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

TUESDAY, OCTOBER 13, 2020

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This symposium is provided by Med Learning Group and supported by an educational grant from Lilly.

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

FACULTY

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Andrew Charles, MD
Professor of Neurology
Director, UCLA Goldberg Migraine Program
Meyer and Renee Luskin Chair in Migraine and Headache Studies
David Geffen School of Medicine at University of California
President-Elect, American Headache Society
Los Angeles, CA

PROGRAM OVERVIEW
This case-based live virtual activity will cover the treatment and management of patients with headache disorders, including migraine and cluster headache.

TARGET AUDIENCE
This activity is intended for primary care providers, including family practice physicians, physician assistants, and nurse practitioners who are involved in the care of patients with headache disorders, including migraine and cluster headache.

Learning Objectives
- Implement best practices for the timely and accurate diagnosis of primary headache disorders in primary care settings and for referral to specialists when necessary
- Identify the mechanisms of action and clinical profiles of new and emerging therapeutic options for the acute and preventative treatment of patients with primary headache disorders
- Design individualized evidence-based treatment plans for patients with primary headache disorders, with focus on cluster headache, in the primary care setting
- Utilize patient-specific factors to select therapies for patients with primary headache disorders, including quality-of-life assessment and goal setting
- Implement strategies to effectively communicate with patients and educate them in order to establish treatment plans and encourage adherence

ACCREDITATION STATEMENT
Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
This CME activity was planned and produced in accordance with the ACCME Essentials.

CREDIT DESIGNATION STATEMENT
Med Learning Group designates this live virtual activity for a maximum of 1.5 *AMA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the live virtual activity.

NURSING CREDIT INFORMATION
Purpose: This program would be beneficial for nurses involved in the long-term treatment and management of patients with headache disorders, including migraine and cluster headache. **CNE Credits:** 1.5 ANCC Contact Hours.

CNE ACCREDITATION STATEMENT

Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.5 contact hours of continuing nursing education of RNs and APNs.

AMERICAN ASSOCIATION OF FAMILY PHYSICIANS

The AAFP has reviewed Diagnosing and Managing Primary Headache Disorders in the Primary Care Setting: Challenges and Opportunities and deemed it acceptable for up to 1.50 Online Only, Live AAFP Prescribed credit. Term of Approval is from 10/13/2020 to 10/13/2020. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AMERICAN ASSOCIATION OF PHYSICIAN ASSISTANTS

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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 receives consulting fees from Alder, Amgen, Biohaven, Eli Lilly, and eNeura. He has conducted research for Takeda Pharmaceuticals.

CME Content Review

The content of this activity was independently peer-reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer-reviewed by a nurse reviewer.
The reviewer of this activity has nothing to disclose.

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There are no fees for participating and receiving CME credit for this enduring activity. To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures;
2. Participate in the live streamed activity; and
3. Complete pre-and-post surveys and evaluation.

Participants will receive their certificate as a downloadable file.

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AGENDA

- **Overview of Primary Headache Disorders**
  - Epidemiology, impact on disability and quality of life, societal impact, economical burden
  - Headache screening and useful questions to ask
  - Diagnosis: differentiating between types of headache
  - Types of primary headache disorders (e.g., CM, EM, CCH, ECH)
  - Excluding secondary causes
- **Initial Treatment Considerations**
  - Case study
  - The headache treatment map
    - Lifestyle, biobehavioral, pharmacologic, neuromodulation, complementary/integrative
  - When to refer
  - Improving communication
- **Q/A**
- **A New Era in Targeting the Underlying Pathology of Migraine and Cluster Headache**
  - Types of treatment/prevention
  - Guidelines
  - Traditional therapies
  - Role of CGRP and the 5HT1F serotonin receptor in the pathophysiology of primary headache disorders (e.g., migraine and CH)
  - Clinical profiles of CGRP mAbs and 5HT1F serotonin receptor agonists headache management
  - Ongoing clinical trials
- **Conclusions and Q/A**

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Disclosures

- **Dr. Buse** is a consultant for Allergan, Amgen, Biohaven, Dr. Reddy's/ Promeius, Lilly, and Teva.
- **Dr. Charles** is a consultant for Alder, Amgen, Biohaven, Eli Lilly, and eNeura. He has conducted research for Takeda Pharmaceuticals.
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Learning Objectives

- 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

Headache Impact

Dawn C. Buse, PhD

Migraine Prevalence

One in five US adults has migraine

Sex	Race	Risk factors for migraine
9.7% of males	American Indian or Alaska Native: 18.4%	People who are unemployed: 21.4%
20.7% of females	Black or African American: 16.2%	Annual family income < $35,000: 19.9%
	White: 15.4%	Ages 18-44: 17.9%
	Asian: 11.3%	Elderly or disabled: 16.4%

Saguil A, Lax JW. *Am Fam Physician.* 2014;89:742-744. Burch R, et al. *Headache.* 2018;58(4):496-505.

Migraine Impact and Disability

Migraine is the 2nd leading cause of years lived with disability (YLD) worldwide[1*]

- Across all ages and sexes
- #1 cause of YLDs in people aged 15-49

Migraine can negatively impact virtually all important aspects of life:[2,3]

- Work, school, family, financial, personal, identify, social, etc
- Patient, family, community, colleagues, employers and society

Global Burden of Disease study (2016)

- #1 Back pain
- # 2 Migraine
- #3 Age-related hearing loss
- #4 Iron-deficiency anemia
- #5 Major depression

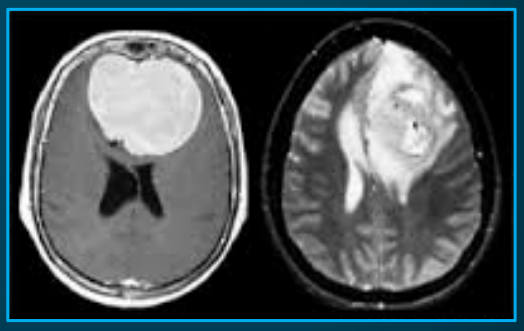
*YLD represents number of years of healthy life lost as a result of disability caused by the non-fatal experience of disease or injury in a population.

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2017;390:1211-1259. 2. Buse D, et al. *Mayo Clin Proc.* 2016;91:596-611. 3. Lampl C, et al. *J Headache Pain*. 2016;17:9.

Diagnosis

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.

ICHD-3 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. https://ichd-3.org/.

Cluster Headache Diagnostic Criteria

At least 5 attacks fulfilling these criteria:

- **Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 min** (when untreated)
- Either 1 or both of the following:

  1. At least 1 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

IHS Classification ICHD-3. https://ichd-3.org/.

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.

Chronic Migraine

ICHD-3 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. IHS Classification - ICHD-3. https://ichd-3.org/1-migraine/1-3-chronic-migraine/. 2. OnabotulinumtoxinA [Botox®] prescribing information (www.allergan.com/assets/pdf/botox_pi.pdf). Accessed 10-30-17.

Migraine Attack: Phases

Menu

YOU ARE HERE

Phases | Characteristics | Diagnosis criteria | Menstrual-related

Prodrome	Aura	Headache phase	Postdrome	Interictal phase
Yawning Polyuria Diarrhea Fatigue Depression Neck pain Photophobia Nausea	CLICK TO LEARN MORE ABOUT Aura	Nausea Vomiting Light/smell/sound sensitivity Neck pain/stiffness	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	

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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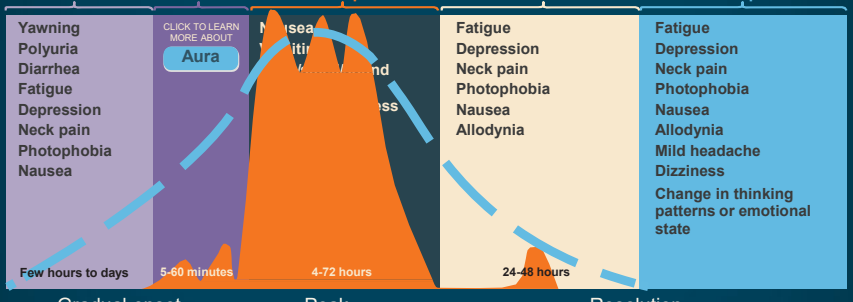

Gradual onset | Peak | Resolution

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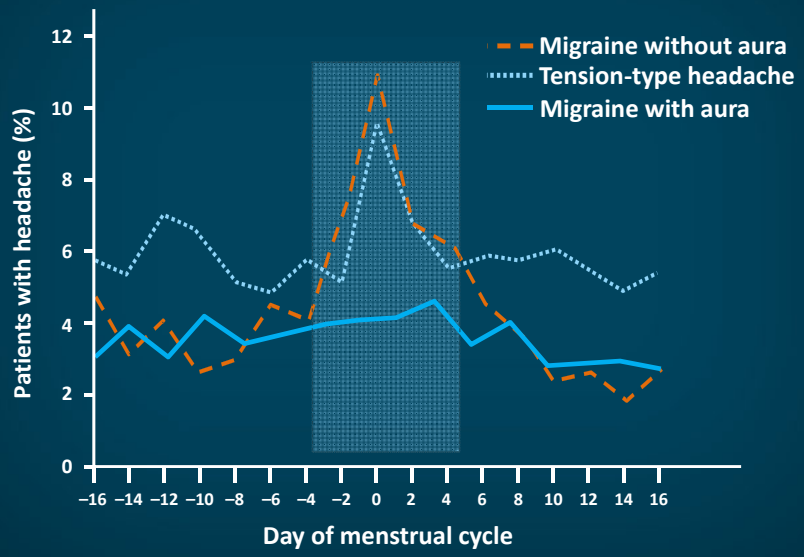
Migraine With Aura

Headache preceded by ≥1 neurologic symptom

ICHD, 3rd edition. https://ichd-3.org/. Kesari S. *Arch Neurol.* 2004;61:1464-1465.

Menstrual-Related Migraine



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

Chronic Migraine

- Episodic migraine (EM) occurs in 12% of the population, CM in 1%[1,2]
- CM evolves as a complication of EM (2.5%/year) and is much more disabling[1,3]
- Risk factors for development of CM include:[4]
  - Headache features (attack frequency, cutaneous allodynia)
  - Headache-related disability
  - Comorbidities (anxiety, depression, obesity)
  - Iatrogenic factors (medication type and frequency of use)

1. Lipton RB, et al. *Neurology*. 2007;68(5):343-9. 2. Buse DC, et al. *Headache*. 2012;52(10);1456-70. 3. Bigal ME, et al. *Curr Opin Neurol*. 2009;22(3):269-76. 4. Buse DC, et al. *Headache*. 2019;59(3):306-38.

Headache Tool 1 (Patient Symptoms)

Note: a link to the following tool is located in the interactive resources folder so you can explore further.

Headache Type: Decision Tool Part 1

Menu

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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Headache Type: Decision Tool Part 1

Menu

HELP How to Use

Meet the Faculty

Decision Aid: Pt. 1

Migraine Headache

ETTH

Decision Aid: Pt. 2

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

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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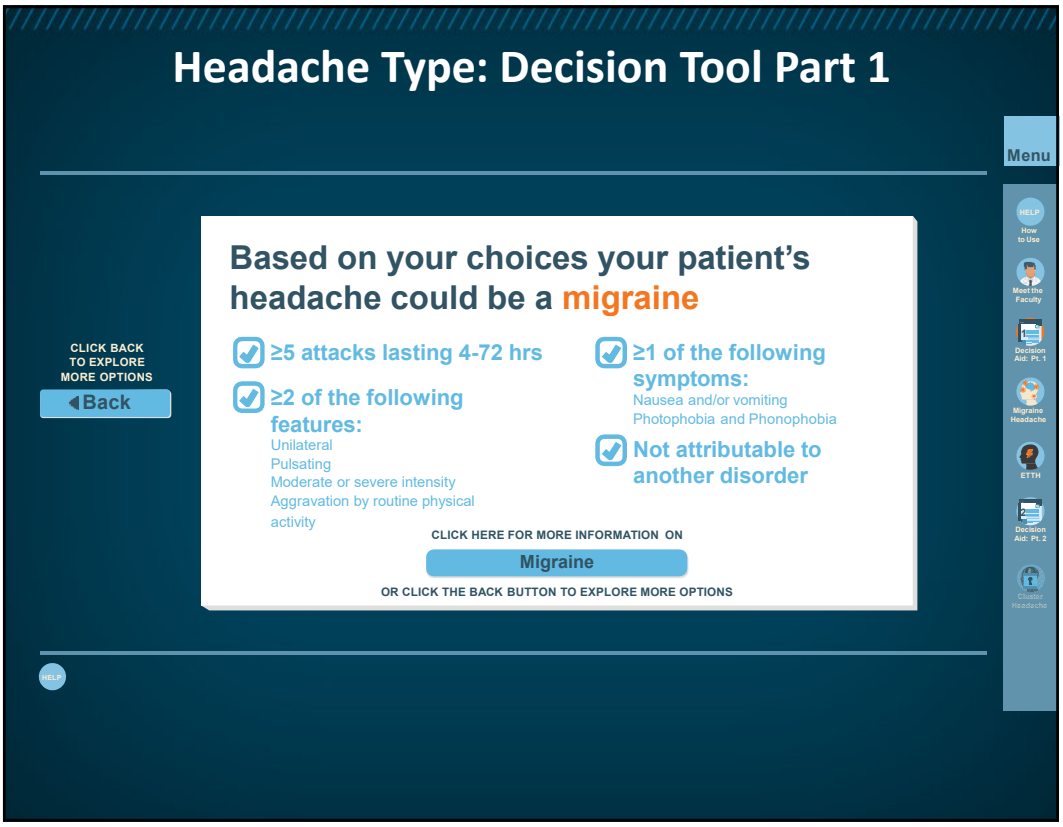
CLICK HERE TO Reset

PLEASE CLICK TO Submit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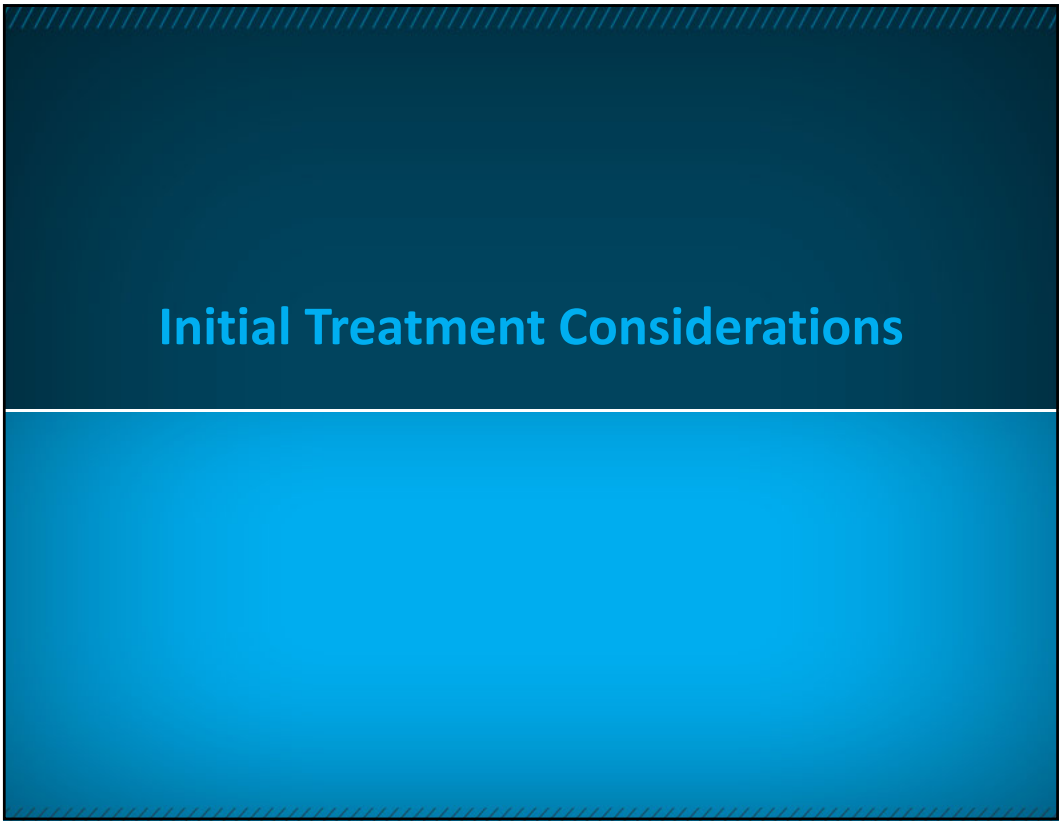
Cluster Headache
CLICK BACK TO EXPLORE MORE OPTIONS
Back
Based on your choices your patient's headache could be a migraine
≥5 attacks lasting 4-72 hrs
≥2 of the following features:
Unilateral
Pulsating
Moderate or severe intensity
Aggravation by routine physical activity
≥1 of the following symptoms:
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


Initial Treatment Considerations

Headache Tool 2
(Patient Case)

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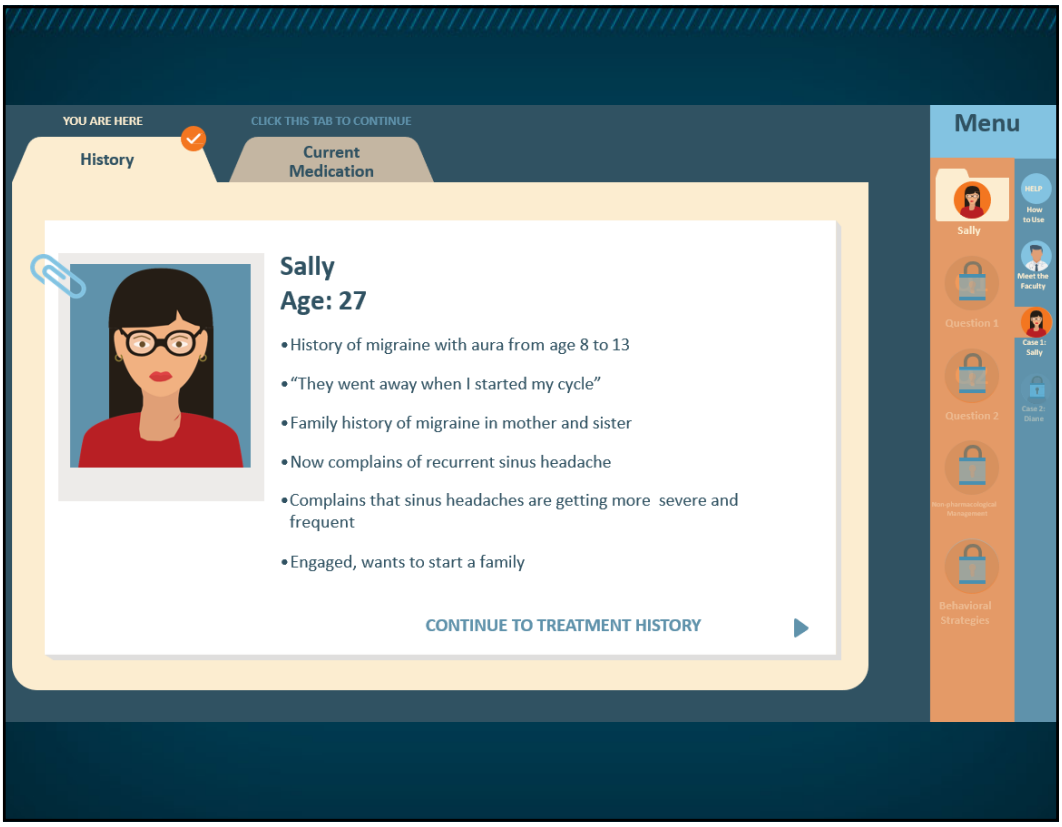
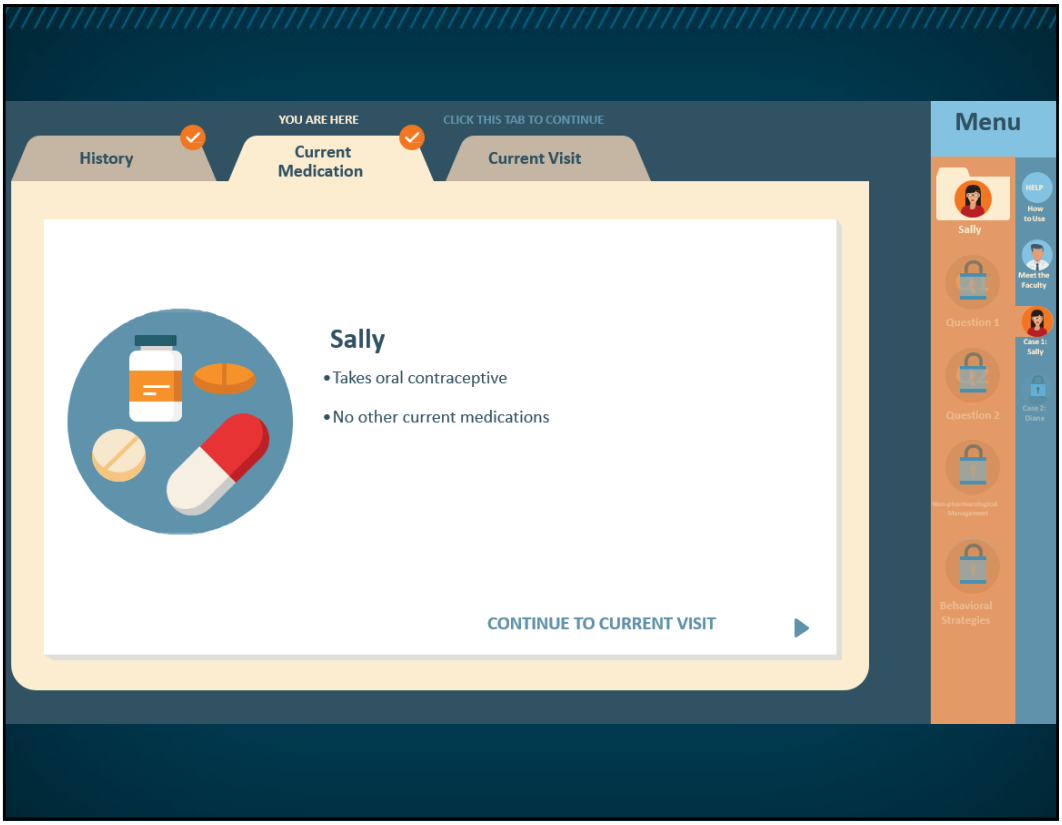
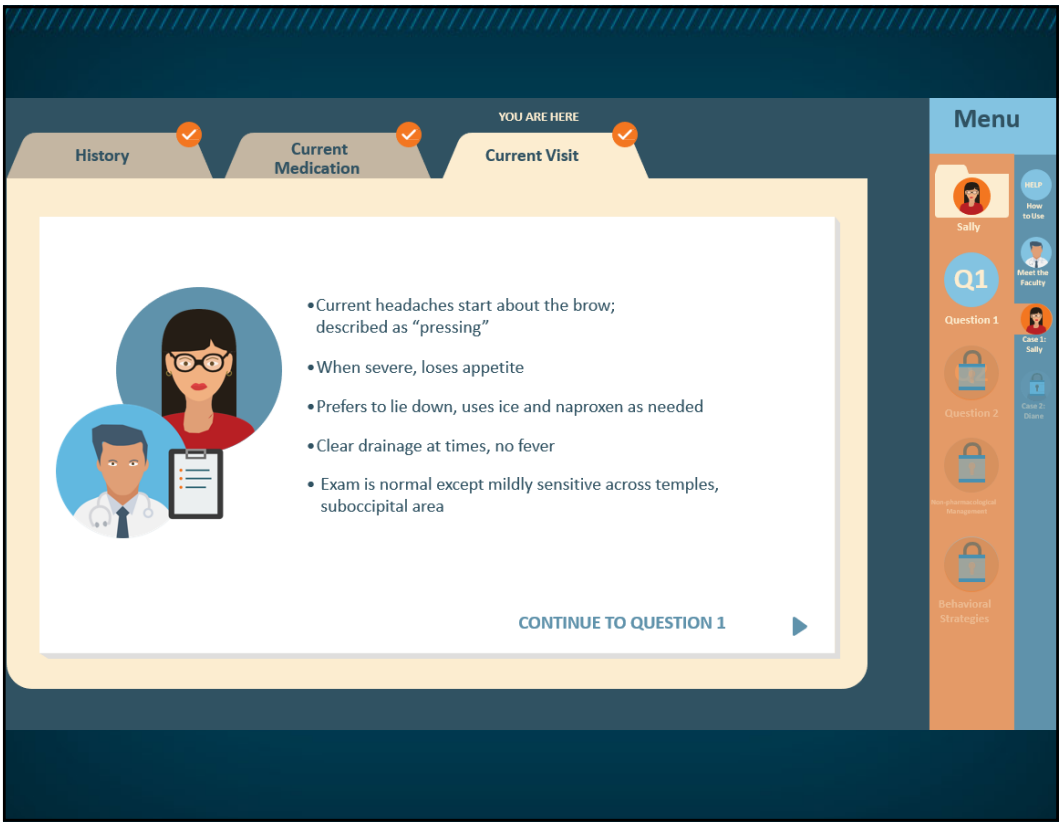
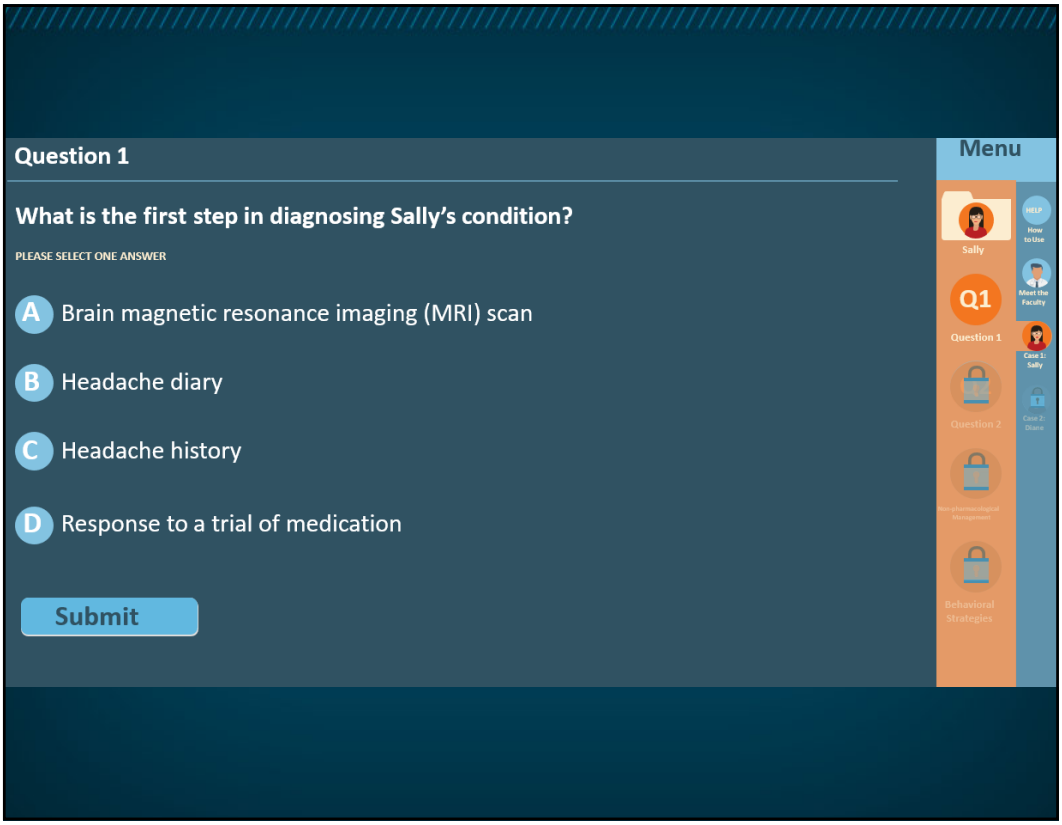
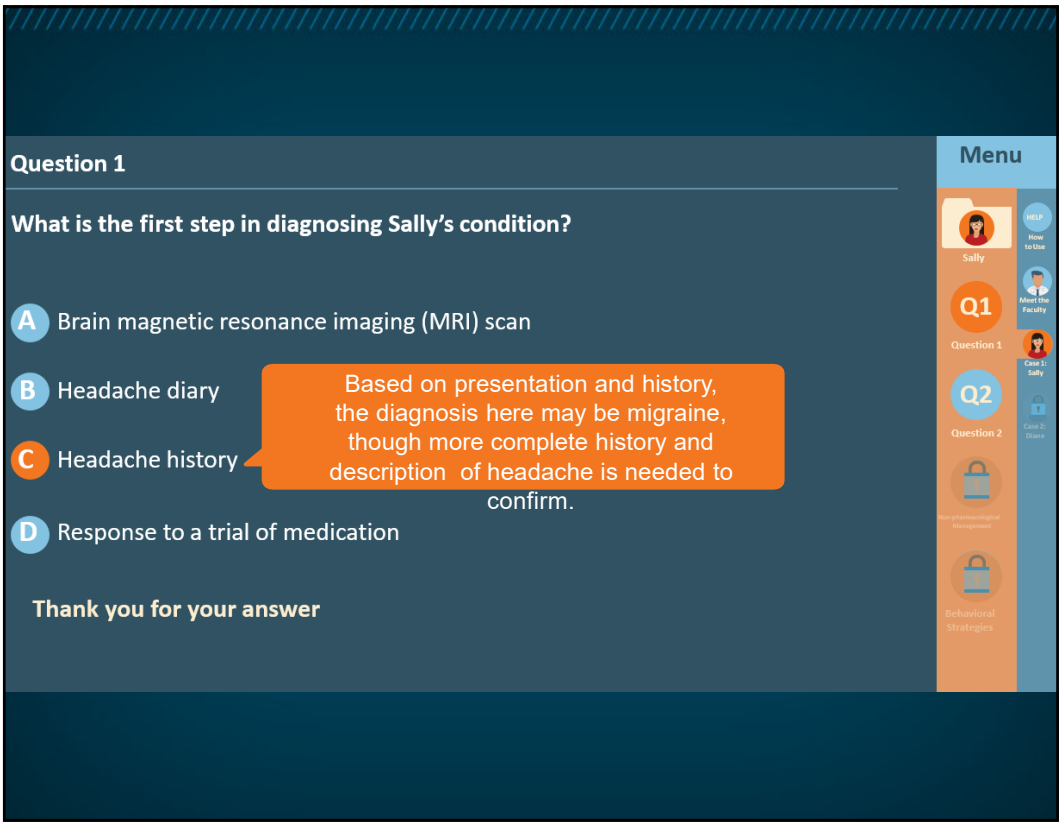
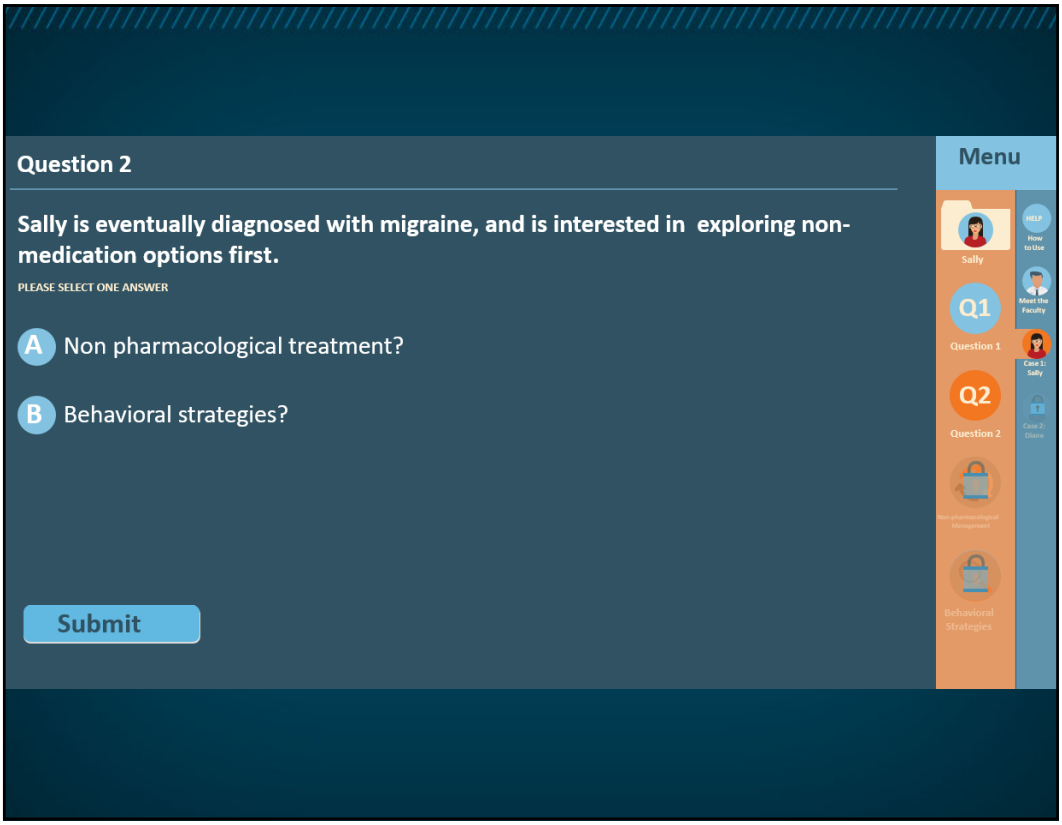

YOU ARE HERE
CLICK THIS TAB TO CONTINUE
History
Current Medication
Menu
Sally
Age: 27
•History of migraine with aura from age 8 to 13
•"They went away when I started my cycle"
•Family history of migraine in mother and sister
•Now complains of recurrent sinus headache
•Complains that sinus headaches are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


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


YOU ARE HERE
History
Current Medication
Current Visit
Menu
Sally
Q1
Question 1
Question 2
Behavioral Strategies
•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


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


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 may be migraine, though 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


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

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

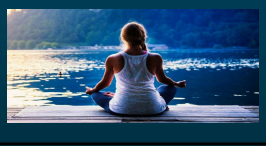
The Headache Treatment Map

Education & Lifestyle

Behavioral

Pharmacologic

Neuromodulation



Complementary & Integrative

Lifestyle (Headache Hygiene) & Education

SLEEP

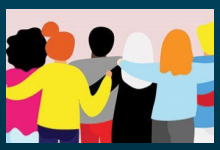
EXERCISE

EATING

HYDRATION

STRESS MANAGEMENT

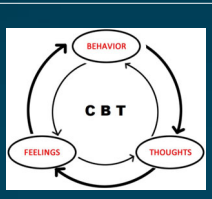
SOCIAL SUPPORT



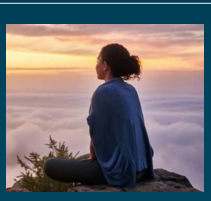
EDUCATION

Biobehavioral Therapies

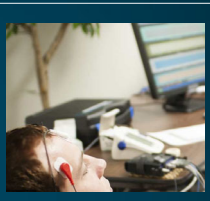
Grade A Evidence



Cognitive Behavioral Therapy

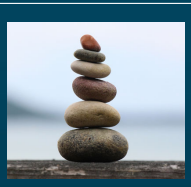


Relaxation Training

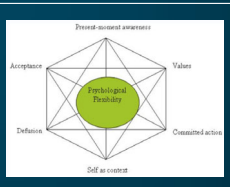


Biofeedback

Emerging Techniques



Mindfulness Based Therapies (MBCT, MBSR)



Acceptance & Commitment Therapy (ACT)

MBCT: Mindfulness-based cognitive therapy; MBSR: Mindfulness-based stress reduction

Pharmacologic Treatments

Acute	Preventive	Interventional
NSAIDs Triptans Ditans Ergotamines Gepants	CGRP-targeted mAbs Beta-blockers Calcium-channel blockers Antidepressants Anticonvulsants OnabotulinumtoxinA	Trigger points Nerve blocks Other therapies

NSAID = nonsteroidal antiinflammatory drug; CGRP = calcitonin gene-related peptide; mAb = monoclonal antibody.

Neuromodulation

sTMS mini™

gammaCore®

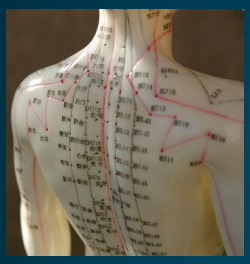
Relivion®

Approved in Europe

Nerivio™

Cefaly®

Complementary and Integrative Medicine



Acupuncture

Nutritional Supplements

Yoga

Light Therapy
Therapeutic glasses Green Light

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/

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

Questions and Answers

Headache Treatment

Andrew Charles, MD

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

Headache Treatment
(continued)

- Effective management depends on:
  - Making an accurate diagnosis
  - Addressing headache impact
  - Engaging patients 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, and duration of migraine attacks and associated disability
  - For both types of treatment: minimal adverse effects, eg, dizziness, cognitive dysfunction, weight change, etc.

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.

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

AE = adverse effect/event.

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

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.

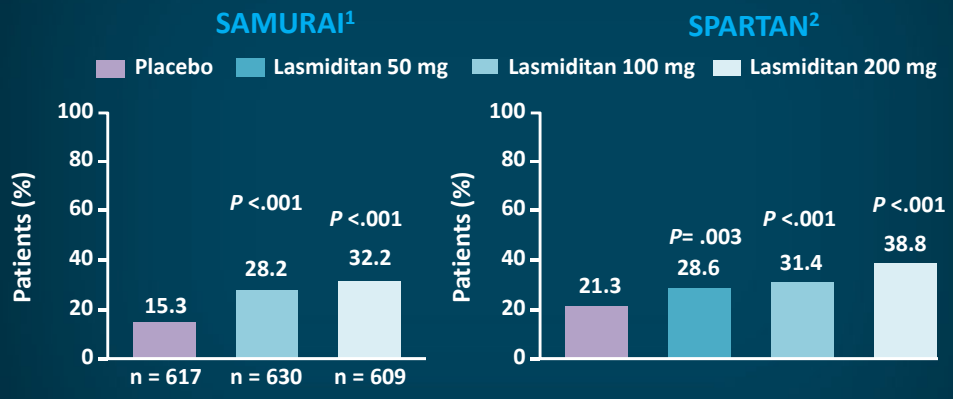
Recently Approved Acute Therapies

- 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

Lasmiditan

SAMURAI and SPARTAN Phase 3 Studies

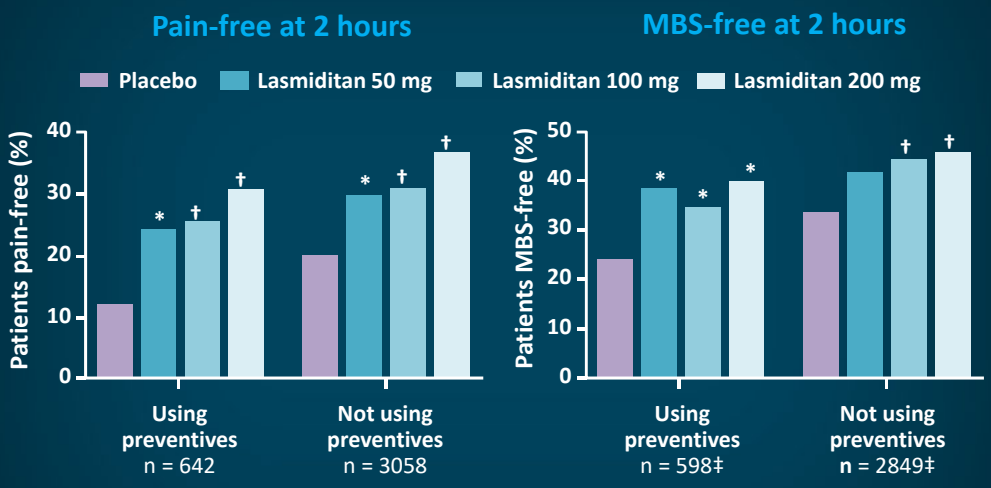
Primary endpoint: proportion of patients free from pain at 2 hours post-dose



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

1. Kuca B, et al. *Neurology.* 2018;91:e2222-e2232. 2. Goadsby PJ, et al. *Brain.* 2019;142:1894-1904.

Lasmiditan: Pain-Free and MBS-Free at 2 Hours



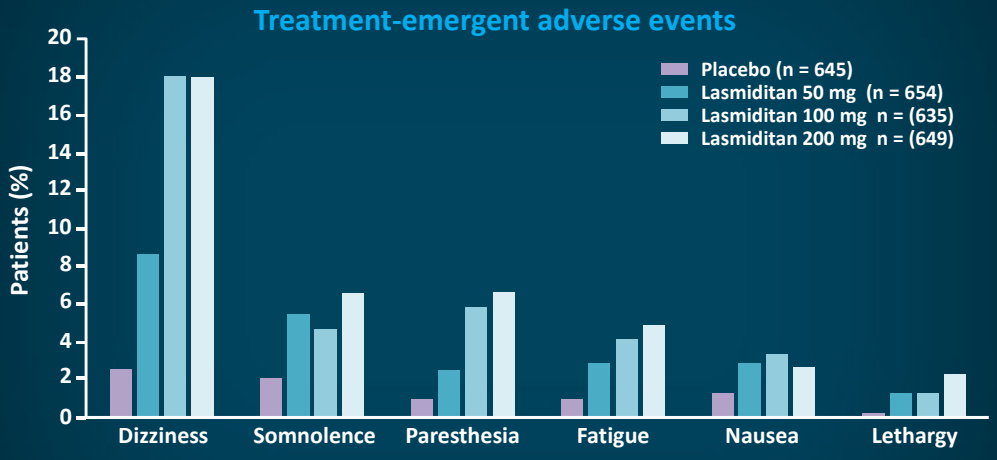
*P <.05; †P <.001 compared to placebo; ‡Number of patients reporting MBS-free outcomes was lower than for pain-free outcome because not all patients reported a most bothersome symptom at baseline.

MBS = most bothersome symptom.

Loo LS, et al. *J Headache Pain.* 2019;20:84.

Lasmiditan in Acute Treatment of Migraine

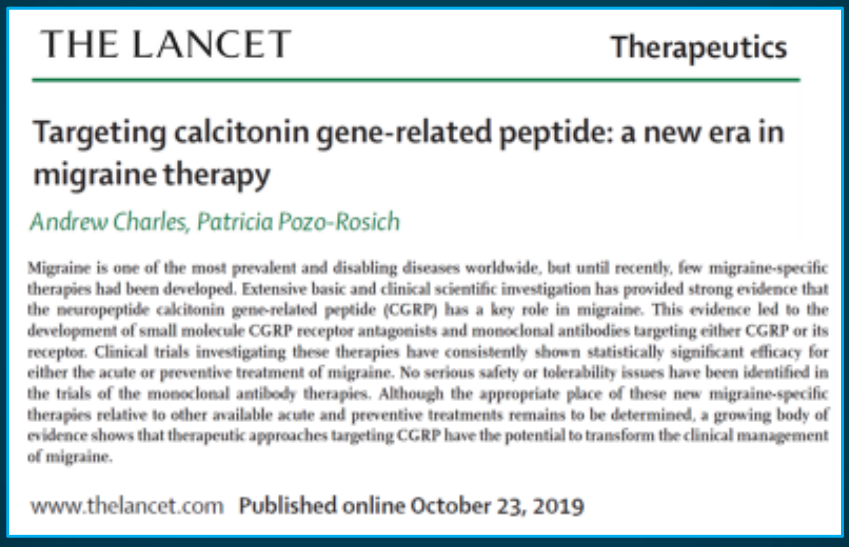
SPARTAN Results—Safety and Tolerability



- **Serious AEs:** 5, with 2 considered treatment related (dystonic reaction and presyncope)
- **Discontinuation on treatment:** 1 on lasmiditan 200 mg (fatigue and dizziness)
- **Tests: n**o laboratory or electrocardiogram differences

Goadsby PJ, et al. *Brain.* 2019;142:1894-1904.

A New Era in Migraine Therapy…



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**

Charles A, Pozo-Rosich P. *Lancet*. 2019;394:1765-1774.

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 (ie, gepants) effectively abort migraine attacks
- Anti-CGRP and anti-CGRP-receptor monoclonal antibodies prevent episodic migraine and chronic migraine

Adapted from AHS Comprehensive Migraine Education Program (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

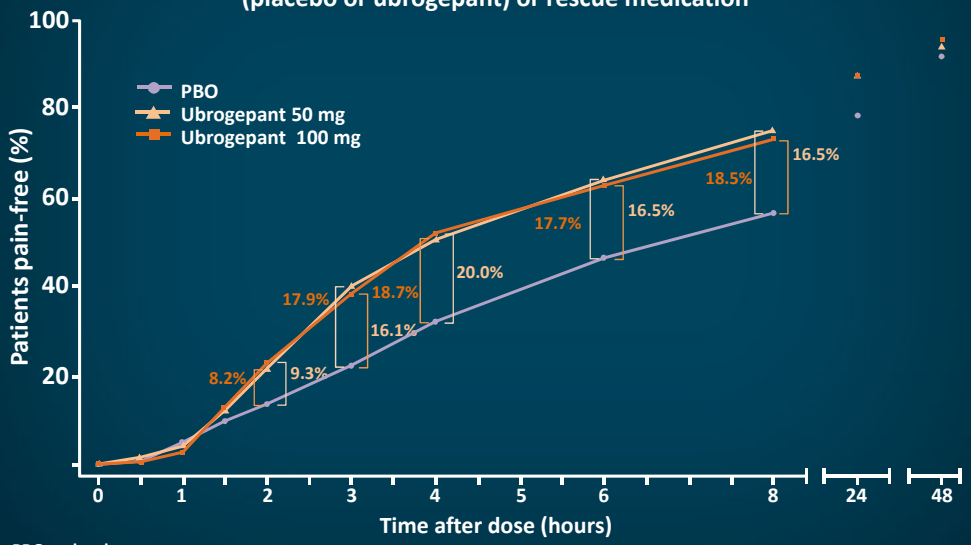
- **Acute treatment of migraine**
  - **Olcegepant** (IV) worked; comparable to triptans: proof of concept[1]
  - **BI 44370 TA** (oral): effective vs placebo in phase 2[2]
  - **Telcagepant** showed promise and efficacy comparable with triptans, but development stopped due to liver toxicity in phase 3[3]
  - **MK3207**: effective and well tolerated in phase 2 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

IV = intravenous; MRM = menstrual related migraine.

ACHIEVE I: Ubrogepant

Freedom from Headache Pain

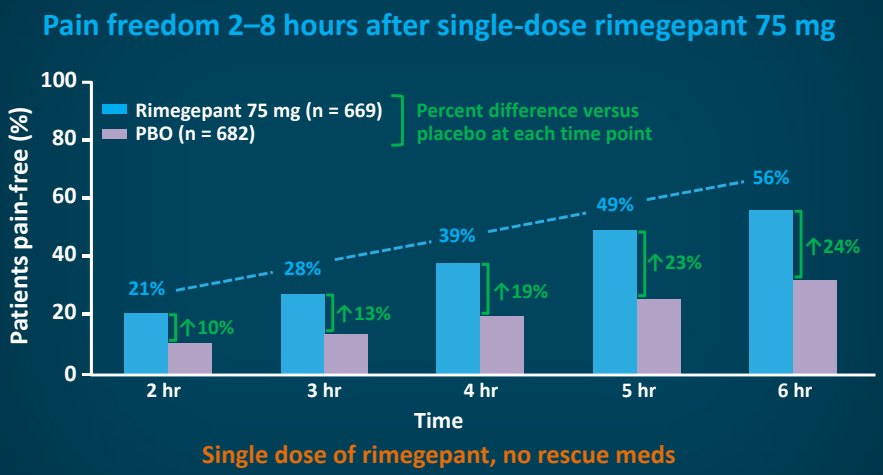
Includes data collected after the use of optional second dose of study medication (placebo or ubrogepant) or rescue medication



PBO = placebo.

Dodick DW, et al. *N Engl J Med.* 2019;381:2230-2241.

Increasing Benefit in Pain Freedom Over Time After Single Dose of Rimegepant 75 mg ODT*

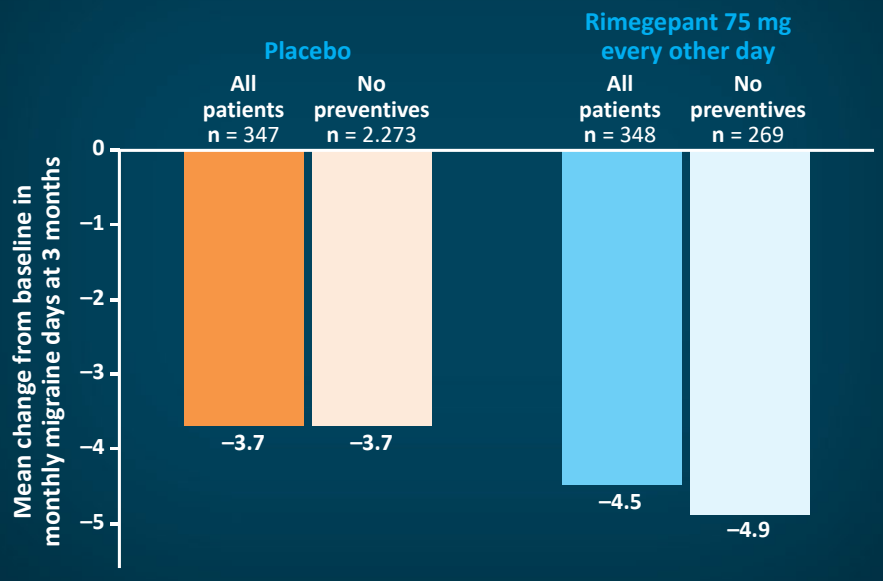


Estimates computed using the modified intention-to-treat (mITT) population and Cochran-Mantel-Haenszel (CMH) methods. Subjects using rescue medications at or before the assessment and those not providing data, are classified as failures.

ODT = orally disintegrating tablet. *Zydis® ODT formulation.

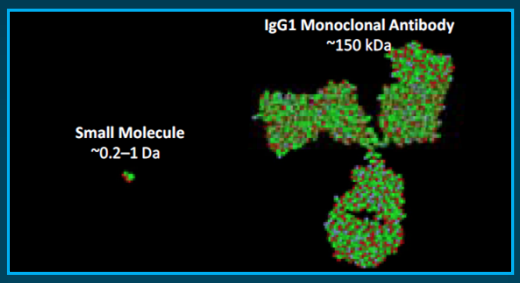
Croop R, et al. *Lancet.* 2019;394:737-745.

Rimegepant Met Primary Endpoint of Reduction in Monthly Migraine Days



Practical Neurol. 3/30/2020. (https://practicalneurology.com/news/rimegepant-reduced-migraine-frequency-in-clinical-trial). Accessed 6/19/2020.

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

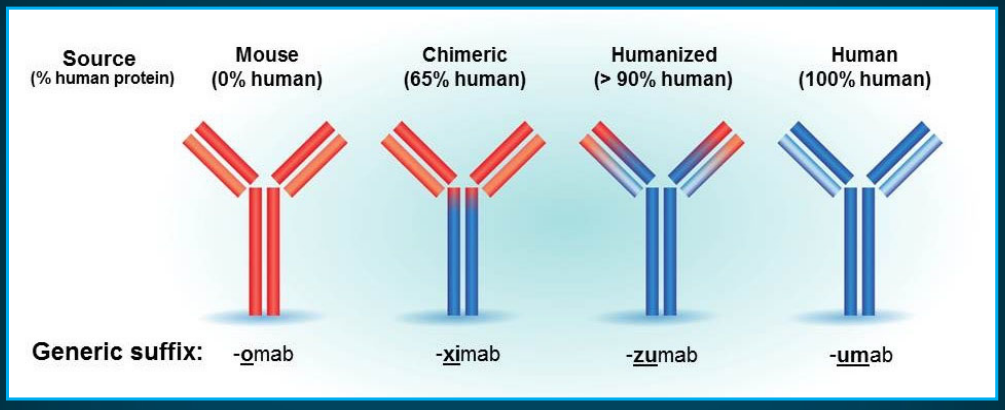


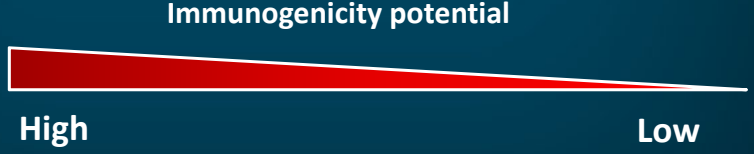
Small molecules	Monoclonal antibodies
Target specificity lower	Target specificity high
Clearance (liver, kidney)	Clearance RES
Size <1 kD	Size ~150 kD
Oral	Parenteral
Can cross BBB	Do not cross BBB
Half-life = minutes to hours	Half-life = 3–6 weeks
Immunogenicity (no)	Immunogenicity (yes)

RES = reticuloendothelial system; BBB = blood-brain barrier.

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

Naming Conventions For Therapeutic mAbs





World Health Organization (WHO) Monoclonal antibodies 2009 (www.who.int/medicines/services/inn/generalpoliciesmonoclonalantibodiesjan10.pdf). Silberstein S, et al. *Headache*. 2015;55:1171-1182.

Four Injectable Monoclonal Antibodies to CGRP or Its Receptor

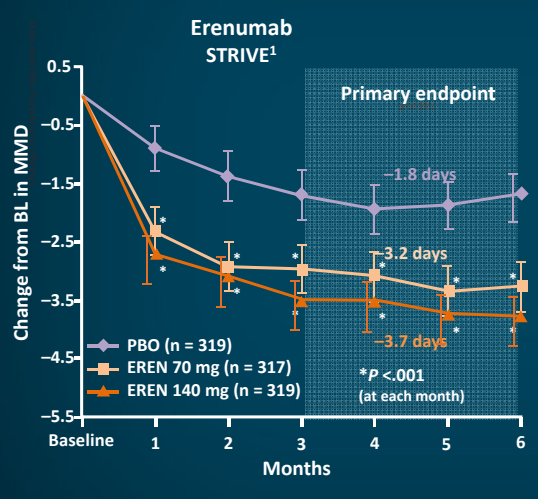
	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab
Studied for	EM, CM	EM, CM, eCH, cCH	EM, CM, eCH, cCH	EM, CM
Dosing	Monthly SC	Monthly or Q3 month SC; IV load for CH	Monthly SC	Q3 month IV
AB Type	Fully human	Humanized	Humanized	Humanized
Target	CGRP receptor	CGRP peptide or ligand	CGRP peptide or ligand	CGRP peptide or ligand
Indication(s)	**Migraine prevention**	**Migraine prevention**	**Migraine prevention, Cluster headache**	**Migraine prevention**

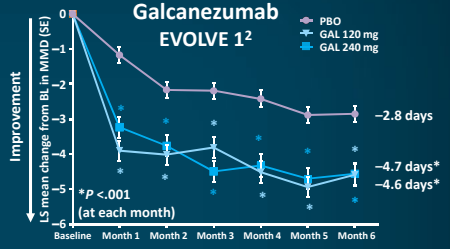
eCH = episodic cluster headache; cCH = chronic cluster headache.

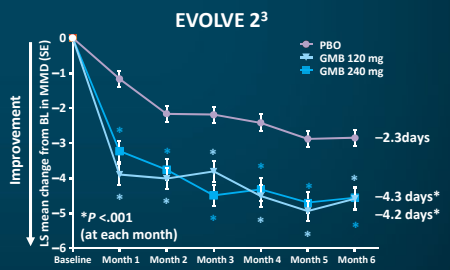
Phase 3 Trials: 6-Month EM Prevention

Erenumab (EREN) and Galcanezumab (GAL) Efficacy

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







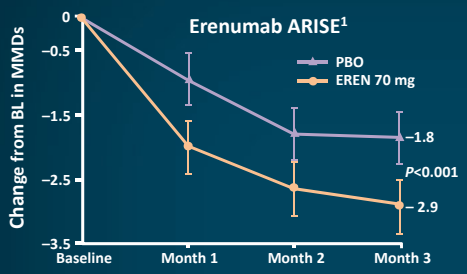
BL = baseline; LS = least squares; SE = standard error.

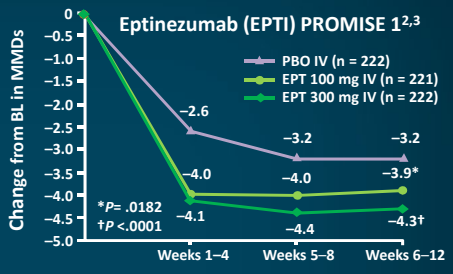
1. Goadsby PJ, et al. *N Engl J Med.* 2017;377:2123-2132. 2. Stauffer VL, et al. *JAMA Neurol.* 2018;75:1080-1088. 3. Skljarevski V, et al. *Cephalagia.* 2018;38:1442-1454.

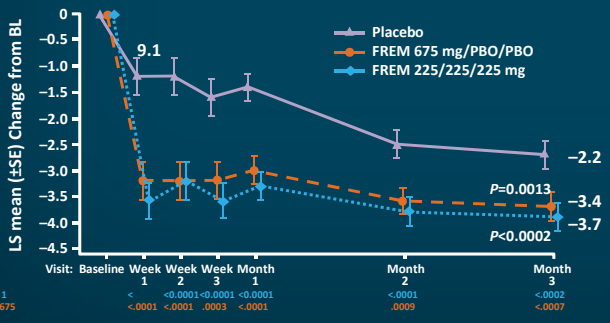
Phase 3 Trials: 3-Month EM Prevention

Erenumab, Fremanezumab (FREM), and Eptinezumab (EPT) Efficacy

Primary endpoint: reduction of MMDs







Fremanezumab HALO EM[4,5]

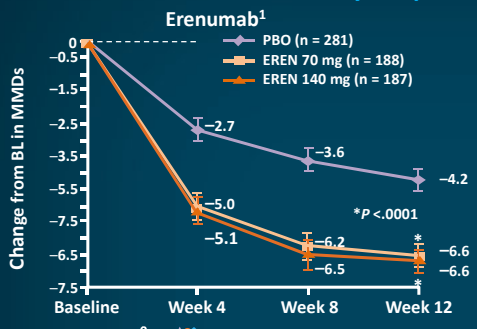
Equally effective whether administered subcutaneously monthly or quarterly

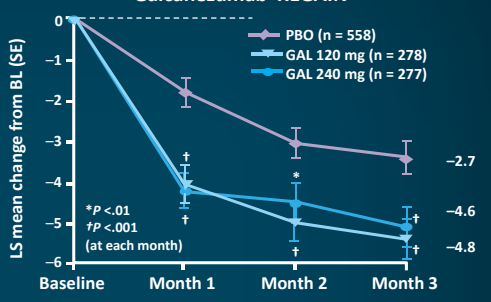
1. Ashina M, et al. *Neurology.* 2017;89:1237-1243. 2. Saper J ,et al. *Cephalagia.* 2017;37(1 suppl):337 (abstr PO-01-194). 3. Ashina M, et al. *Cephalagia.* 2020;40:241-254. 4. Bigal M, et al. *Cephalagia.* 2017;37(1 suppl):106 (abstr PO-01-082). 5. Dodick DW, et al. *JAMA.* 2018;319:1999-2008.

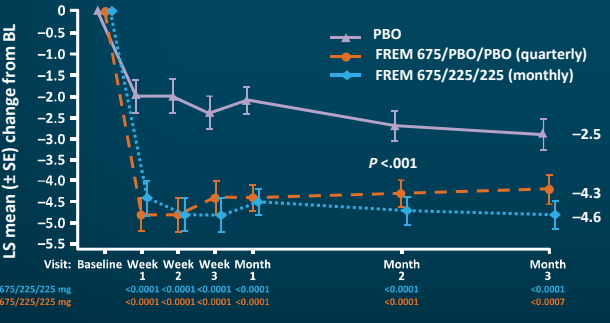
Pivotal or Phase 3 CM Trials

Erenumab, Galcanezumab, and Fremanezumab Efficacy

Primary endpoint: reduction in MMDs





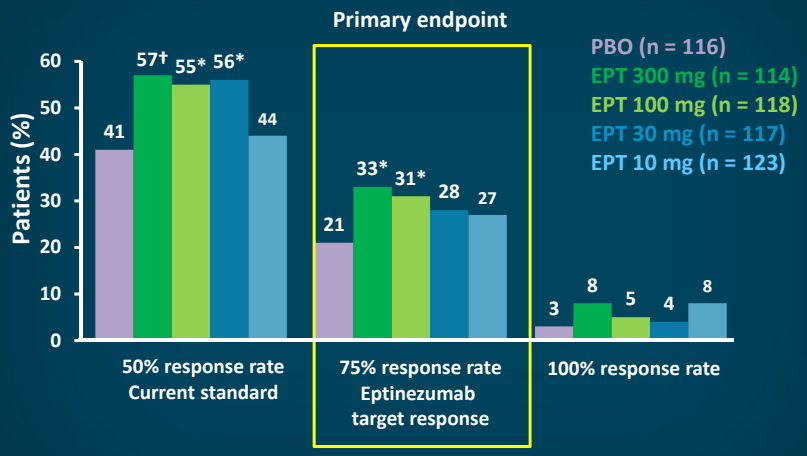


Fremanezumab HALO CM[3]

Equally effective whether administered subcutaneously monthly or quarterly

1. Tepper S, et al. *Lancet Neurol.* 2017;16:425-434. 2. Detke HC, et al. *Neurology.* 2018;91:e2211-e2221. 3. Silberstein SD, et al. *N Engl J Med.* 2017;377:2113-2122.

Eptinezumab Phase 2 CM Prevention



*P <.05; †P <.005 vs placebo (one-sided, not corrected for multiplicity)

Dodick DW, et al. *Cephalagia*. 2019;39:1075-1085. Smith J, et al. *Headache*. 2017;57 (suppl 3): 130 (IOR06).

Trial of Galcanezumab in Prevention of Episodic Cluster Headache

End Point	Placebo (N=57)	Galcanezumab (N=49)	P Value
Change in Weekly Frequency of Cluster Headache *(least-squares mean; wks 1-3)*	-5.2 ± 1.4	-8.7 ± 1.4	0.04
% Response at Wk 3	53%	71%	0.046

Goadsby PJ, et al. *NEJM*. 2019;381:132-41.

Safety and Tolerability of mABs

- In phase 2 and 3 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

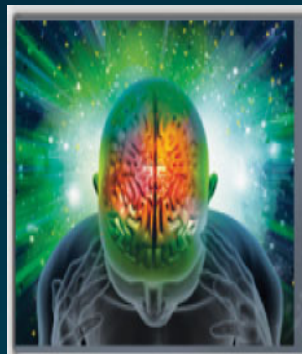
Clinical Utility of the 4 mAbs

- 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 galcanezumab EM registration studies[2,3] and eptinezumab phase 2 CM studies,[4] ≥75% responder rates were ≥33%
- All 4 mAbs work in CM prevention with medication overuse and without (pre-specified secondary analyses)[4-7]
- Erenumab (140 mg) worked better in patients who had failed ≥2 preventive meds vs none, odds ratio 4.2 vs 1.3 (pre-specified secondary analysis)[8]

Tepper S, et al. *Lancet Neurol.* 2017;16:425-434. 2. Stauffer VL, et al. *JAMA Neurol.* 2018;75:1080-1088. 3. Skljarevski V, et al. *Cephalagia.* 2018;38:1442-1454. 4. Dodick DW, et al. *Cephalagia.* 2019;39:1075-1085. 5. Tepper S, et al. *Lancet Neurol.* 2017;16:425-434. 6. Detke HC, et al. *Neurology.* 2018;91:e2211-e2221. 7. Silberstein SD, et al. *N Engl J Med.* 2017;377:2113-2122. 8. Ashina M, et al. *Cephalagia.* 2018;38:1611-1621.

Conclusions: Reasons for Optimism

- 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



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

Extra Resources

- Click here for the Interactive Decision Tree
- Click here for the Interactive Headache Cases
- Click here for the Migraine Advances Website

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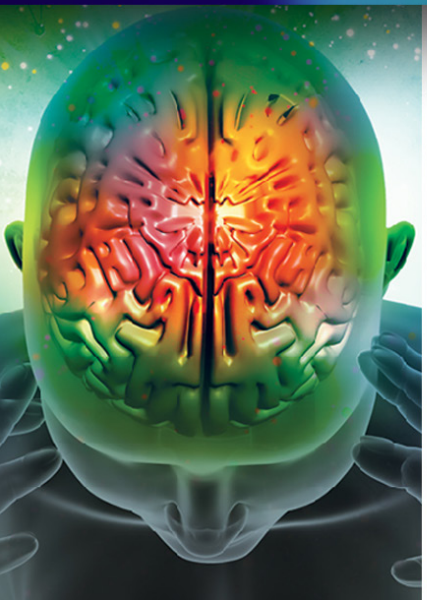

Diagnosing and Managing Primary Headache Disorders in the Primary Care Setting: Challenges and Opportunities

Please visit

HTTPS://MIGRAINE.POSTERPROGRAM.COM/

Toolkit

Additional Reading

Resource	Address
Ahmed F. Headache disorders: differentiating and managing the common subtypes. *Br J Pain*. 2012;6(3):124–32.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4590146/
Bakar N, et al. Quality of life in primary headache disorders: A review. *Cephalalgia*. 2016;36(1):67-91.	https://pubmed.ncbi.nlm.nih.gov/25888584/
Berk T. Diagnosis and treatment of primary headache disorders in older adults. *J Am Geriatr Soc*. 2018;66(12):2408-16.	https://pubmed.ncbi.nlm.nih.gov/30251385/
Brandt R, et al. Pharmacotherapy for cluster headache. *CNS Drugs*. 2020;34(2):171–84.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7018790/
Burstein R, et al. Migraine: Multiple processes, complex pathophysiology. *J Neurosci*. 2015;35(17):6619–29.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4412887/
Ceriani CE, et al. Novel medications for the treatment of migraine. *Headache*. 2019;59:1597-1608.	https://pubmed.ncbi.nlm.nih.gov/31559638/
Buse D, et al. Life with migraine: Effects on relationships, career, and finances from the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache*. 2019;59:1286-99.	https://pubmed.ncbi.nlm.nih.gov/31407321/
Doesborg P. Cluster headache: new targets and options for treatment. *F1000Res*. 2018;7:339.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5861507/
Goadsby P, et al. Primary headache disorders: Five new things. *Neurol Clin Pract*. 2019;9(3):233-40.	https://pubmed.ncbi.nlm.nih.gov/31341711/
Gooriah R, et al. Evidence-based treatments for cluster headache. *Ther Clin Risk Manag*. 2015;11:1687–96.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4646474/
Ha H, et al. Migraine headache prophylaxis. *Am Fam Physician*. 2019;99(1):17-24.	https://pubmed.ncbi.nlm.nih.gov/30600979/
Jensen R, et al. Tension-type headache - the normal and most prevalent headache. *Headache*. 2018;58:339-45.	https://pubmed.ncbi.nlm.nih.gov/28295304/
Ljubisavljevic S, et al. Cluster headache: Pathophysiology, diagnosis and treatment. *J Neurol*. 2019;266(5):1059-66.	https://pubmed.ncbi.nlm.nih.gov/30120560/
Peters GL, et al. Migraine overview and summary of current and emerging treatment options. *Am J Manag Care*. 2019;25:S23-S34.	https://pubmed.ncbi.nlm.nih.gov/30681821/
Sohn J, et al. Clinical features of probable cluster headache: A prospective, cross-sectional multicenter study. *Front Neurol*. 2018;9:908.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6212551/
Terwindt GM, et al. Emerging treatments for headache: Advances in 2019. *Lancet Neurol*. 2020 Jan;19(1):7-8.	https://pubmed.ncbi.nlm.nih.gov/31839249/
Weatherall M, et al. The diagnosis and treatment of chronic migraine. *Ther Adv Chronic Dis*. 2015;6:115–23.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4416971/

Resources and Societies

Resource	Address
American Headache Society	https://americanheadachesociety.org/
American Migraine Foundation	https://americanmigrainefoundation.org/
International Headache Society Classification; ICHD-3	https://ichd-3.org/
International Headache Society	https://www.ihs-headache.org/
Migraine Research Foundation	https://migraineresearchfoundation.org/
National Headache Foundation	https://headaches.org/
National Institute of Neurological Disorders and Stroke	https://www.ninds.nih.gov/Disorders/All-Disorders/Headache-Information-Page