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Disclosures

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

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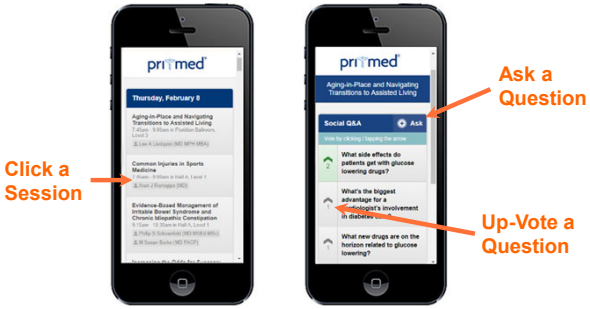

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INTRODUCTION AND PRETEST QUESTIONS

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Lankenau Medical Center
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Syllabi/slides for this program are a supplement to the live CME session and are not intended for other purposes.

Learning Objectives

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

6

CASES IN EPISODIC AND CHRONIC MIGRAINE

7

MARIA

33 YEARS OLD

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

MARIA'S STORY

WHAT DO YOU DO NEXT?

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Basics of the History and Physical Exam: Headache Screening

INQUIRE ABOUT	Timing/ frequency	Exacerbating factors/triggers • What medications have been tried • Use/overuse of medications	Location	Intensity	Nature of pain	Associated symptoms • Visual, motor, sensory, GI
EVALUATE	Patient walking, body language	Assess symmetry of CN, motor, sensory, coordination, DTRs	Palpate head, arteries, trigger points	Examine neck for stiffness and ROM	Perform fundoscopic exam	Examine oral cavity/ TMJ

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

Institute for Clinical Systems Improvement. Diagnosis and Treatment of Headache. 2009; Updated January 2013.

ID Migraine™—A VALIDATED SCREENER

Closing the HA Diagnosis Gap

Choose **Yes** or **No**

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

2/3 Yes
FOR MIGRAINE
Sensitivity: **0.81**
Specificity: **0.75**

→ Positive predictive value of **93%** in primary care setting

HA=headache.

Lipton RB, et al. *Neurology*. 2003;61:375-382.

Pitfalls in Diagnosis

Neck and Sinus Pain During Migraine[1]

75% of patients with migraine experience neck pain

Migraine Misdiagnosis as Sinus Headache[2,3]

- **86-88%** with self-diagnosis of sinus headache actually have ICHD migraine or probable migraine headache[1,3]
- **≤50%** of patients report their headache is influenced by weather
- **≥80%** report ≥1 cranial autonomic symptom
  - 63% nasal congestion
  - 40% rhinorrhea
  - 38% lacrimation

ICHD=International Classification of Headache Disorders.

1. Kaniecki R. *Neurology*. 2002;58(suppl 6):S15-S20. 2. Schreiber CP, et al. *Arch Intern Med*. 2004;164:1769-1772. 3. Barbanti P, et al. *Cephalalgia*. 2002;22:256-259. 4. Eross E, et al. *Headache*. 2007;47:213-224.

Definitions: EM by ICHD Criteria

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

At least 2 of the following:	At least 1 of the following:	No organic disease
• Unilateral • Pulsating • Moderate to severe pain • Aggravated by or avoidance of routine physical activity	• Nausea and/or vomiting • Photo- and phonophobia	

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

At least 1 fully reversible symptom without motor	At least 2 of the following:	1.1 begins with aura or in ≤60 minutes	No organic disease
• Visual + and/or - • Sensory + and/or - • Speech or language dysfunction	• At least 1 aura symptom develops gradually over ≥5 minutes or different symptoms occur in succession over ≥5 minutes • Each symptom lasts ≥5 and ≤60 minutes		

EM=episodic migraine.

International Headache Society. *Cephalalgia*. 2018;38:1-211.

Indications for Diagnostic Testing

Diagnostic testing indicated if ANY red flags are present (SSNOOP)

- **S**ystemic symptoms: fever, weight loss
- **S**econdary risk factors: HIV, cancer
- **N**eurologic symptoms or signs
- **O**nset: new, sudden, abrupt, or split-second
- **O**lder: especially >50 years
- **P**attern change

Diagnostic testing NOT indicated if only green flags present

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

CHOOSING WISELY

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

 Dodick D. *Adv Stud Med*. 2003;3:87-92.

DISCUSSION

How will you treat Maria?

General Approach to Headache Treatment[1,2]

EDUCATION!

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

PREVENTIVE
Taken to reduce attack frequency, severity, and duration

NONPHARMACOLOGIC
(behavioral, neuromodulation, complementary/alternative)

 1. Simpson DM, et al. *Neurology*. 2016;86. 2. Silberstein SD, et al. *Neurology*. 2012;78.

Principles of Management for the Patient[1,2]

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

 1. Simpson DM, et al. *Neurology*. 2016;86. 2. Silberstein SD, et al. *Neurology*. 2012;78.

Behavioral Strategies

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

A headache diary can help identify possible triggers.

Ha H, Gonzalez A. *Am Fam Physician*. 2019;99:17-24.

Acute (Abortive) Migraine Medications[1]

Nonspecific
- NSAIDs
- Combination analgesics
- Neuroleptics/ antiemetics
- Corticosteroids

Specific
- Triptans
- Ergotamine/DHE

New formulations (FDA-approved)
- Breath-powered intranasal sumatriptan dry powder[2]
- New sumatriptan autoinjectors[3]
- Sumatriptan nasal spray with permeation enhancer[4]

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

CHOOSING WISELY

Don't recommend prolonged or frequent use of OTC pain meds for headache.

DHE=dihydroergotamine. HFA= hydrofluoroalkane.

1. Silberstein S. *Expert Opin Pharmacother*. 2012;13:1961-1968. 2. Tepper SJ. *Headache*. 2016;56:817. 3. Landy S, et al. *J Headache Pain*. 2018;19:69. 4. Munjal S, et al. *J Headache Pain*. 2017;18:17. 5. Kuca B, et al. *Neurology*. 2018;91:e2222-e2232.

When to Start Migraine Prevention Therapy[1,2]

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

1. Simpson DM, et al. *Neurology*. 2016;86. 2. Silberstein SD, et al. *Neurology*. 2012;78.

Migraine, Conception, and Pregnancy[1,2]

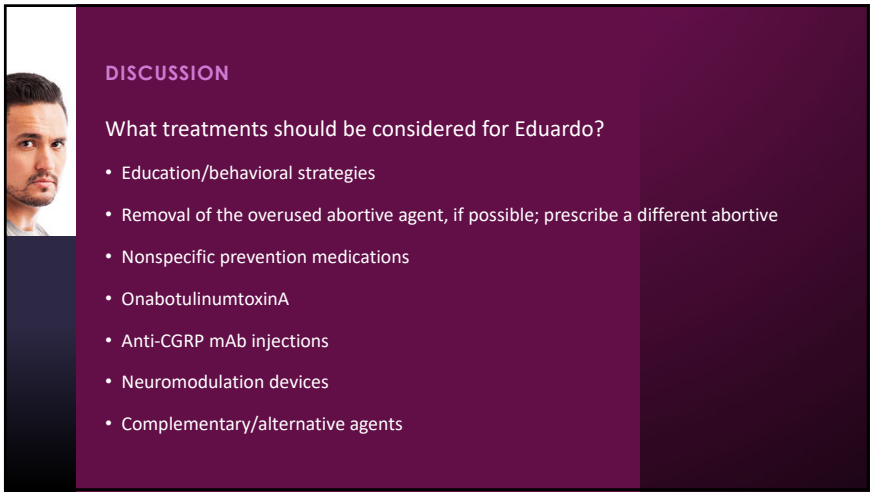
- Best to discuss medication options before conception
- Most patients with migraine note decreased headache frequency after first trimester
- New-onset migraines in pregnancy warrant workup to rule out secondary causes
- Because of their long half-life, consider stopping mAbs 5-6 months before conception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

1. Afridi SK. *Obstet Med*. 2018;11:154-159. 2. American Migraine Foundation. https://americanmigrainefoundation.org/resource-library/pregnancy-lactation-migraine-management/.

Definitions: Chronic Migraine and Medication Overuse Headache

Chronic Migraine	Medication Overuse Headache
Headache ≥15 days/month AND duration ≥4 hours/day for >3 months	Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder
≥8 days/month are migrainous	Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
Not just more episodic migraine	Not better accounted for by another ICHD-3 diagnosis
Evolves as complication of episodic migraine (2.5%/year)	
More disabling with higher costs	
Can be reversed; goal is to revert back to episodic migraine	

1. Natoli JL, et al. *Cephalalgia*. 2010;30:599-609; 2. CDCP. State population projections request at http://wonder.cdc.gov/population-projections.html. Accessed May 20, 2019. 3. Buse DC, et al. *J Neurol Neurosurg Psychiatry*. 2010;81:428-432. 4. Blumenfeld AM, et al. *Cephalalgia*. 2011;31:301-315. 5. http://www.americanheadachesociety.org/assets/1/7/Stephen_Silberstein_-_Medication_Overuse_Headache.pdf. 6. International Headache Society. *Cephalalgia*. 2018;38:1-211.



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

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

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

*FDA-approved. †Not in original paper.
TCA=tricyclic antidepressant. SNRI=selective norepinephrine reuptake inhibitor. ACE=Angiotensin converting enzyme.

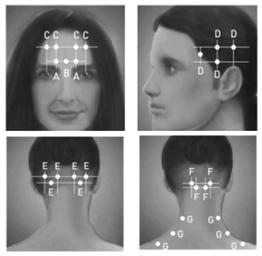
Silberstein SD, et al. *Neurology*. 2012;78;1337-1345.

The First Approved Treatment (Specific) for Chronic Migraine

OnabotulinumtoxinA
(Specific FDA-approved medication)

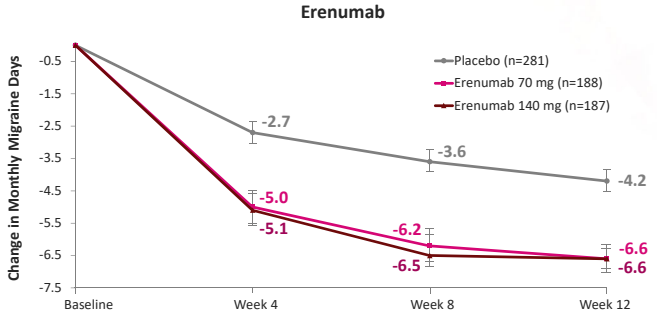
- Approved for prophylaxis of chronic migraine (≥15 headache days/month)
- 8-9 fewer headache days/month compared to 6-7 with placebo
- 31 injection sites into head/neck Q3 months
- Boxed warning: possibility for spread causing weakness in distant area(s)

OnabotulinumtoxinA blocks the presynaptic release of neurotransmitters such as CGRP



 1. Linsenmeyer TA. *J Spinal Cord Med*. 2013;36:402-419. 2. Botox [package insert]. Irvine, CA: Allergan Pharmaceuticals. 2011.

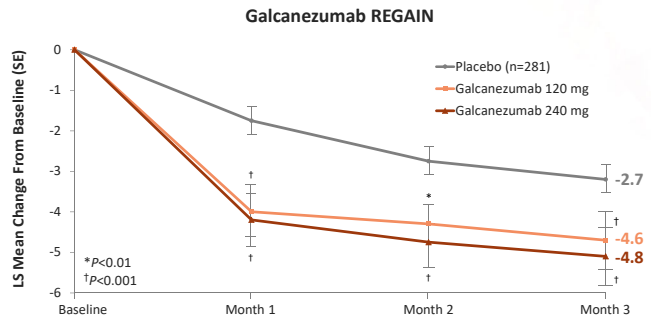
Specific Migraine Treatment With Anti-CGRP mAb: Effects of Erenumab in Chronic Migraine



LS=least squares. SE=standard error.

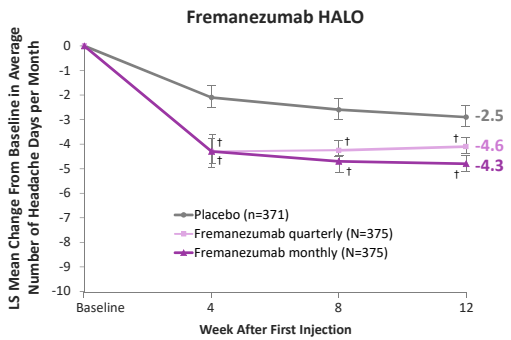
 Tepper S, et al. *Lancet Neurol*. 2017;16:425-434.

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



 Detke HC, et al. *Neurology*. 2018;91(24):e2211-e2221.

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



Fremanezumab was equally effective in preventing EM and CM whether administered subcutaneously monthly or quarterly (primary endpoints)

Difference between fremanezumab quarterly and placebo during 12-week period: -1.8±0.3 days/month (*P*<0.001)

Difference between fremanezumab monthly and placebo during 12-week period: -2.1±0.3 days/month (*P*<0.001)

CM=chronic migraine.

 Silberstein SD, et al. *N Eng J Med*. 2017;377:2113-2122.

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DISCUSSION

When Could a mAb Be Offered to Eduardo?

Complementary and Alternative Considerations

Riboflavin	Physical therapy
Magnesium	Exercise
Coenzyme Q10	Massage
Melatonin	Yoga
Acupuncture	Hypnotherapy
Spinal/osteopathic manipulation	Cold therapy
Tai chi	

31 | American Migraine Foundation. https://americanmigrainefoundation.org/resource-library/headache-prevention-complementary-alternative-medicine. Accessed May 20, 2019.

Summary

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

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

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

Initiate nonspecific preventive medications early

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

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THE NEW ERA OF MIGRAINE TREATMENT

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

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Overview

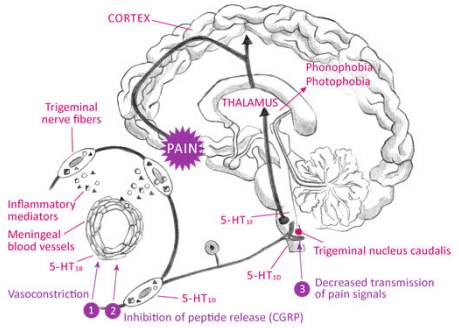
- Pathophysiology leads to pharmacology and neuromodulation: translational research made real
- New classes of acute medication in development
  - Gepants, lasmiditan
- New classes of preventive medication FDA-approved or in development
  - Anti-CGRP or CGRP receptor mAbs, gepants
- Neuromodulation
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

PATHOPHYSIOLOGY AND NEUROTRANSMITTER TARGETS

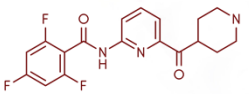
- Serotonin
- CGRP

SEROTONIN AS A MIGRAINE TARGET

The Role of Serotonin (5-HT) in Migraine Pathophysiology[1-4]



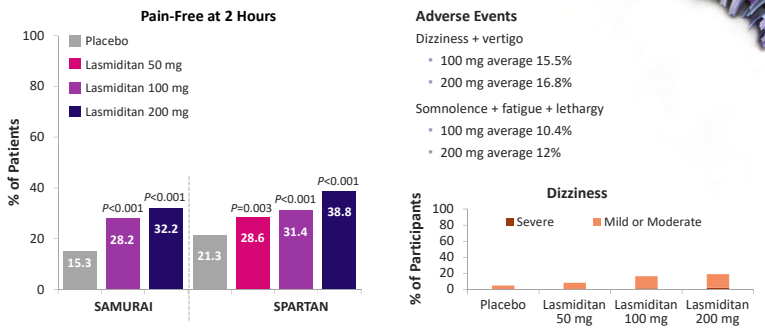
Lasmiditan



- Triptans are 5-$HT_{1B/1D}$ agonists
- Lasmiditan is a novel, centrally acting serotonin (5-HT_{1F}) agonist
- Lacks vasoconstrictive activity
- Submitted to the FDA in October 2018

1. Adapted from Hargreaves RJ, Shepheard SL. *Can J Neurol Sci*. 1999;26(suppl 3):S12-S19. 2. Kuca B, et al. *Neurology*. 2018;91:e2222-e2232.3. Wietecha LA, et al. AAN 2018, Los Angeles, CA; Abstract S50.008. 4. Oswald JC, Schuster NM. *J Pain Res*. 2018;11:2221-2227.

Phase 3 RCTs of Lasmiditan: SAMURAI and SPARTAN[1-3]



Adverse Events

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

Somnolence + fatigue + lethargy
- 100 mg average 10.4%
- 200 mg average 12%

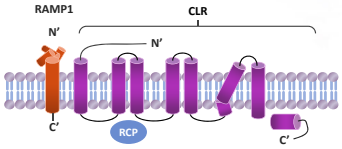
RCTs=randomized controlled trials.

1. Kuca B, et al. *Neurology*. 2018;91:e2222-e2232. 2. Wietecha LA, et al. AAN 2018, Los Angeles, CA. Abstract S50.008. 3. Oswald JC, Schuster NM. *J Pain Res*. 2018;11:2221-2227.

CGRP AS A MIGRAINE TARGET

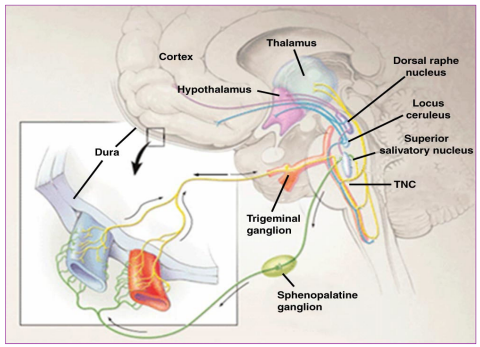
Calcitonin Gene-Related Peptide

- First discovered as a potent vasodilator
- Initially considered important in migraine because of its potential peripheral actions
  - Vasodilation
  - Neurogenic inflammation
- Present at all migraine pathogenesis sites
- Belongs to calcitonin family (calcitonin, amylin, adrenomedullin, intermedin) in humans, α-CGRP and β-CGRP isoforms



1. Brain SD, et al. *Nature*. 1985;313(5997):54-56. 2. Edvinsson L, Uddman R. *Brain Res Brain Res Rev*. 2005;48:438-456. 3. McCulloch J, et al. *Proc Natl Acad Sci USA*.1986;83:5731-5735. 4. Moskowitz MA. *Neurol Clin*. 1990;8:801-815. 5. Naot D, Cornish J. *Bone*. 2008;43:813-818. 6. Benarroch EE. *Neurology*. 2011;77:281-287. 7. Edvinsson L, et al. *Nat Rev Neurol*. 2018;14:338-350.

Migraine Pathophysiology



Goadsby PJ, et al. *N Engl J Med*. 2002;346:257-270.

Data Highlighting the Role of CGRP in Patients With Migraine[1-3]

When measured from external jugular vein, CGRP concentrations rise during spontaneous migraine attacks

After administration of triptans, CGRP serum levels decrease in parallel with symptomatic relief in patients with migraine

In patients with migraine, intravenous infusion of CGRP triggers attacks that are indistinguishable from spontaneous attacks

Blocking or removing CGRP terminates migraine acutely and prevents migraine

43 | 1. Tso AR, Goadsby PJ. *Curr Treat Options Neurol*. 2017;19:27. 2. Raddant AC, Russo AF. *Expert Rev Mol Med*. 2011;13:e36. 3. Tepper SJ. *Headache*. 2018;58 (suppl 3):238-275.

GEPANTS: SMALL-MOLECULE CGRP RECEPTOR ANTAGONISTS

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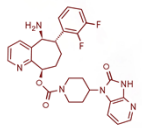
The Small Molecule CGRP Receptor Antagonists: The Gepants

ACUTE Treatment of Episodic Migraine

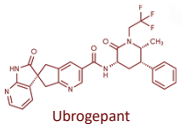
- 6 gepants have demonstrated efficacy in acute migraine treatment
- Early gepants reportedly liver toxic; development halted
- **Ubrogepant** and **rimegepant** have reported positive regulatory results
- Ubrogepant submitted for acute migraine treatment; rimegepant to be submitted next
- 2-hour pain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

PREVENTIVE Treatment of Episodic Migraine

- **Atogepant** vs placebo reported positive Phase 2; will proceed to Phase 3
- **Rimegepant** to be tested for prevention in Phase 2/3



Rimegepant



Ubrogepant

45 | 1. Tfelt-Hansen P. *Headache*. 2011;51:118-123. 2. Tfelt-Hansen P, Do TP. IHC 2017; Vancouver, Canada. Abstract PO-01-48. 3. Allergan press release. February 6, 2018. https://www.allergan.com/news/news/thomson-reuters/allergan-announces-positive-top-line-phase-3-resul. Accessed April 26, 2018. 4. Biohaven press release. March 26, 2018. http://biohavenpharma.com/biohaven-announces-successful-achievement-of-both-co-primary-regulatory-endpoints-in-two-pivotal-phase-3-trials-of-rimegepant-an-oral-cgrp-receptor-antagonist-for-the-acute-treatment-of-migraine/. Accessed April 26, 2018.

PREVENTION: MONOCLONAL ANTIBODIES

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Syllabi/slides for this program are a supplement to the live CME session and are not intended for other purposes.

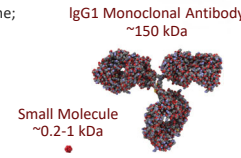
mAbs to CGRP or the CGRP Receptor for Migraine Prevention

How are they different than our current migraine preventive medications?

- mAbs for the most part do not cross the blood-brain barrier[1,2]
- mAbs are eliminated by the reticuloendothelial system—so far, hepatotoxicity has not been seen[1,3,4]
- Because they work, it is likely that peripheral anti-CGRP action is sufficient to prevent migraine

Are they an improvement?[3,4] All 4

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



1. Yu YJ, Watts RJ. *Neurotherapeutics*. 2013;10(3):459-472. 2. Lipton RB, et al. *US Neurology*. 2018;14 (suppl 4):S3-S10. 3. Tepper SJ. *Headache*. 2018;58 (suppl 3):238-275. 4. Tepper SJ. *Headache*. 2018;58 (suppl 3):276-290.

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

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

eCH=episodic cluster headache. cCH=chronic cluster headache. SC=subcutaneous. BLA=biologics license application.

1. Tepper SJ. *Headache*. 2018;58 (suppl 3):238–275. 2. Tepper SJ. *Headache*. 2018;58 (suppl 3):276–290. 3. Edvinsson L. *Headache*. 2018;58 (suppl 1):33-47. 4. Lilly press release. March 5, 2019. https://investor.lilly.com/news-releases/news-release-details/lilly-receives-fda-priority-review-designation-emgality. Accessed April 5, 2019. 5. Alder press release. February 22, 2019. 6. https://www.globenewswire.com/news-release/2019/02/22/1740250/0/en/Alder-BioPharmaceuticals-Submits-Biologics-License-Application-to-the-U-S-Food-and-Drug-Administration-for-Eptinezumab.html. Accessed April 5, 2019.

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

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

SAFETY

Syllabi/slides for this program are a supplement to the live CME session and are not intended for other purposes.

Safety Considerations

ERENUMAB (70 mg once monthly; 140 mg once monthly)	FREMANEZUMAB (225 mg monthly; 675 mg quarterly)	GALCANEZUMAB (240 mg loading dose, then 120 mg monthly)
Injection site reactions (6%, 5%) Constipation (1%, 3%) Cramps, muscle spasms (<1%, 2%)	Injection site reactions (43%, 45%)	Injection site reactions (18%)
Placebo	**Placebo**	**Placebo**
Injection site reactions (3%) Constipation (1%) Cramps, muscle spasms (<1%)	Injection site reactions (38%)	Injection site reactions (13%)

- **Liver**: So far, LFT abnormalities have not been seen in excess of placebo
- **URI**: So far, not with every product and not always in excess of placebo
- Will losing CGRP or its receptor result in loss of compensatory vasodilation/homeostatic vascular protective mechanisms necessary to prevent stroke or infarction in the setting of ischemia?

LFT=liver function test. URI=upper respiratory infection.

1. MaassenVanDenBrink A, et al. *Trends Pharmacol Sci*. 2016;37:779-788. 2. Aimovig [package insert]. Thousand Oaks, CA: Amgen Inc.; 2018. 3. Ajovy [package insert] North Wales, PA: Teva Pharmaceuticals USA, Inc; 2018.

RCT: IV Erenumab Did Not Make Angina Worse

Objective

- Test whether erenumab at 140 mg IV would worsen stress-induced myocardial ischemia in patients with stable angina and ≥1 angina episode per month
  - IV dosing used rather than approved, SC in order to achieve instant C_{max}

Participants

- 88 patients with stable angina due to documented coronary artery disease

Results

No difference in

- Change from baseline in exercise duration
- Time to onset of ≥1 mm ST-segment depression
- Time to onset of exercise-induced angina during treadmill exercise test

No infarctions, no evidence for failure of compensatory mechanisms

Depre C, et al. *Headache*. 2018;58:715-723.

How Are They Changing Practice?

Preventive Medications Before mAbs

- 83% of patients were discontinuing oral prophylaxis within 1 year—terrible adherence
- Designed for other therapeutic areas
- Numerous adverse events
- Take 2-4 months to be effective
- Have ≥50% responder rates of <50%
- May lose effectiveness in medication overuse headache (MOH)
- Sometimes don't lower acute medication use

mAbs' Potential

- Specificity: designed for primary migraine prevention
- Wide therapeutic targets: EM, CM, MOH, and eCH
- Speed—time to onset: <1 week to 1 month
- Tolerability: similar to placebo
- Safety: no safety signal
- Unprecedented responder rates at ≥75% or more
- Lower all acute medication use

We can potentially use these specific preventive biologics first line.

The paradigm shift is occurring depending on cost and access.

1. Aimovig [package insert]. Thousand Oaks, CA: Amgen Inc; 2018. 2. Ajovy [package insert]. North Wales, PA: Teva Pharmaceuticals USA Inc; 2018. 3. Emgality [package insert]. Indianapolis, IN: Eli Lilly and Company; 2018. 4. An Open Label Trial of ALD403 (Eptinezumab) in Chronic Migraine (PREVAIL); https://clinicaltrials.gov/ct2/show/NCT02985398. 5. Hepp Z, et al. *Cephalalgia*. 2017;37:470-485.

Who Should Receive the mAbs: AHS Consensus Statement

1 | **Lower frequency EM (4-7 headache days/month)**

- Lack of success with 2 **AEDs** (VPA, TPM), **TCAs** (amitriptyline, nortriptyline), **beta-blockers**, **SNRIs**, other Level A or B migraine preventive medications
- Documented at least moderate disability or impact by the migraines

2 | **High frequency EM (8-14 days/month)**

- Same requirements as 1, but no need to document disability, as they are clearly impacted

3 | **CM (≥15 days/month)**

- Same requirements as 1, with **onabotulinumtoxinA** as an additional choice, and no need to document disability, as they are clearly impacted

AHS=American Headache Society. AED=antiepileptic drug. VPA=valproate. TPM=topiramate.

American Headache Society. *Headache*. 2019;59:1-18.

NONINVASIVE NEUROMODULATION: ANOTHER THERAPEUTIC OPTION

4 FDA-Cleared, Noninvasive, Nonsignificant Risk Neurostimulators

External Trigeminal Stimulation (eTNS)[1]

- FDA-cleared for acute and preventive migraine treatment
- Purchased online for $550
- Little or no insurance coverage
- Preventatively: wear nightly for 20 minutes; acutely: use different program for 60 minutes

Single Pulse Transcranial Magnetic Stimulation (sTMS)[1]

- FDA-cleared for acute and preventive migraine treatment
- Rent for $220/month
- Little or no insurance coverage
- 4 pulses twice daily; extra pulses as needed, up to 17 pulses/day

Noninvasive Vagal Nerve Stimulation (nVNS)[1]

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

Remote Electrical Neuromodulation (REN)[2]

- Recently FDA-cleared for acute migraine pain
- Planned for launch after Q4 2019
- Attaches to the arm
- Controlled by smart phone application

1. Tepper SJ, Tepper DE. *Practical Neurology*. 2018;17:42-45.
2. www.https://theranica.com/ Accessed June 18, 2019.

Conclusions

This is a watershed moment in migraine treatment

New acute medication classes, devices, formulations, and combinations offer opportunity to match patient needs to treatments

Older, nonspecific oral medications with adverse events and poor adherence are giving way to new designer medications and neuromodulators

mAbs are specific for migraine, given monthly or quarterly, and well-tolerated and safe; start to work within 1-4 weeks; and reduce acute medication use while improving quality of life

The 2019 AHS consensus statement highlights the importance of documenting prescriptions and drug failures so appropriate patients can qualify for these agents

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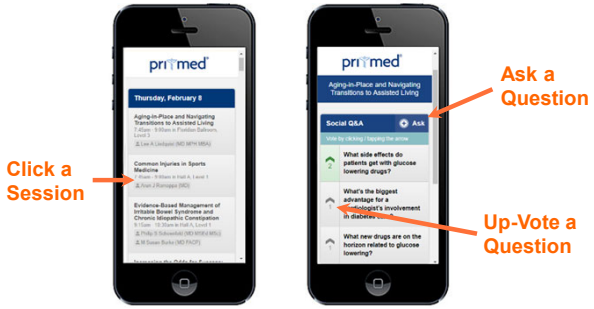

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