Question 2
Behavioral Strategies
HELP
How to Use
Meet the Faculty
Case 1: Sally

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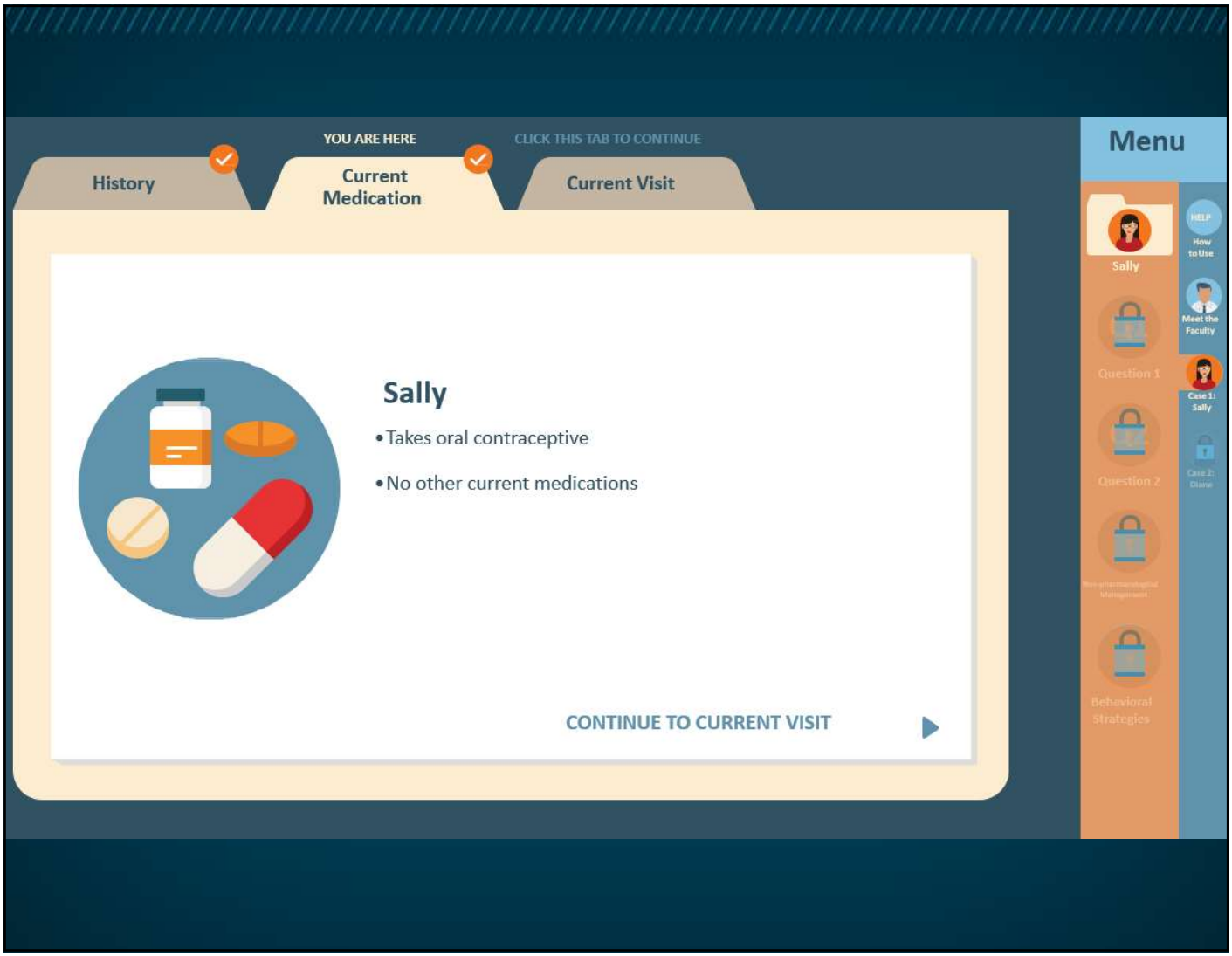
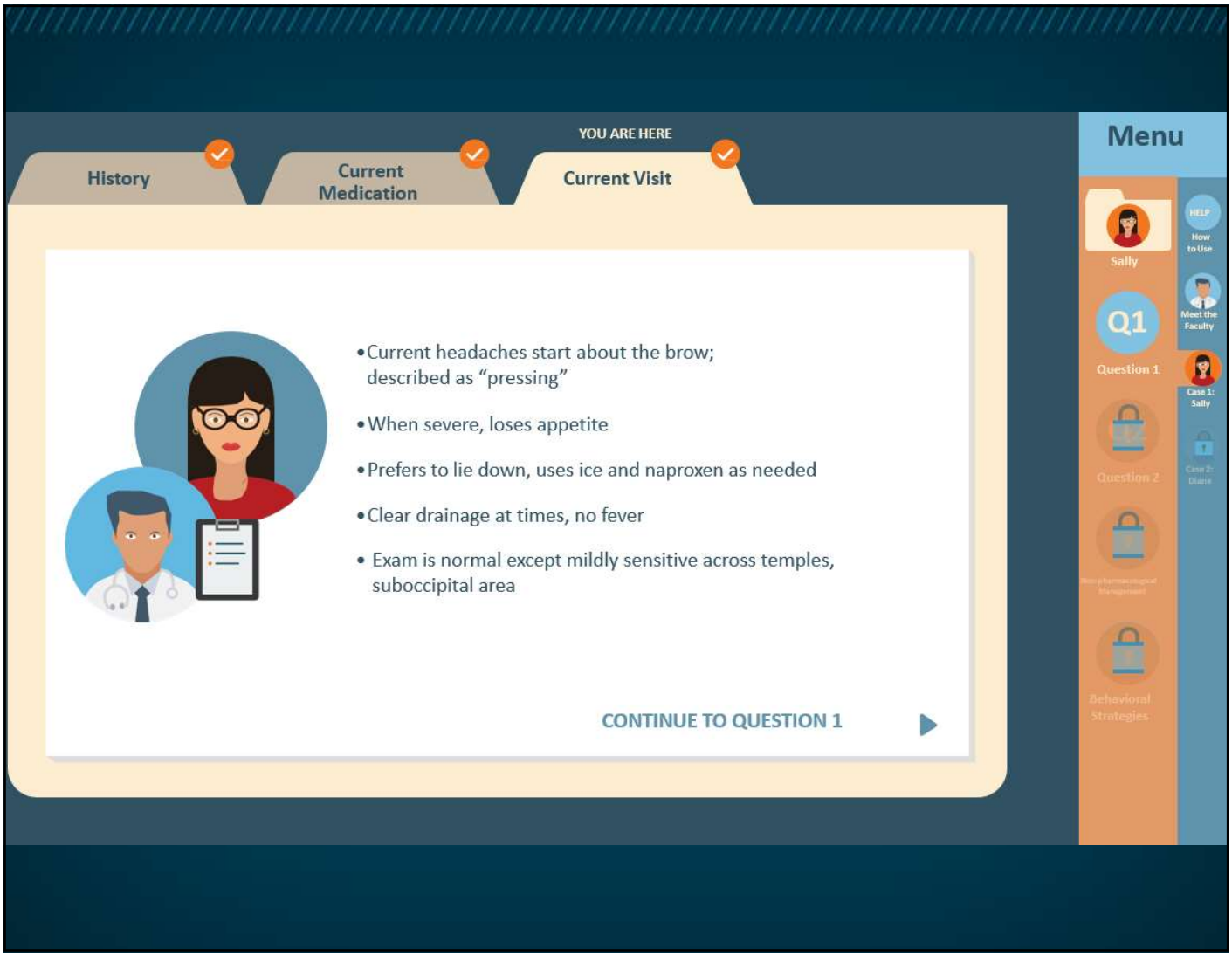
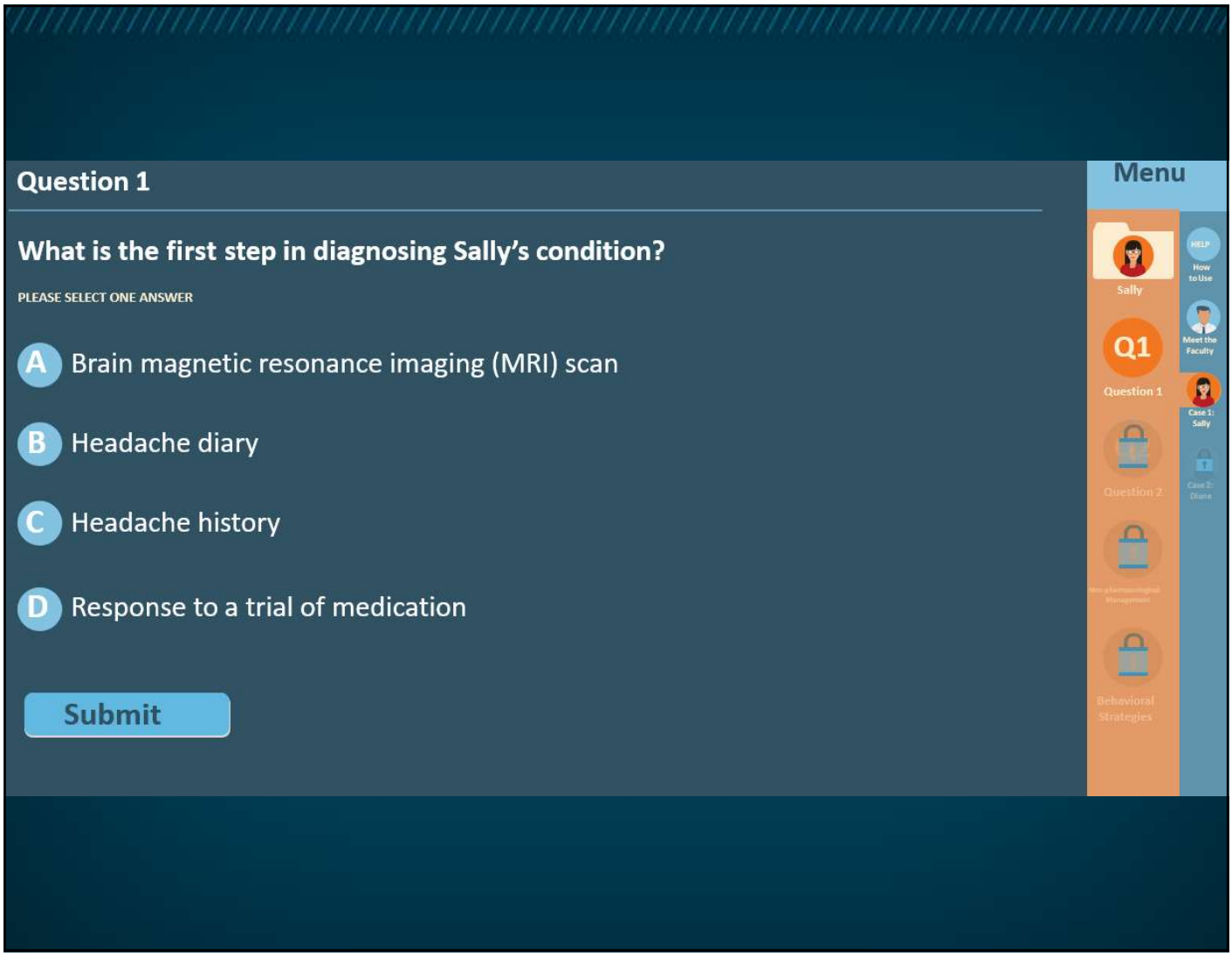

YOU ARE HERE
CLICK THIS TAB TO CONTINUE
History
Current Medication
Current Visit
Menu
Sally
HELP
How to Use
Meet the Faculty
Question 1
Case 1: Sally
Question 2
Case 2: Diane
Behavioral Strategies
Sally
• Takes oral contraceptive
• No other current medications
CONTINUE TO CURRENT VISIT

45


YOU ARE HERE
History
Current Medication
Current Visit
Menu
Sally
Q1
Question 1
Question 2
Behavioral Strategies
HELP
How to Use
Meet the Faculty
Case 1: Sally
•Current headaches start about the brow; described as "pressing"
•When severe, loses appetite
•Prefers to lie down, uses ice and naproxen as needed
•Clear drainage at times, no fever
• Exam is normal except mildly sensitive across temples, suboccipital area
CONTINUE TO QUESTION 1

46


Question 1
What is the first step in diagnosing Sally's condition?
PLEASE SELECT ONE ANSWER
A Brain magnetic resonance imaging (MRI) scan
B Headache diary
C Headache history
D Response to a trial of medication
Submit
Menu
Sally
Q1
Question 1
Question 2
Behavioral Strategies
HELP
How to Use
Meet the Faculty
Case 1: Sally

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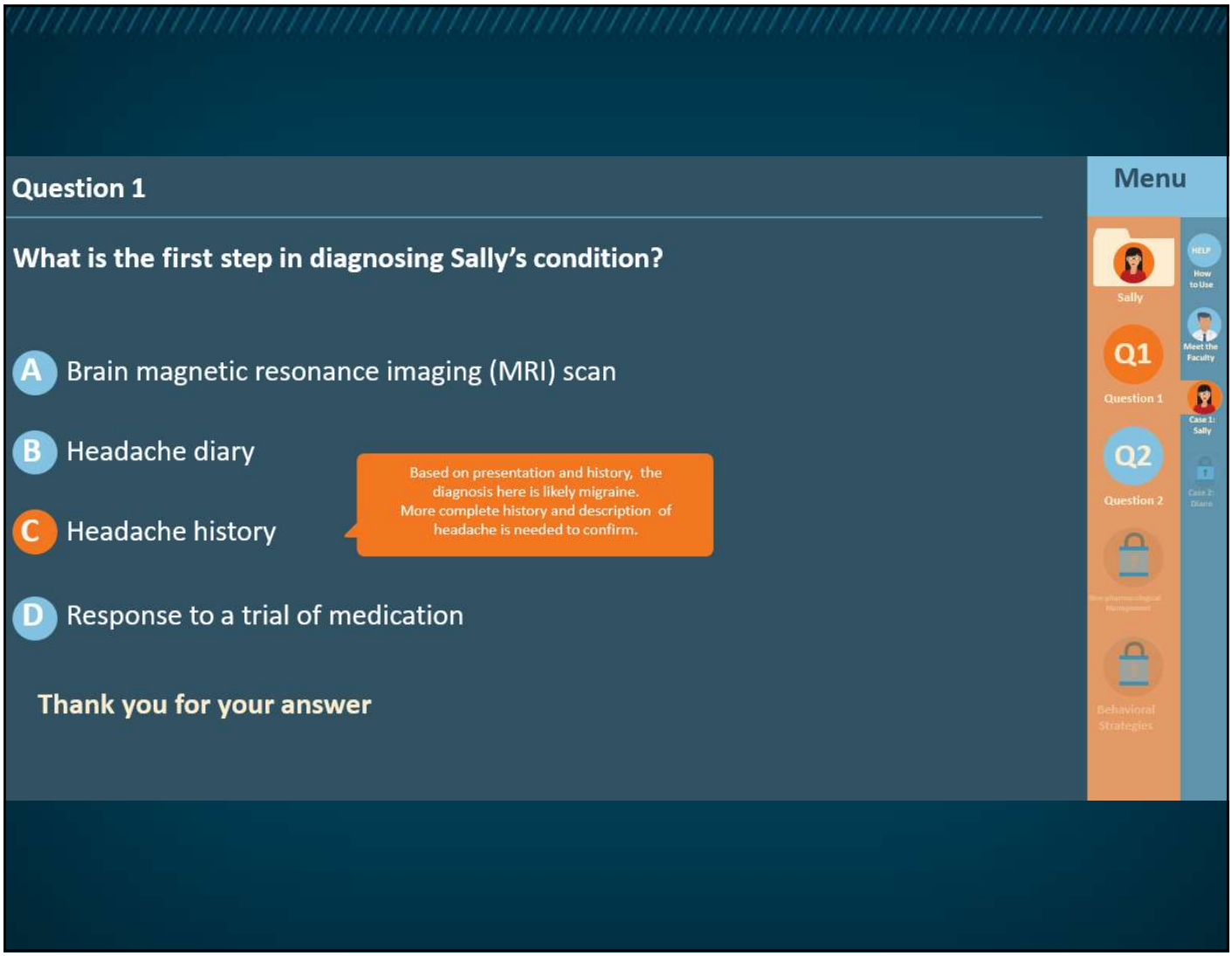
Question 1
What is the first step in diagnosing Sally's condition?
A Brain magnetic resonance imaging (MRI) scan
B Headache diary
C Headache history
D Response to a trial of medication
Based on presentation and history, the diagnosis here is likely migraine. More complete history and description of headache is needed to confirm.
Thank you for your answer
Menu
Sally
Q1
Question 1
Q2
Question 2
Behavioral Strategies
HELP
How to Use
Meet the Faculty
Case 1: Sally

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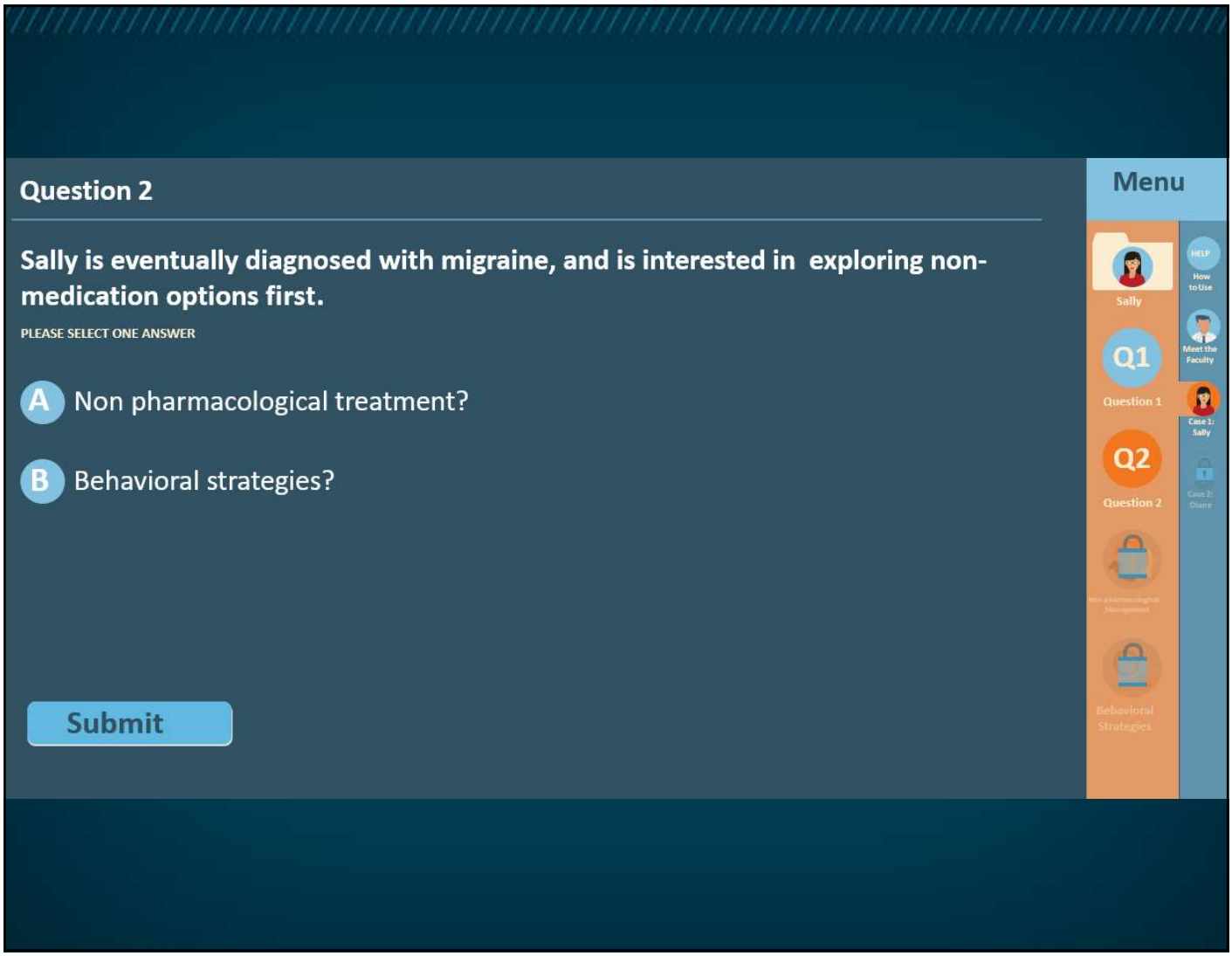
Question 2
Sally is eventually diagnosed with migraine, and is interested in exploring non-medication options first.
PLEASE SELECT ONE ANSWER
A Non pharmacological treatment?
B Behavioral strategies?
Submit
Menu
Sally
Q1
Question 1
Q2
Question 2
Behavioral Strategies
HELP
How to Use
Meet the Faculty
Case 1: Sally

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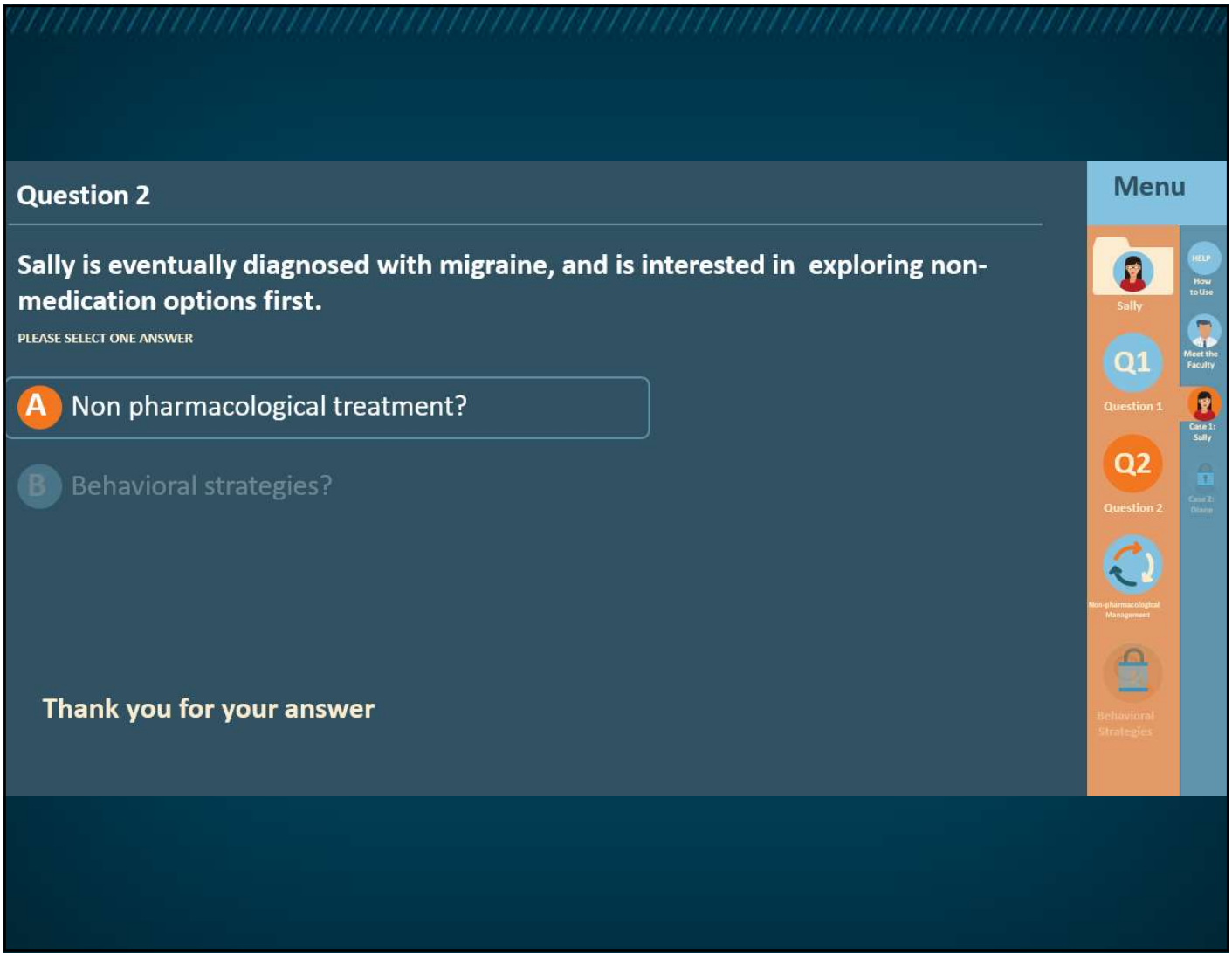
Question 2
Sally is eventually diagnosed with migraine, and is interested in exploring non-medication options first.
PLEASE SELECT ONE ANSWER
A Non pharmacological treatment?
B Behavioral strategies?
Thank you for your answer
Menu
Sally
Q1
Question 1
Q2
Question 2
Non-pharmacological Management
Behavioral Strategies
HELP
How to Use
Meet the Faculty
Case 1: Sally
Case 2: Diane

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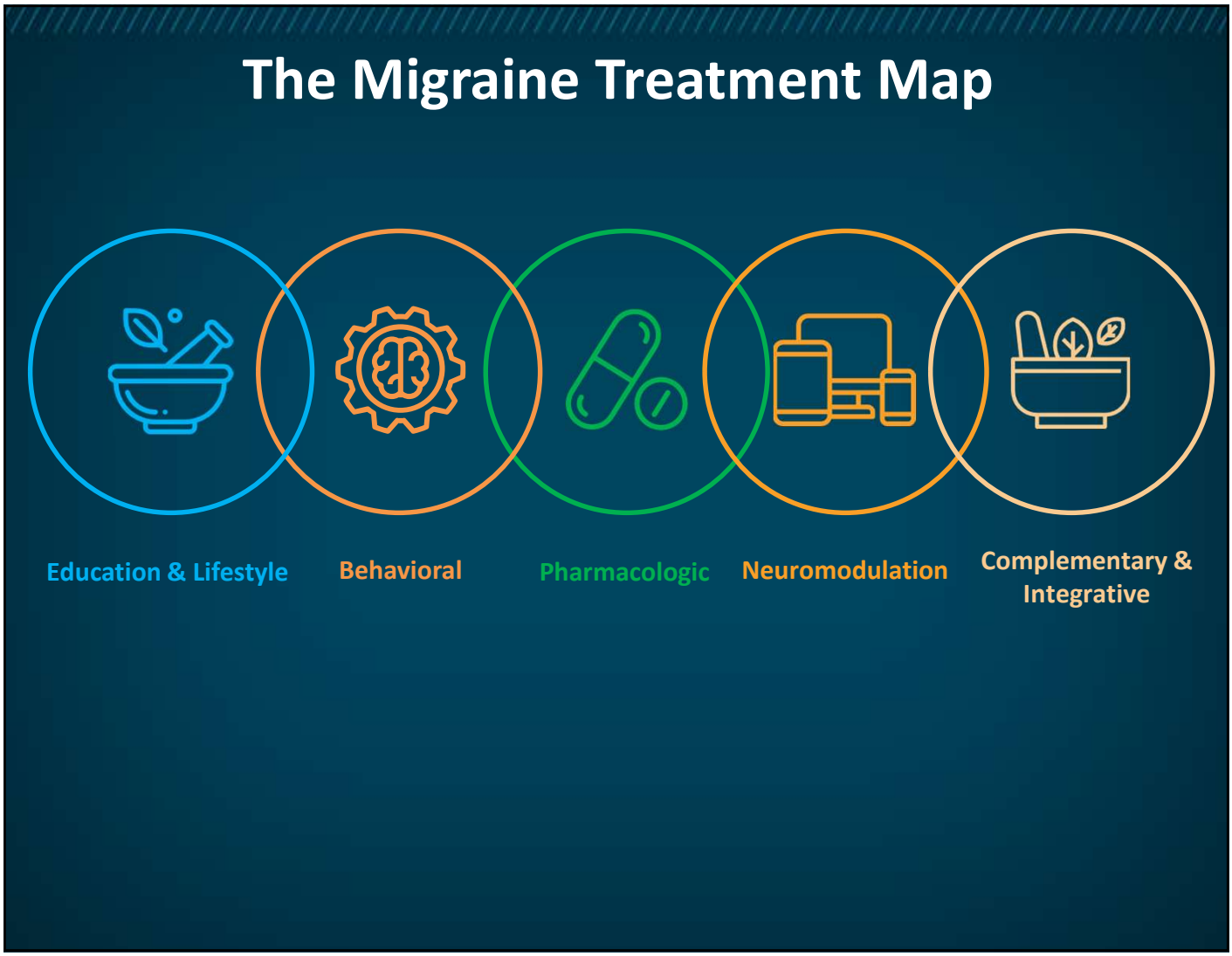
The Migraine Treatment Map
Education & Lifestyle
Behavioral
Pharmacologic
Neuromodulation
Complementary & Integrative

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Lifestyle (Headache Hygiene) & Education

SLEEP

EATING

EXERCISE

HYDRATION

STRESS MANAGEMENT

SOCIAL SUPPORT

EDUCATION

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Biobehavioral Therapies

GRADE A EVIDENCE

EMERGING

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Pharmacologic Treatments

ACUTE	PREVENTIVE	INTERVENTIONAL
NSAIDs	CGRP Targeted mAbs	Trigger Points
Triptans	Beta-blockers	Nerve Blocks
Ditans	Calcium-channel blockers	Other therapies
Ergotamines	Antidepressants	
Gepants	Anticonvulsants	
	Botox (*CM)	

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Neuromodulation

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Complementary and Integrative Medicine

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When to Refer to a Specialist?

- When diagnosis is uncertain
- When patient does not respond to usual acute or preventitive treatment
- When the patient has new neurologic signs
- When the patient is getting progressively worse

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Improving Communication

Patient education is KEY:

- What to do at headache onset
- What to do for prevention
- What to do if treatment is not helping, ie, what is the rescue plan?
- Awareness of side effects of any existing/new medications
- What is a red flag or emergency? What to do.
- Special instructions: travel; stressful events; pregnancy

Perets A et al. American Migraine Foundation. https://americanmigrainefoundation.org/understanding-migraine/communication-making-sure-you-have-success/

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Treatment of Migraine

Andrew Charles, MD

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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 of attacks
- Some newer therapies have overlapping acute and preventive properties

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Headache Treatment (continued)

- Effective management depends on:
  - Making an accurate diagnosis
  - Addressing headache impact
  - Engaging patient in their therapy
- Ultimate goals of treatment:
  - Identify and remove exacerbating factors (including medications)
  - For acute treatment: Rapid and sustained relief from pain and other symptoms (acute treatment)
  - For preventive treatment: Reduced frequency, severity, duration of migraine attacks, and associated disability
  - For both types of treatment: Minimal adverse effects such as dizziness, cognitive dysfunction, weight change, etc.

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Consider Prevention When...

- Migraine significantly interferes with patients‘ daily routine despite acute treatment
- Frequent attacks (>1 day /week) with risk of CM or MOH
- Acute medications are ineffective, contraindicated, have troublesome AEs, or are overused
- Patient preference
- Special circumstances such as:
  - Hemiplegic migraine
  - Migraine with brainstem aura (basilar migraine)
  - Migraine with prolonged aura
  - Migrainous infarction

CM = chronic migraine; MOH = medication-overuse headache; AE = adverse effect.

Silberstein SD. *Neurology.* 2000;55:754-762.

62

Traditional Acute Migraine Treatments

Non-specific

- NSAIDs
- Combination analgesics
- Neuroleptics/antiemetics
- Corticosteroids

Specific

- Ergotamine/DHE
- Triptans

New formulations

- FDA-approved
  - Breath-powered intranasal sumatriptan dry powder[2,3]
  - New sumatriptan autoinjectors[4]
- In development
  - Microneedle-array skin patches (zolmitriptan, sumatriptan)
  - Orally inhaled (zolmitriptan, DHE)
  - New intranasal delivery
    - Sumatriptan liquid spray with enhanced permeation[5]

NSAID = non-steroidal antiinflammatory drug; DHE = dihydroergotamine.

1. Silberstein S. *Expert Opin Pharmacother*. 2012;13:1961-8. 2. Tepper SJ et al. *Headache.* 2015;55:621-35. 3. Tepper D *Headache.*2016;56:817. 4. 4. Andre et al. *Patient Prefer Adherence.* 2017;11:121-129. 5. Munjal S et al. *J Headache Pain.* 2017;18:17.

AAN Preventive Guidelines

Level A: Effective	Level B: Probably effective	Level C: Possibly effective	Level U: Inadequate/ Conflicting	Ineffective
AEDs Divalproex Valproate Topiramate **β-blockers** Metoprolol Propranolol Timolol **ARB** Candesartan*	**SNRI/TCA** Amitriptyline Venlafaxine **β-blockers** Atenolol Nadolol	**ACE inhibitor** Lisinopril **α-agonists** Clonidine Guanfacine **AEDs** Carbamazepine **β-blockers** Nebivolol Pindolol **Leukotriene antagonist** Cyproheptadine	**CA inhibitor** Acetazolamide **Anticoagulants** Coumadin Picotamide **SSRI/SSNRI** Fluvoxamine Fluoxetine **AEDs** Gabapentin **TCAs** Protriptyline **β-blockers** Bisoprolol **Ca channel blockers** Nicardipine Nifedipine Nimodipine Verapamil	**NOT effective** Lamotrigine **Probably NOT effective** Clomipramine **Possibly NOT effective** Acebutolol Clonazepam Nabumetone Oxcarbazepine Telmisartan

***Studies now suggest level A evidence**

AAN = American Academy of Neurology; AED = antiepileptic drug; ARB = angiotensin-receptor blocker; ACE = angiotensin-converting enzyme; Ca = calcium.

Adapted from Silberstein SD. *Neurology*. 2012;78:1337Y1345.

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RECENTLY APPROVED ACUTE THERAPIES

- NEW TRIPTAN FORMULATIONS
  - Breath powered intranasal sumatriptan powder
  - Sumatriptan liquid spray with enhanced permeation
- NEUROMODULATION
  - Transcranial magnetic stimulation (sTMS mini)
  - Transcutaneous supraorbital nerve stimulation (Cephaly)
  - Transcutaneous vagus nerve stimulation (Gammacore)
- LASMIDITAN
- UBROGEPANT
- RIMAGEPANT

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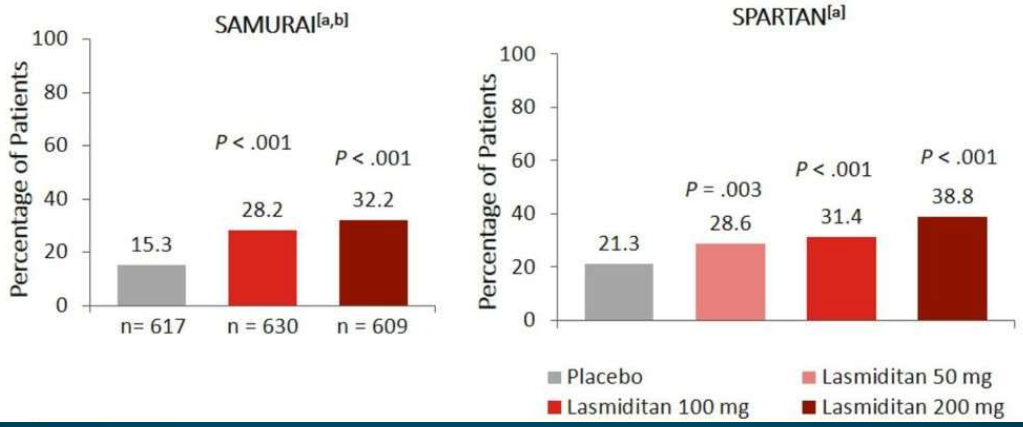
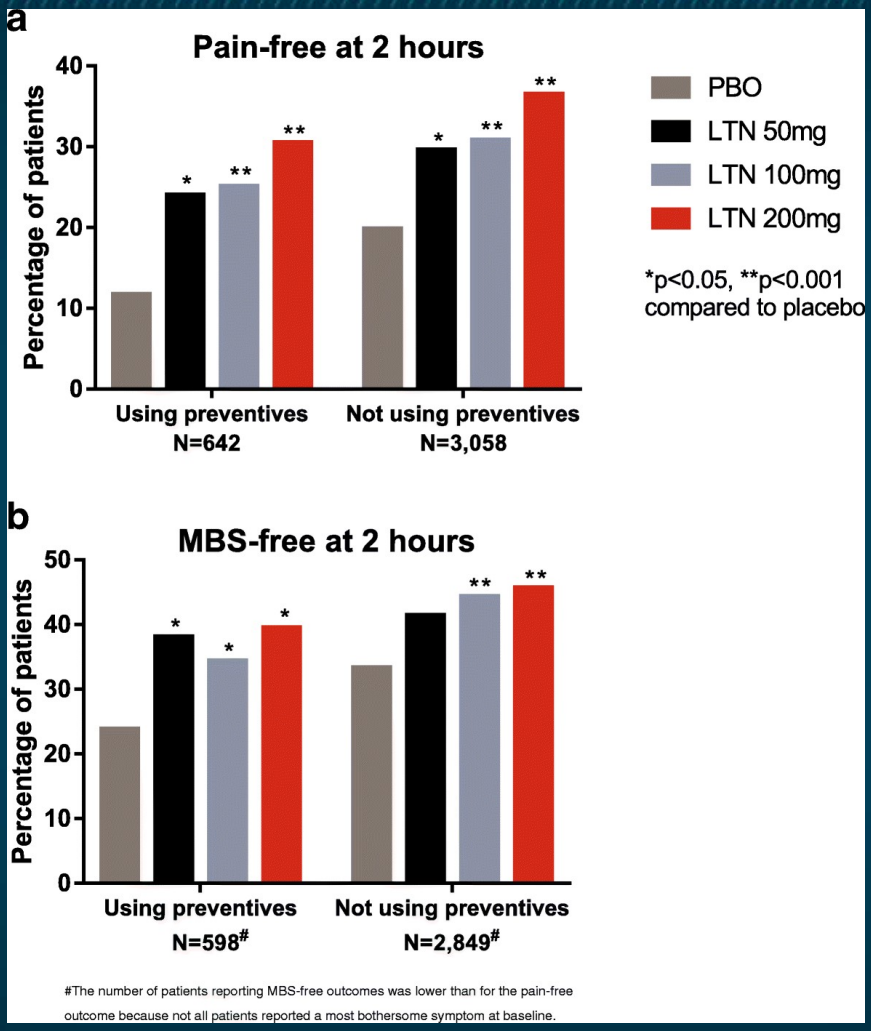
Lasmiditan

SAMURAI and SPARTAN Phase 3 Studies

Primary Endpoint: Proportion of Patients Free From Pain at 2 Hours Post-Dose



- **Selective 5HT1F receptor agonist**
- **Unlike triptans, no effects on vasculature**


a
Pain-free at 2 hours
Percentage of patients
40
30
20
10
0
*
**
*
**
*
**
Using preventives
N=642
Not using preventives
N=3,058
PBO
LTN 50mg
LTN 100mg
LTN 200mg
*p<0.05, **p<0.001
compared to placebo
b
MBS-free at 2 hours
Percentage of patients
50
40
30
20
10
0
*
*
*
**
**
Using preventives
N=598#
Not using preventives
N=2,849#
#The number of patients reporting MBS-free outcomes was lower than for the pain-free outcome because not all patients reported a most bothersome symptom at baseline.

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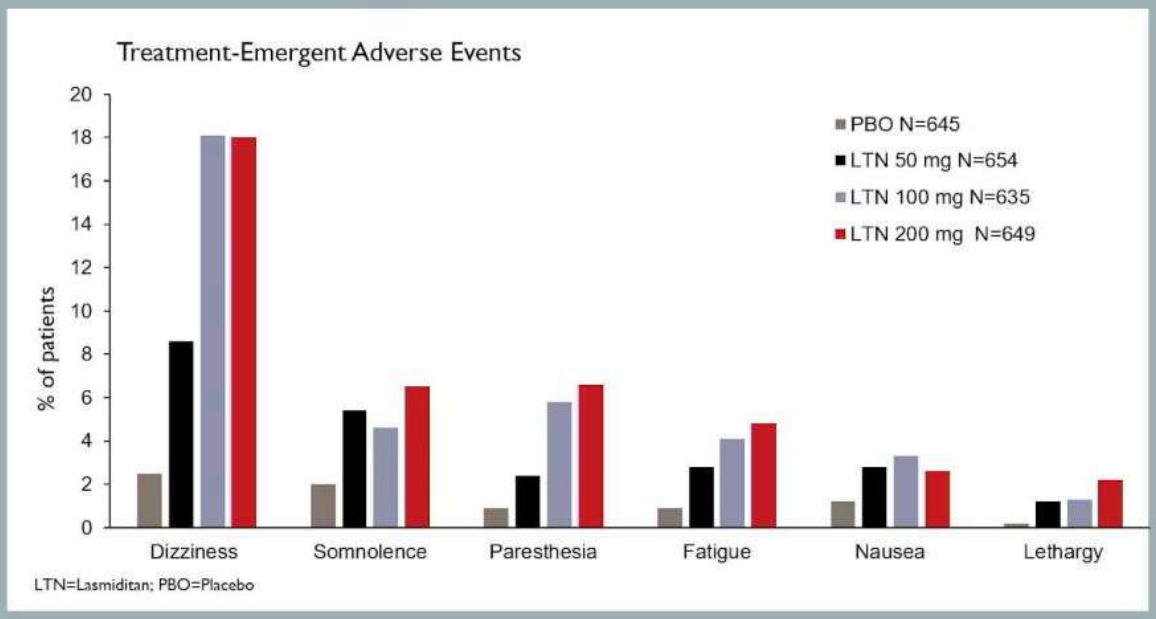
LASMIDITAN IN ACUTE TREATMENT OF MIGRAINE

SPARTAN RESULTS - *SAFETY AND TOLERABILITY*



SAEs: five, two considered treatment related (dystonic reaction and presyncope)
Discontinuation on treatment: one on lasmidtan 200 mg (fatigue and dizziness)
Tests: No laboratory or electrocardiogram differences

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THE LANCET Therapeutics

Targeting calcitonin gene-related peptide: a new era in migraine therapy

Andrew Charles, Patricia Pozo-Rosich

Migraine is one of the most prevalent and disabling diseases worldwide, but until recently, few migraine-specific therapies had been developed. Extensive basic and clinical scientific investigation has provided strong evidence that the neuropeptide calcitonin gene-related peptide (CGRP) has a key role in migraine. This evidence led to the development of small molecule CGRP receptor antagonists and monoclonal antibodies targeting either CGRP or its receptor. Clinical trials investigating these therapies have consistently shown statistically significant efficacy for either the acute or preventive treatment of migraine. No serious safety or tolerability issues have been identified in the trials of the monoclonal antibody therapies. Although the appropriate place of these new migraine-specific therapies relative to other available acute and preventive treatments remains to be determined, a growing body of evidence shows that therapeutic approaches targeting CGRP have the potential to transform the clinical management of migraine.

www.thelancet.com **Published online October 23, 2019**

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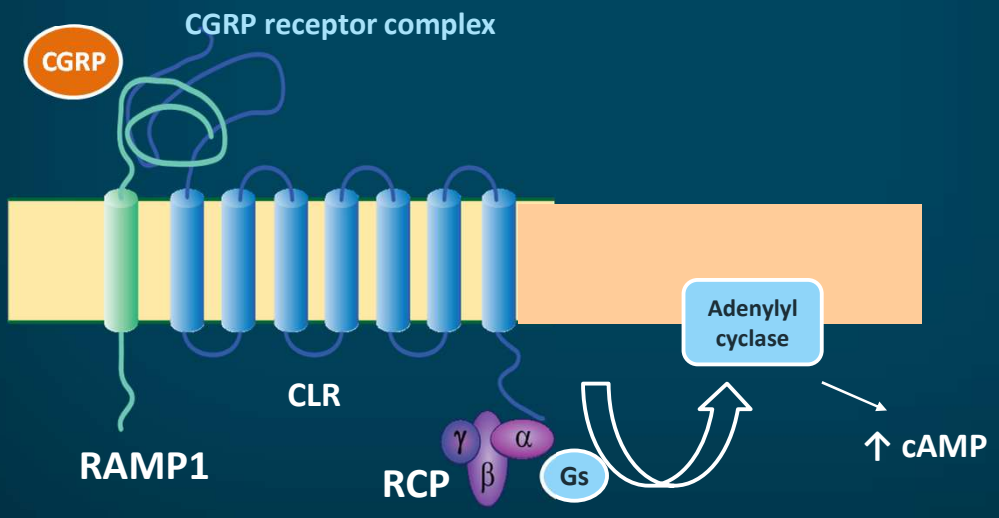
Calcitonin Gene-Related Peptide (CGRP)

- Neuropeptide belonging to calcitonin family (calcitonin, amylin, adrenomedullin, intermedin)
- In humans, two forms: α-CGRP (37-amino-acid peptide) and β-CGRP (main isoform of enteric nervous system); differ in 3 amino acids
- Binds to CGRP receptor complex



RAMP = receptor activity-modifying protein; CLR = calcitonin receptor-like receptor; RCP = receptor component protein; cAMP = cyclic adenosine monophosphate.

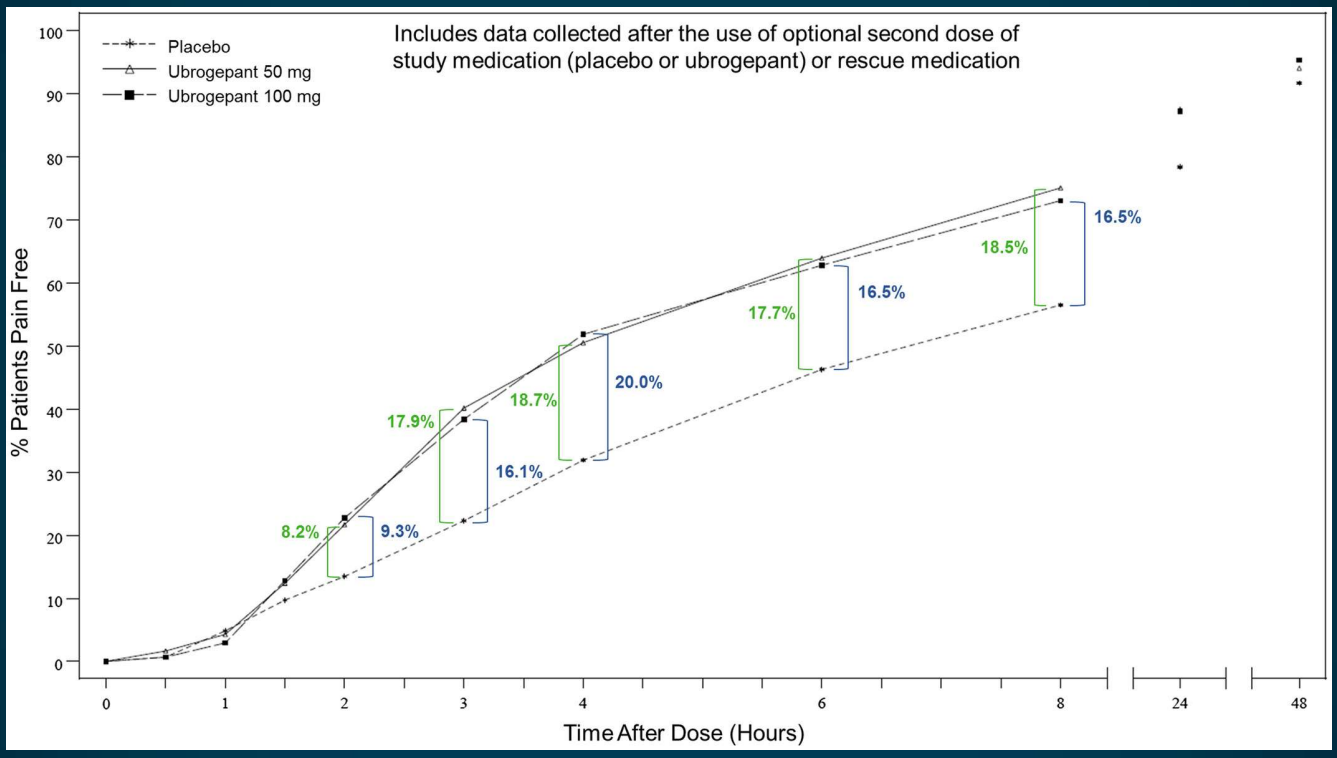
CGRP in Migraine

- CGRP immunoreactive nerves innervate human cerebral arteries
- CGRP is a potent vasodilator of human cerebral arteries
- CGRP is released into jugular venous system during migraine
- Serum CGRP levels are elevated in chronic migraine
- CGRP infusion evokes migraine
- Small-molecule CGRP-receptor antagonists (gepants) effectively abort migraine attacks
- Anti-CGRP and anti-CGRP-receptor monoclonal antibodies prevent episodic migraine (EM) and chronic migraine (CM)

Adapted from AHS CMEP. Edvinsson L et al. *Neurosci Lett.* 1985;58:213-217. McCulloch J et al. *Proc Natl Acad Sci USA*. 1986;83:5731-5735. Edvinsson L et al. *Ann Neurol.* 1987;21:431-437. Lassen LH et al. *Cephalalgia*. 2002;22:54-61. Goadsby PJ, Edvinsson L. *Brain*. 1994;117:427-434. Olesen J et al. *N Engl J Med*. 2004;350:1104-1110. Ho TW et al. *Neurology*. 2008;70:1304-1312. Voss T et al. *Cephalalgia*. 2016;36:887-898.

Small-Molecule CGRP Receptor Antagonists: Gepants

- **Acute treatment of migraine**
  - **Olcegepant** (IV) worked; comparable to triptans: proof of concept[1]
  - **BI 44370 TA** (oral): effective vs placebo in phase 2[2]
  - **Telcagepant** showed promise and efficacy comparable to triptans, but development stopped due to liver toxicity in phase 3[3]
  - **MK3207**: effective and well tolerated in phase 2[6] but liver toxic
  - **Rimegepant**: FDA approved for acute treatment of migraine
  - **Ubrogepant**: FDA approved for acute treatment of migraine
- Preventive treatment of migraine
  - **Telcagepant** studied in 2 incomplete studies, with one terminated early due to hepatotoxicity and the other for evaluation of liver in MRM mini-prevention
  - Rimegepant phase 3 study demonstrated efficacy in migraine prevention with every other day dosing
  - **Atogepant** vs placebo underway in phase 2 for migraine prevention


Placebo
Ubrogepant 50 mg
Ubrogepant 100 mg
Includes data collected after the use of optional second dose of study medication (placebo or ubrogepant) or rescue medication
% Patients Pain Free
Time After Dose (Hours)
8.2%
9.3%
17.9%
16.1%
18.7%
20.0%
17.7%
16.5%
18.5%
16.5%

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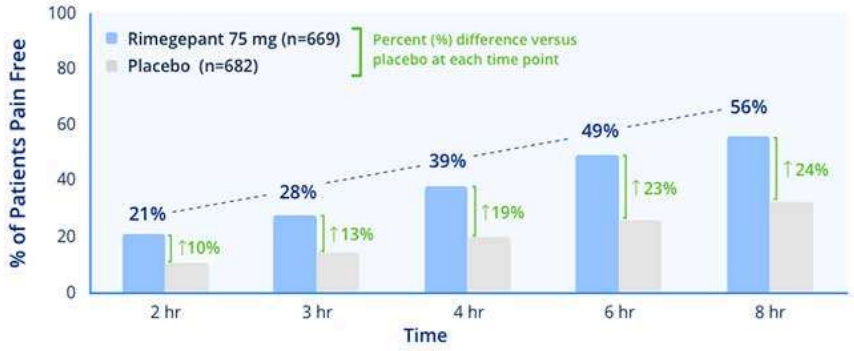
Increasing Benefit Over Time on **Pain Freedom** After Single Dose of Rimegepant 75 mg Zydis ODT Formulation

RIMEGEPANT (BHV-3000) PHASE 3 TOPLINE - STUDY 303, RIMEGEPANT 75 MG ZYDIS ODT

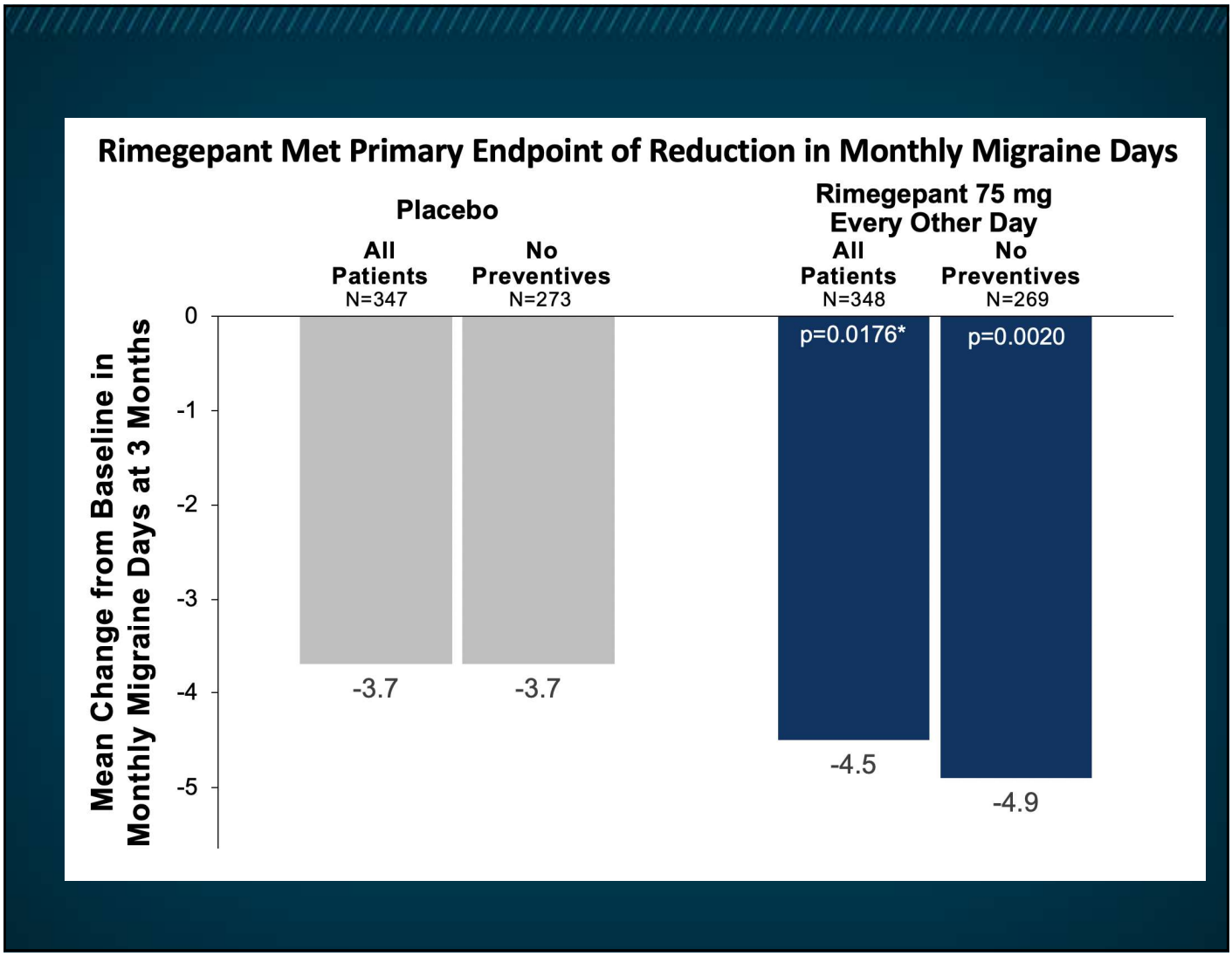
Pain Freedom 2-8 Hours

Post-Single Dosing with Rimegepant 75 mg Zydis ODT



Single Dose of Rimegepant, No Rescue Meds

Estimates computed using the mITT population and CMH methods. Subjects using rescue medications at or before the assessment, and subjects not providing data, are classified as failures.


Rimegepant Met Primary Endpoint of Reduction in Monthly Migraine Days
Placebo
Rimegepant 75 mg Every Other Day
All Patients N=347
No Preventives N=273
All Patients N=348
No Preventives N=269
Mean Change from Baseline in Monthly Migraine Days at 3 Months
0
-1
-2
-3
-4
-5
p=0.0176*
p=0.0020
-3.7
-3.7
-4.5
-4.9

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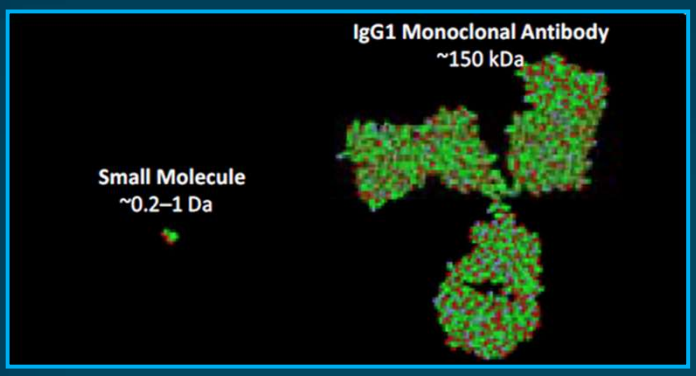
Small Molecules (Gepants) vs Large Molecules (Monoclonal Antibodies)



Small Molecules	Monoclonal Antibodies
Target specificity lower	Target specificity high
Clearance (liver, kidney)	Clearance RES
Size <1 kD	Size ~150 kD
Oral	Parenteral
Can cross BBB	Do not cross BBB
Half-life = minutes to hours	Half-life = 3–6 weeks
Immunogenicity (no)	Immunogenicity (yes)

Bigal ME et al. *Brit J Clin Pharmacol*. 2015;79:886-895.

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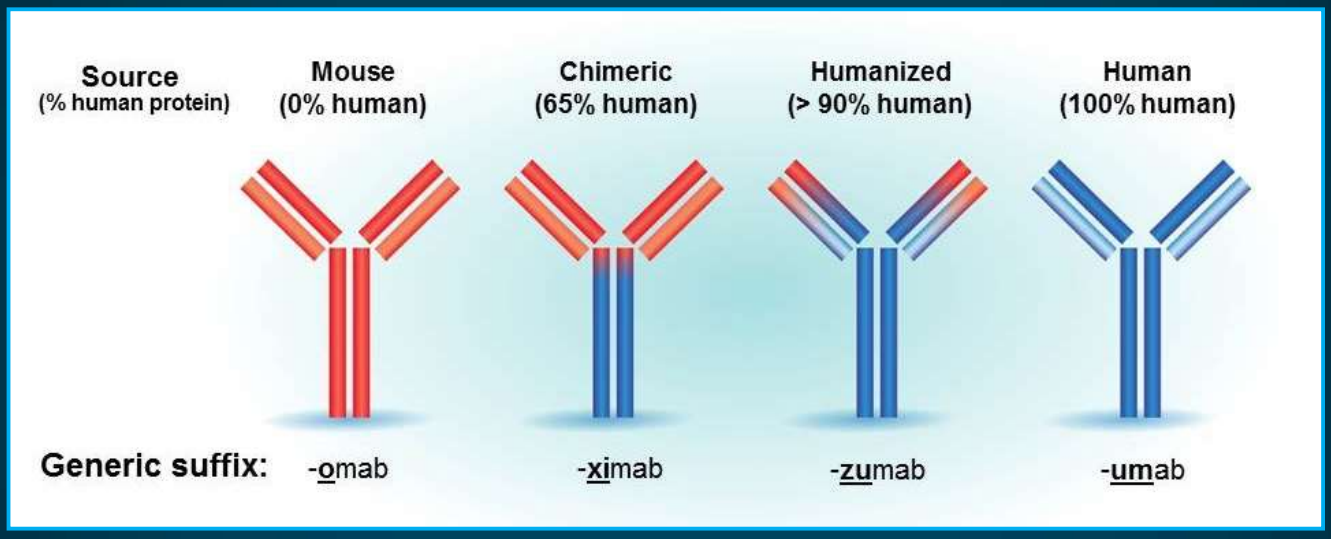
Naming Conventions For Therapeutic mABs



Immunogenicity potential

High

Low

WHO (www.who.int/medicines/services/inn/generalpoliciesmonoclonalantibodiesjan10.pdf). Silberstein S et al. *Headache.* 2015;55:1171-1182.

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Four Injectable Monoclonal Antibodies to CGRP or Its Receptor

	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab*
Studied for	EM, CM	EM, CM, eCH, cCH	EM, CM, eCH, cCH	EM, CM
Dosing	Monthly SC	Monthly or Q3 month SC; IV load for CH	Monthly SC	Q3 month IV
	Fully human	Fully Humanized	Humanized	Humanized
Target	CGRP receptor	CGRP peptide or ligand	CGRP peptide or ligand	CGRP peptide or ligand
Regulatory status as of Oct, 2018	**FDA Approved May 17, 2018**	**FDA Approved Sep 16, 2018**	**FDA Approved Sep 27, 2018**	**FDA Approved**

***Not currently approved for migraine.**
Terms: umab = fully human; zumab = humanized, 90% human; fully humanized 95% human.
eCH = episodic cluster headache; cCH = chronic cluster headache.

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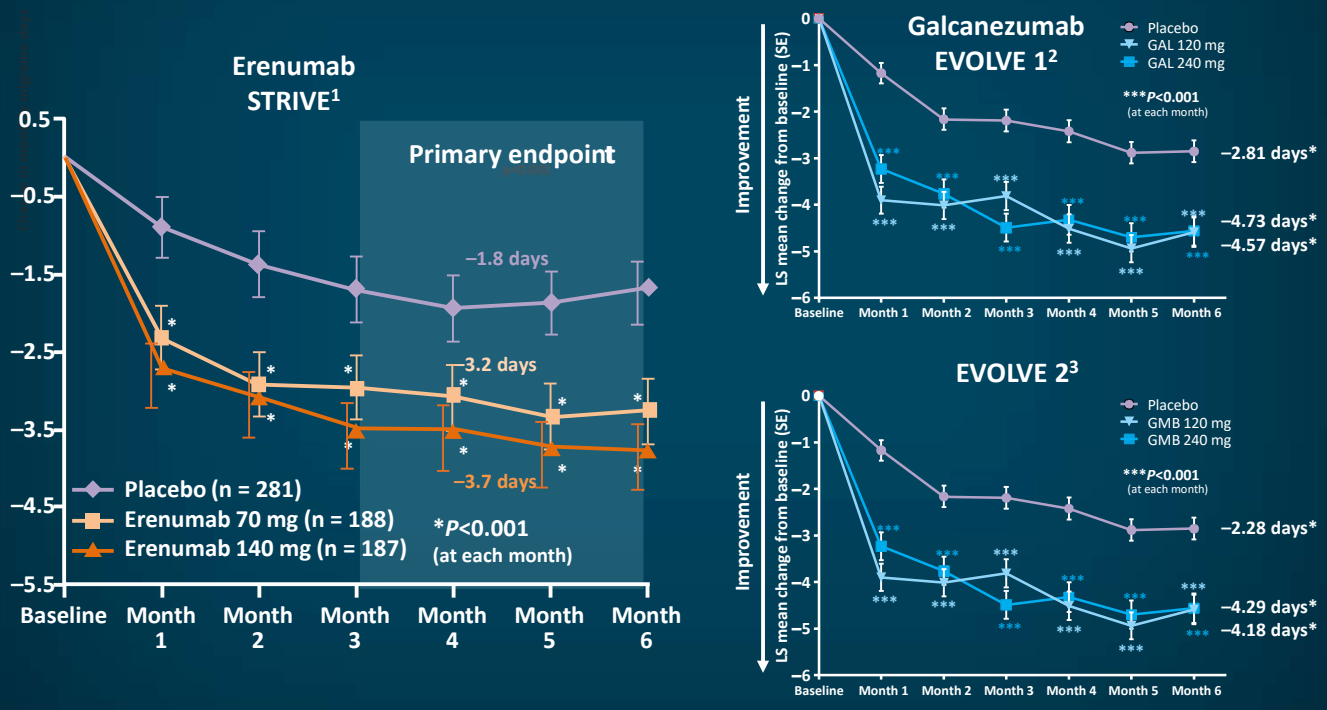
Phase 3 Trials: 6-Month *EM* Prevention

Erenumab and Galcanezumab Efficacy

Primary endpoint: monthly migraine day (MMD) reduction vs placebo

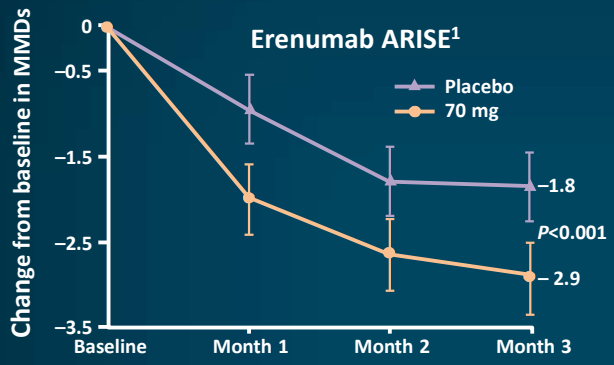


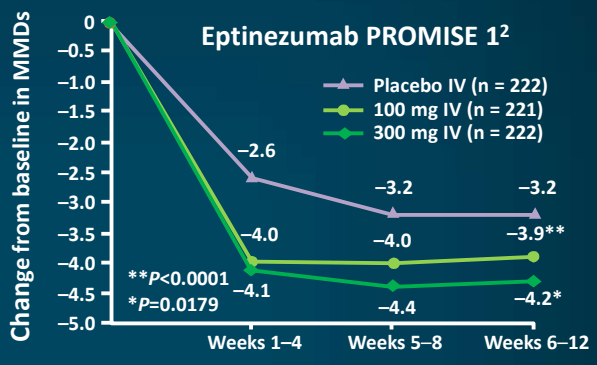
1. Goadsby PJ et al. *Headache.* 2017;57(S3): 128-129 (abstract IOR04). 2. Stauffer VL et al. *Headache.* 2017;57:1336 (abstract PS88LB).
3. Skljarevski V et al. *Headache.* 2017;57:1312 (abstract IOR-12LB).

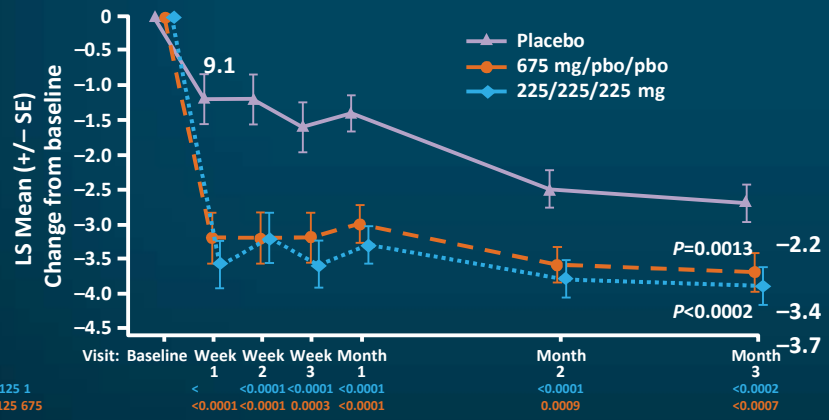
Phase 3 Trials: 3-Month *EM* Prevention

Erenumab, Fremanezumab, and Eptinezumab Efficacy

Primary endpoint: reduction of MMDs







Fremanezumab HALO EM[3]

Equally effective whether administered subcutaneously monthly or quarterly

1. Ashina M et al. *Neurology.* 2017;89:1237-1243. 2. Smith J et al. IHC poster, PO-01-194, Vancouver 2017. 3. Bigal M et al. PO-01-082, IHC, Vancouver 2017.

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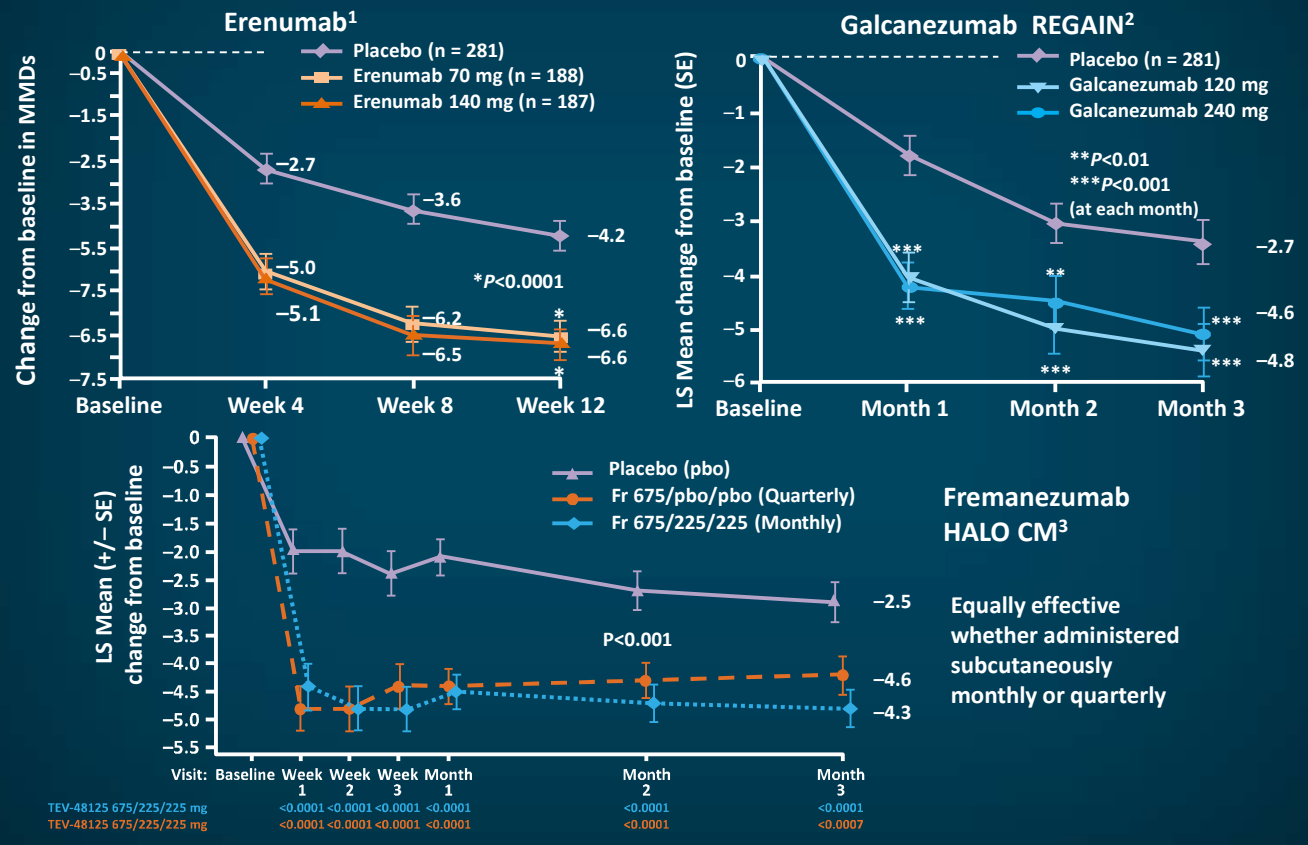
Pivotal or Phase 3 CM Trials

Erenumab, Galcanezumab, and Fremanezumab Efficacy

Primary endpoint: reduction in MMDs

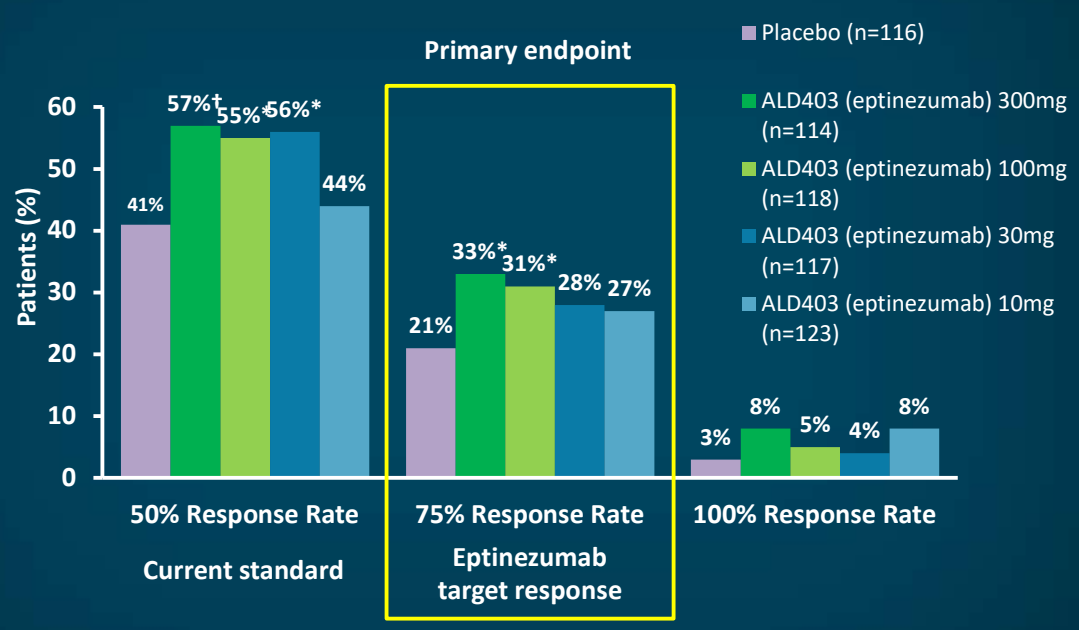


Fremanezumab HALO CM[3]

Equally effective whether administered subcutaneously monthly or quarterly

1. Tepper S et al. *Lancet Neurol.* 2017;16:425-434. 2. Detke HC et al. *Headache* 2017;57:1336-1337(PS89LB). 3. Aycardi E et al. *Headache.* 2017;57:1311(IOR-05).

Eptinezumab *Phase 2* CM Prevention



*P<0.05; †P<0.005 vs placebo (one-sided, not corrected for multiplicity)

Smith J et al. *Headache*. 2017;57 (suppl 3): 130 (IOR06).

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Safety and Tolerability of mABs

- In phase 2 trials of mABs, discontinuation rate due to AEs was 0–3.7% vs 8–27% for placebo; this discontinuation for mABs is **much** lower than occurred in studies and occurs clinically with currently approved oral preventive drugs
- The tolerability of the mABs is excellent, and injection-site reactions are the only AEs seen a bit more often than with placebo in the 3 subcutaneous mABs
- Safety also has been excellent, with no safety signals and no plan for requiring blood monitoring or other monitoring

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The Four mABs

- US FDA suggested a consistent primary endpoint: reduction of monthly migraine days
- All four:
  - are positive for EM and CM prevention in phase 2
  - are positive for EM prevention in phase 3
- 3 of 4 have already reported or published positive findings for CM prevention in phase 3
- 40–60% of CM registration study subjects had medication overuse
- All four:
  - have quick onset, separating from placebo within 1 week
  - show clinically meaningful response by one month
  - have favorable responder rates for ≥50% and higher
  - have safety and tolerability similar to placebo
- Almost all secondary endpoints are also positive, with decreased acute medication days, improved impact, disability, and/or quality of life

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Will the mABs Be an Improvement? The 4 mABs

- All data announced to date for EM and CM have shown a reduction in mean MMDs with a magnitude of 1–3 days drop over placebo, similar to the registration studies for onabotulinumtoxin A
- Using MMDs is necessary from a regulatory standpoint
- However, MMDs are not a useful clinical endpoint for estimating value since the clinical effect is underestimated due to inclusion of placebo
- More useful is the drop from baseline and the secondary endpoints, such as responder rates

MMDs = monthly migraine days

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Clinical Utility of the 4 mABs

- For example, with erenumab in CM prevention, a 6.7 day reduction in MMDs was found in the pivotal trial, which would represent 79 fewer migraine days per year[1]
- In the galcanezumab EM registration studies[2] and the eptinezumab Phase 2 CM studies,[5] the ≥75% responder rates were ≥33%
- All 4 mABs work in CM prevention with medication overuse and without (pre-specified secondary analyses)[3]
- Erenumab worked better in patients who had failed ≥2 preventive meds vs none, odds ratio 4.18 vs 1.33 (pre-specified secondary analysis)[4]

1. Tepper S et al. *Lancet Neurol.* 2017;16:425-434. 2. Skljarevski V et al. AHS meeting June 2017 (abstract IOR-12LB).
3. Tepper S et al. AHS meeting, E-poster (EP-01-013), Sept 8, 2017. 4. Ashina M et al. PO-01-180. IHC, Sept 2017 (abstract PO-01-180).
5. Smith J et al. *Headache*. 2017;57 (suppl 3): 130 (IOR06).

Additional Recent Trials

- Ashina, et al:

  "Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study."

- Buse, et al:

  "Migraine-related disability, impact, and health-related quality of life among patients with episodic migraine receiving preventive treatment with erenumab."

- Depre, et al:

  "A randomized, double-blind, placebo-controlled study to evaluate the effect of erenumab on exercise time during a treadmill test in patients with stable angina."

- Camporeale, et al:

  "A phase 3, long-term, open-label safety study of galcanezumab in patients with migraine."

Additional Recent Trials

- Ford, et al:

  "Patient satisfaction, health care resource utilization, and acute headache medication use with galcanezumab: results from a 12-month open-label study in patients with migraine."

- Nichols, et al:

  "Analysis of initial nonresponders to galcanezumab in patients with episodic or chronic migraine: Results from the EVOLVE-1, EVOLVE-2, and REGAIN randomized, double-blind, placebo-controlled studies."

- Cohen, et al:

  "Fremanezumab as add-on treatment for patients treated with other migraine preventive medicines."

- Halker Singh, et al:

  "Sustained reductions in migraine days, moderate-to-severe headache days and days with acute medication use for HFEM and CM patients taking fremanezumab: Post-hoc analyses from phase 2 trials."

Conclusions: Reasons for Optimism in Migraine

- Better recognition of individual patient characteristics
- New routes of administration of existing therapies
- New acute medications in development
- New preventive treatments in development
- Better understanding of migraine physiology

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Post-Test Question 1

1. A 32-year-old woman complains of painful headaches at least 2 times a day for the past two weeks, occurring on the right side near her temple. They have sudden onset and usually resolve within an hour. She reports right-sided tearing and nasal congestion and feels restless during the headaches. Which headache type is most likely?

a. Chronic migraine
b. Episodic tension-type headache
c. Cluster headache
d. Headache due to secondary cause

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Post-Test Question 2

Which of these facts support the role of inhibiting CGRP for headache prevention?

a. CGRP is a neuropeptide with vasodilation properties

b. CGRP levels increase during migraines; experimental injection of CGRP mimics the symptoms of a migraine

c. CGRP modulates acetylcholine and glutamate release

d. CGRP antibodies cross the blood brain barrier

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Post-Test Question 3

Which of the following classes is used for *acute* headache treatment?

a. CGRP inhibitors
b. Botulinum toxin
c. Beta-blockers
d. Gepants

Post-Test Question 4

A 24-year-old married female with a 5-year migraine history presents to your office and you are interested in providing preventive migraine therapy to her. She is actively trying to get pregnant. Which of the following would you start with?

a. Begin with a dosage of preventive therapy slightly higher than abortive therapy
b. Start a preventive agent, then taper/stop after 3 months if well-controlled
c. Discuss medication considerations in pregnancy
d. Recommend daily NSAID or ergotamine use to start

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Thank You!

Questions and Answers