MAYO CLINIC

HEADACHE MEDICINE: THE FUTURE – NEW MEDS ON THE HORIZON

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DISCLOSURES

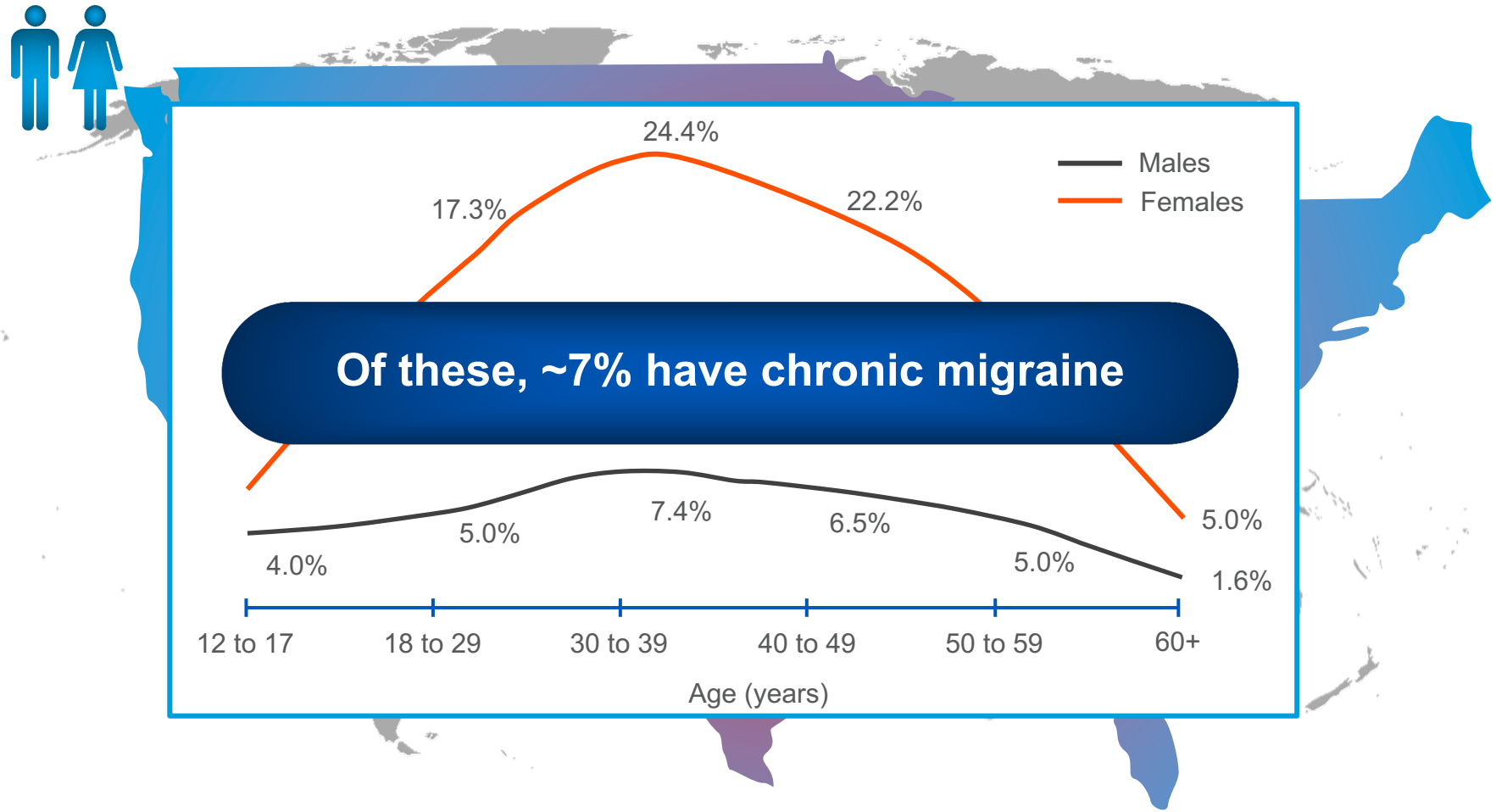
Research: Amgen

Editorial services: *Current Neurology and Neuroscience Reports* (Headache Section Editor), *Headache Journal* (Online & Social Media Editor, Deputy Editor)

OBJECTIVES

1. Identify treatment gaps with traditional therapies
2. Review controlled and real-world evidence on recently approved treatments for migraine
3. Discuss the clinical considerations when using the new treatments for migraine in clinical practice
4. Discuss updates in our understanding of management of migraine during pregnancy

MIGRAINE IS HIGHLY PREVALENT

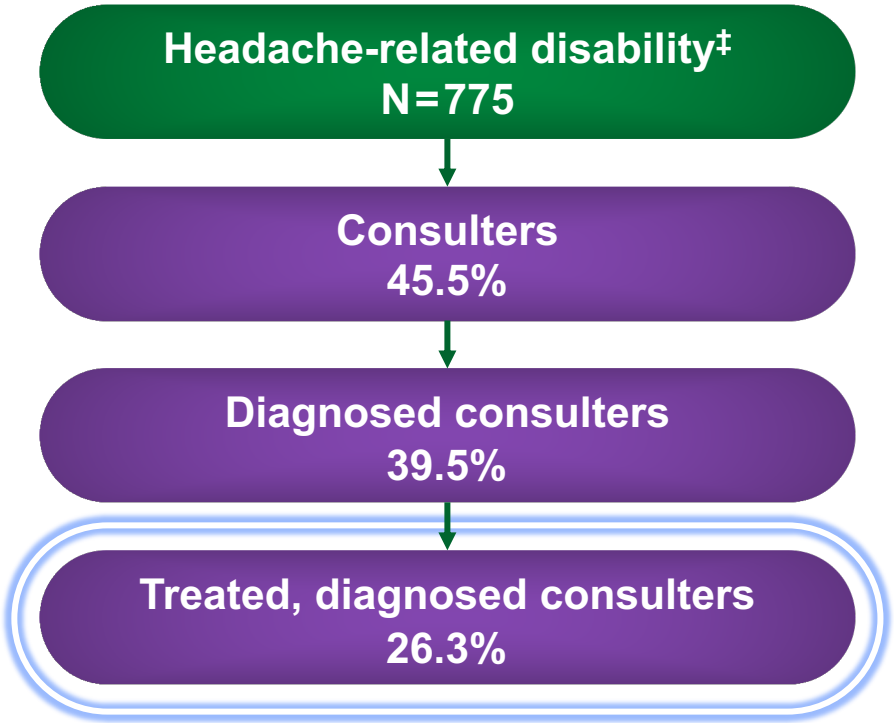


Institute for Health Metrics and Evaluation. Global Burden of Disease 2016. Available from http://www.healthdata.org/gbd/data. Accessed September 15, 2017.

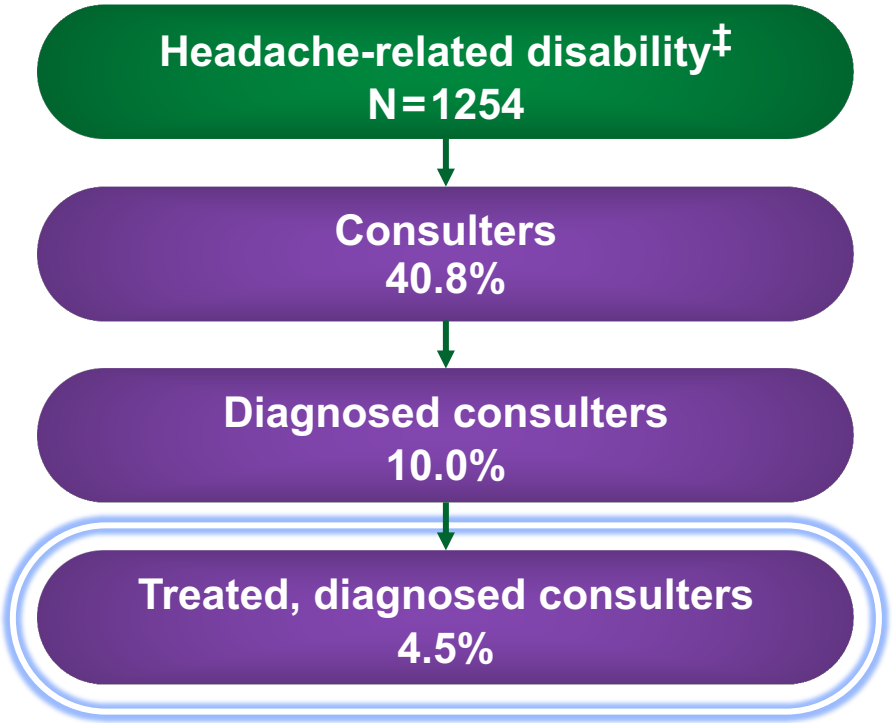
Slide courtesy of American Headache Society Next Gen Program

ASSESSING BARRIERS TO CARE IN MIGRAINE

Episodic Migraine[1*]



Chronic Migraine[2†]



Consulters were patients who had seen a doctor in the past year. Preventive treatment is needed for chronic migraine.
*AMPP study. †CaMEO study. ‡Migraine Disability Assessment Scale (MIDAS) grade >II (mild or greater).
AMPP, American Migraine Prevalence and Prevention; CaMEO, Chronic Migraine Epidemiology and Outcomes.

1. Lipton RB et al. *Headache*. 2013;53:81–92. 2. Dodick DW et al. *Headache*. 2016;56:821–834.

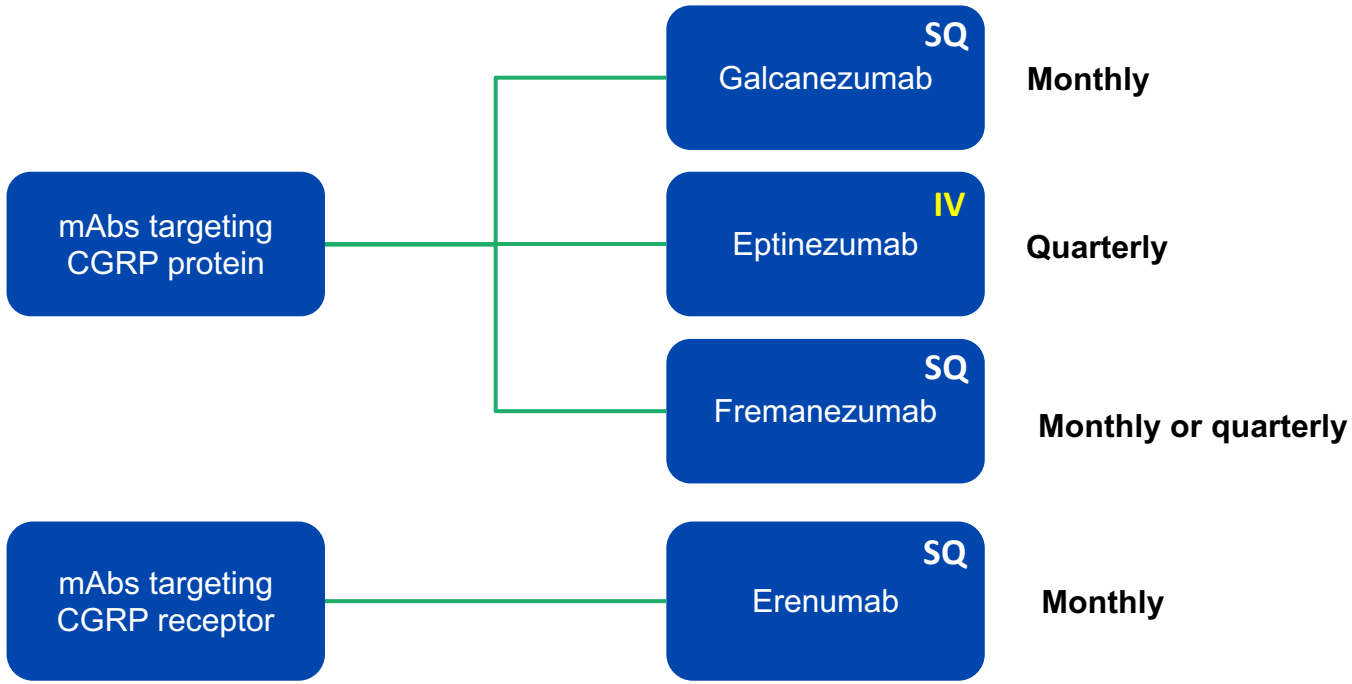
Slide courtesy of American Headache Society Next Gen Program

WHAT ARE THE DRIVING FORCES FOR NEW MIGRAINE TREATMENTS?

- **Prevalence and burden**
  - 15.9% of adults, 21% of women, 10.7% of men[1]
  - 2nd leading cause of YLD worldwide[2]
  - Leading cause of YLD in people 15-49[2]
- **Need for new treatments**
  - Lack of tolerability
    - 80% discontinue oral preventive at 12 months[3]
  - Limited efficacy (40-50%)[3]
  - Triptans used by only 14-18% of people with migraine[4]
  - Lack of options for people with certain comorbidities
    - >20% of people with migraine have CV contraindication to triptan[5]
    - An additional 25% have at least 2 CV risk factors identified as warnings/precautions to triptans[5]

1. Burch et al Headache 2021; 2. GBD 2016, Lancet 2017; 3. Hepp et al Cephalalgia 2017; 4. Lipton et al Headache 2018;
5. Dodick et al J Prim Care Comm Health 2020

Anti-CGRP Monoclonal Antibodies

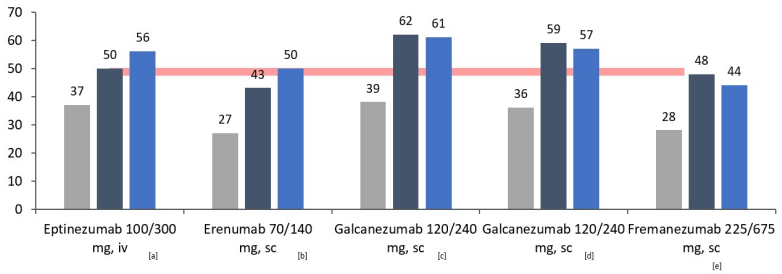


Dodick DW. Cephalalgia. 2019

Clinical Trials: Effectiveness of CGRP mAbs

>50% Responder Rates with CGRP mAbs (Episodic Migraine)

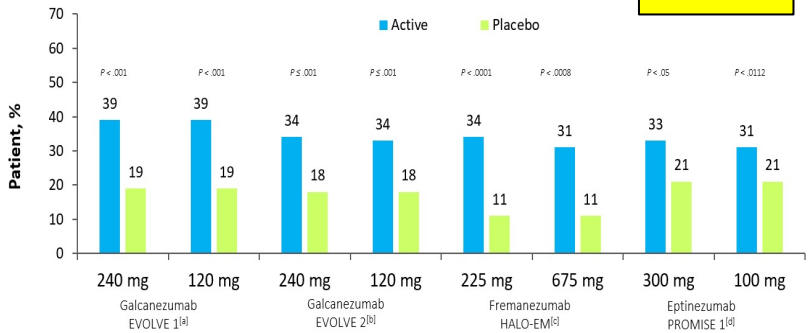
43-62%



Saper J, et al. AAN 2018. Abstract S20; b. Goadsby PJ, et al. *Headache*. 2017;57(Suppl 3):128; c. Stauffer VL, et al. *JAMA Neurol*. 2018.; Skljarevski V, et al. *Cephalagia*. 2018.. Dodick DW. *JAMA.* 2018;319:1999-2008.

Proportion of patients with ≥75% reduction in migraine days (Episodic migraine)

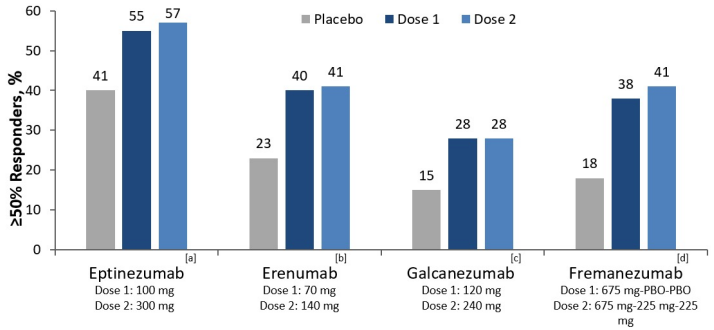
31-39%



Stauffer VL, et al. JAMA Neurol; 2018Skljarevski V, et al. Cephalalgia. 2018. Bigal ME, et al. Lancet Neurol. 2015;14:1081-1090; Smith J, et al. Headache. 2017; 57 (Suppl 1):130. Abstract IOR06.

>50% Responder Rates with CGRP mAbs (Chronic Migraine)

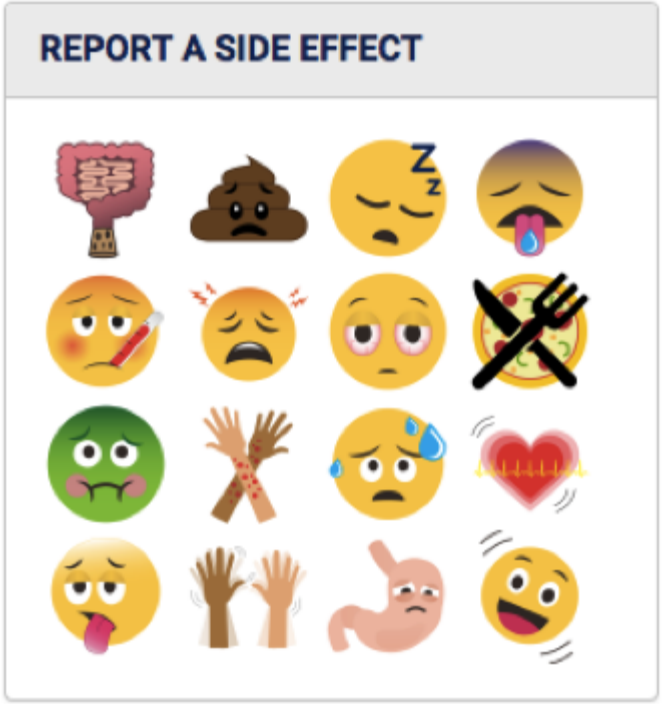
28-55%



a. Smith J, et al. *Headache*. 2017:57 Suppl 3:130; b. Tepper S, et al. *Lancet Neurol*. 2017;16:425-434; c. Detke HC, et al. *Cephalalgia*. 2017;37:338; d. Silberstein SD, et al. *N Engl J Med*. 2017;377:2113-2122.

Side effects seen in clinical trials

- Compared to placebo:
  - No difference in overall and serious adverse events compared to placebo
  - No difference in discontinuation of treatment due to AEs 2.5%
- **Caution**: hypersensitivity (allergic/immune) and injection site reactions
- Constipation (erenumab; 1-3%)



Review

Cephalalgia
International Headache Society

Cephalalgia
2019, Vol. 39(9) 1164–1179

DOI: 10.1177/0333102419829007
journals.sagepub.com/home/cep
SAGE

Safety and tolerability of calcitonin-gene-related peptide binding monoclonal antibodies for the prevention of episodic migraine – a meta-analysis of randomized controlled trials

REVIEW Open Access

Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine – an updated systematic review and meta-analysis

Hong Deng, Gai-gai Li*, Hao Nie, Yang-yang Feng, Guang-yu Guo, Wen-liang Guo and Zhou-ping Tang*

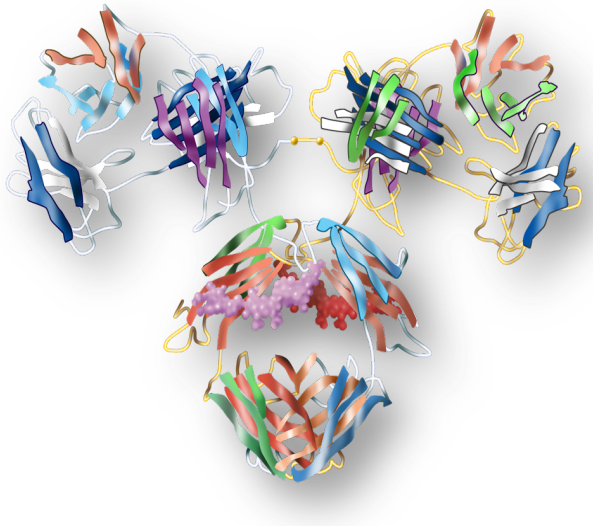
REAL-WORLD EXPERIENCE WITH MABS: WHAT CAN PATIENTS EXPECT?

- Similar efficacy
  - Even if other treatments have failed
  - Even with medication overuse
  - Even with significant comorbidity
- Onset can be within first week or first day
- Can safely and effectively combine CGRP mAbs with onabotulinumtoxinA & gepants
- Efficacy can increase over time
- If one CGRP mAb does is ineffective or not tolerated, can try another

- Higher rate of known AEs (ie - constipation 13-43% with erenumab)
- New AEs (dizziness, fatigue, cramps, joint pain, fatigue, nausea, alopecia, worsening headache)
- Early wearing off (before next dose, over time)
- Women must wait 5 months from last dose to conceive
- New FDA warnings: hypertension & erenumab (majority within 1st week of 1st dose), constipation & erenumab
- All CGRP mAbs are ineffective for some

Silberstein et al 2020; Diener et al 2020; Dodick et al 2020; Mulleners et al 2020; Kanaan et al 2020; Robblee et al 2020; Alex et al 2020; Saely et al 2021; Blumenfeld et al AAN 2021; Blumenfeld et al AAN 2021

CGRP SMALL MOLECULE DRUGS (GEPANTS)



Guidelines Acute Migraine Treatment

Level A

All triptans

DHE NS

NSAIDs: Diclofenac, aspirin, naproxen, ibuprofen

Acetaminophen/aspirin/caffeine 500/500/130 mg

Acetaminophen 1000 mg (for non-incapacitating attacks)

Level B

Anti-emetics: IV Metoclopramide & Prochlorperazine

Anti-dopamine: IV Chlorpromazine & Droperidol IV

Ergots: IM/IV DHE

NSAIDS: Ketorolac

Marmura MJ et al Headache 2015

NEXT GENERATION ORAL ACUTE TREATMENTS

FDA approved for acute treatment

- Gepants
  - Ubrogepant 50mg or 100mg during attack, repeat once as needed
  - Rimegepant 75mg ODT once during attack
- Ditans
  - Lasmiditan 50mg, 100mg, 200mg once during attack

Consider in those who have (any of below)

- Found 2 triptans ineffective/had side effects
- Contraindications to standard therapy

Dodick DW. NEJM 2019; Lipton RB. JAMA 2019; Lipton RB. NEJM 2019; Croop R. Lancet. 2019; Kuca B. Neurology 2018; Goadsby PJ. Brain 2019; Digre K Headache 2018; Ailani J Headache 2021

*Ubro*gepant

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ubrogepant for the Treatment of Migraine

David W. Dodick, M.D., Richard B. Lipton, M.D., Jessica Ailani, M.D., Kaifeng Lu, Ph.D., Michelle Finnegan, M.P.H., Joel M. Trugman, M.D., and Armin Szegedi, M.D.

JAMA | Original Investigation

Effect of Ubrogepant vs Placebo on Pain and the Most Bothersome Associated Symptom in the Acute Treatment of Migraine
The ACHIEVE II Randomized Clinical Trial

Richard B. Lipton, MD; David W. Dodick, MD; Jessica Ailani, MD; Kaifeng Lu, PhD; Michelle Finnegan, MPH; Armin Szegedi, MD; Joel M. Trugman, MD

- Free of pain @ 2 hours
  - 19-22% (mod/severe pain)
  - 39-43% (mild pain)
- Relief of pain @ 2 hours
  - 61-63%
- Nausea, dizziness (~2%)

*Rime*gepant

Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial

Robert Croop, Peter J Goadsby, David A Stock, Charles M Conway, Micaela Forshaw, Elyse G Stock, Vladimir Coric, Richard B Lipton

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rimegepant, an Oral Calcitonin Gene–Related Peptide Receptor Antagonist, for Migraine

Richard B. Lipton, M.D., Robert Croop, M.D., Elyse G. Stock, M.D., David A. Stock, Ph.D., Beth A. Morris, B.A., Marianne Frost, M.A., Gene M. Dubowchik, Ph.D., Charles M. Conway, Ph.D., Vladimir Coric, M.D., and Peter J. Goadsby, M.D., Ph.D.

- Free of pain @ 2 hours
  - 20-21% (treating moderate or severe pain)
- Relief of pain @ 2 hours
  - 58-59%
- Nausea (2%), dizziness (1%)

Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial

Robert Croop, Richard B Lipton, David Kudrow, David A Stock, Lisa Kamen, Charles M Conway, Elyse G Stock, Vladimir Coric, Peter J Goadsby

	MMD reduction	Responder rate (≥50%)
Placebo (n=347)	3.5	41.5
75mg (n=348)	4.3*	49.1**

* p<0.01
** p<0.04

	TRAE	Dropout due to AE	SAE	Nausea
Placebo (n=347)	8.6	1.1	1.1	0.8
75mg (n=348)	10.8	1.9	0.8	2.7

Lancet 2021; 397: 51–60

*Ato*gepant: Small molecule oral drug for prevention

Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial

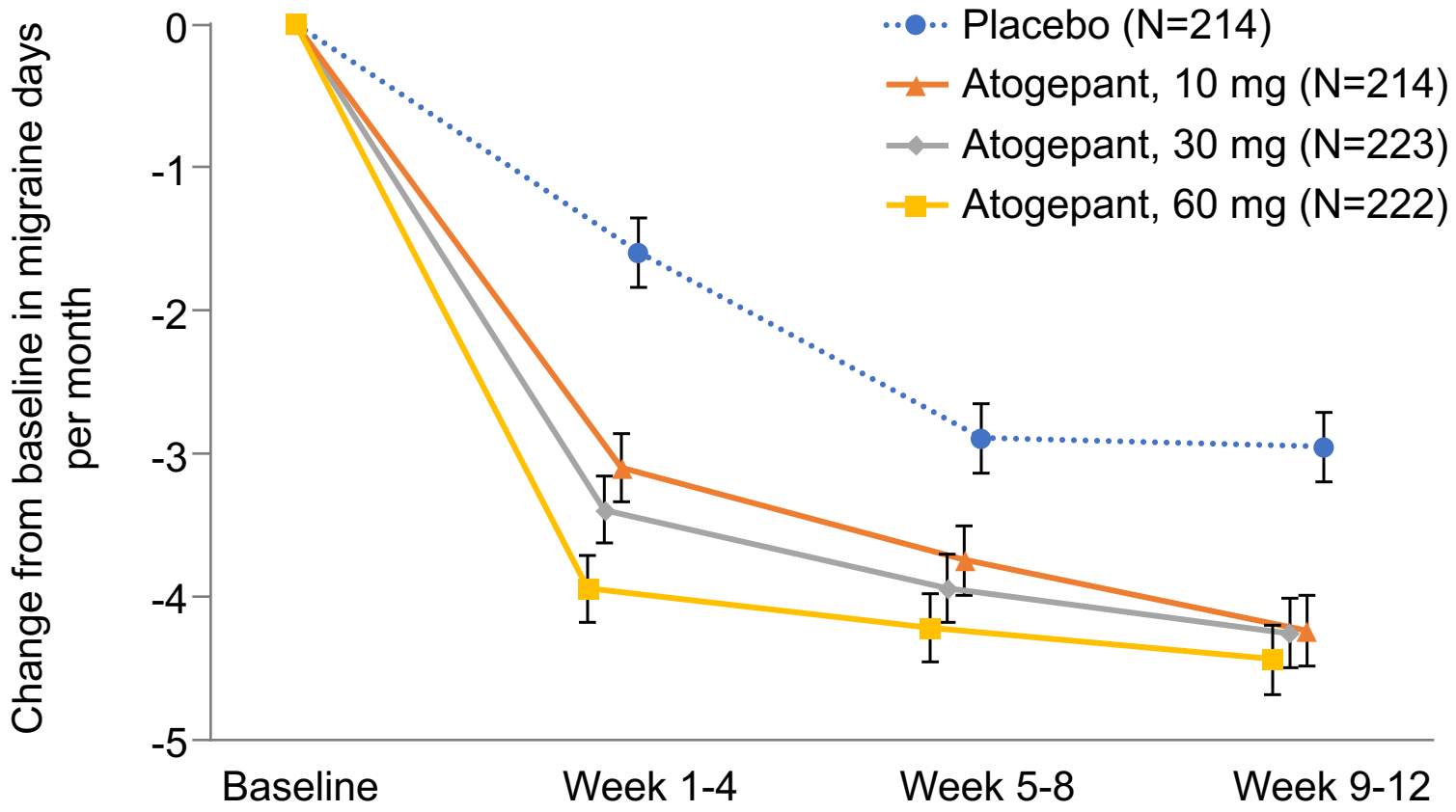
Peter J Goadsby, David W Dodick, Jessica Ailani, Joel M Trugman, Michelle Finnegan, Kaifeng Lu, Armin Szegedi

52-62% were responders (> 50% reduction in migraine days per month)

Side effects: nausea (3-9%), constipation (1-4%); fatigue (1-7%), decreased appetite (3-4%)

Lancet Neuro 2020;19:727-737

*Ato*gepant: Time Course of Efficacy (Modified Intention-to-Treat Population)



Ailani J et al. N Engl J Med 2021;385:695-706

Gepants: Summary

Effective **for acute and preventive** treatment

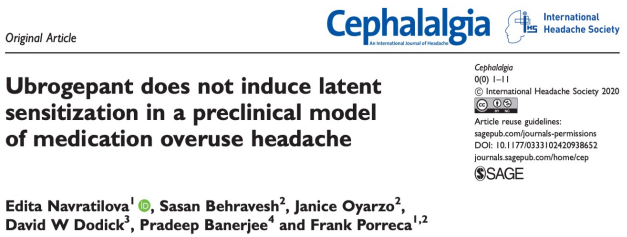
First acute treatment not at risk for MOH

More likely/effective if used when **pain is mild**

Effective in those for whom **triptans failed**

Generally well tolerated (nausea, constipation, fatigue)

Not contraindicated in patients with CV disease


Original Article

Cephalalgia

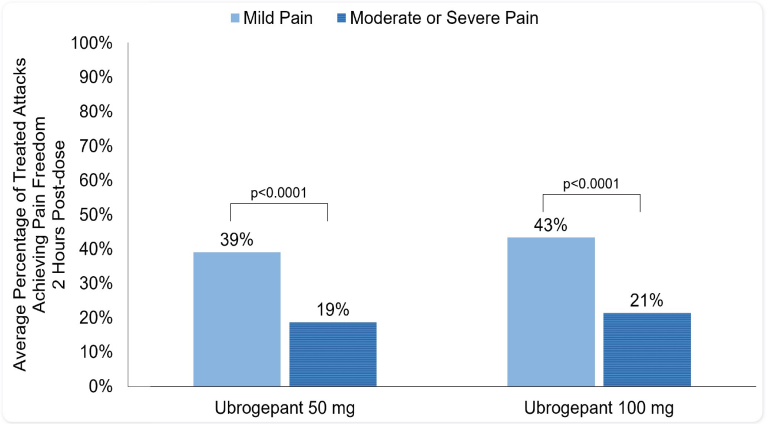
International Headache Society

Ubrogepant does not induce latent sensitization in a preclinical model of medication overuse headache

Cephalalgia
0(0) 1–11

DOI: 10.1177/0333102420938652
journals.sagepub.com/home/cep
SAGE

Edita Navratilova[1], Sasan Behravesh[2], Janice Oyarzo[2], David W Dodick[3], Pradeep Banerjee[4] and Frank Porreca[1,2]



Lipton RB, et al. *Neurology*. 2020;94(15 Suppl): 4726.

Individualizing the Choice of Treatment with Gepants

Ubrogepant (acute treatment)

- For patients who might want the option of a second dose, or different dosing options

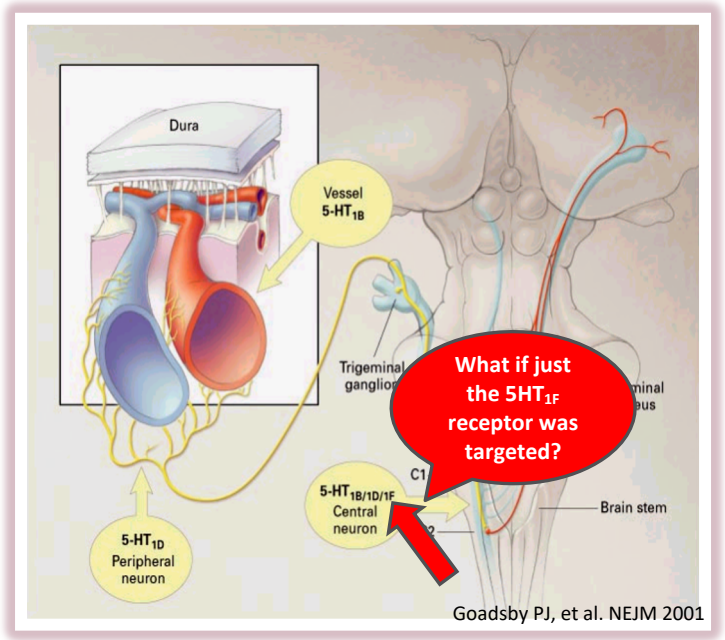
Rimegepant (acute treatment/EM prevention)

- For patients who want the convenience of an oral dissolving tablet for acute treatment
- For patients with episodic migraine who want to try CGRP preventive therapy, but want to try something with a shorter half-life than mAbs

Atogepant (EM prevention)

- For patients with episodic migraine who want to try CGRP preventive therapy, but want to try something with a shorter half-life than mAbs
- For patients who might want an option of different doses to consider

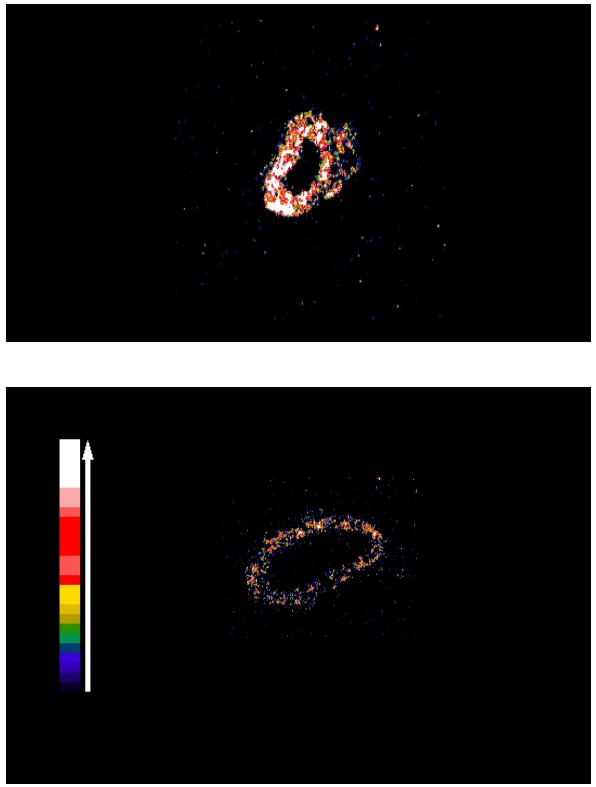
Historical Drug Target For Acute Migraine Treatment
Cerebral Blood Vessels



Triptans= 5HT1B/1D >1F receptor agonists

Middle meningeal artery

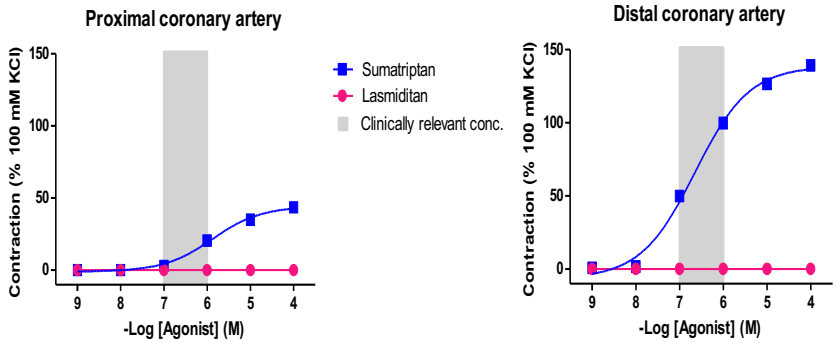
Coronary artery



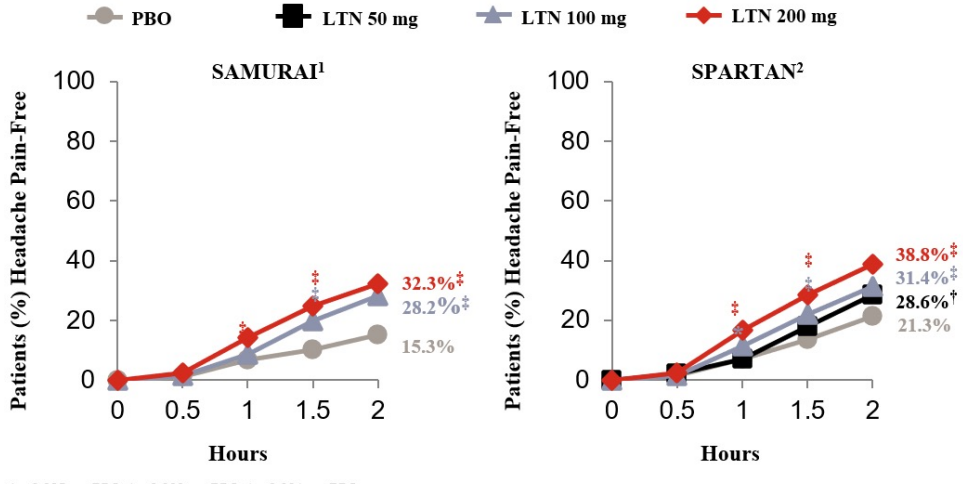
Longmore et al., *Funct Neurol* 1997;12:3-9

Immunohistochemical localization of 5-HT$_{1B}$ receptors

Lasmiditan: Selective 5HT-1F receptor agonist



MaassenVanDenBrink A et al. Pharmacol & Ther 2018

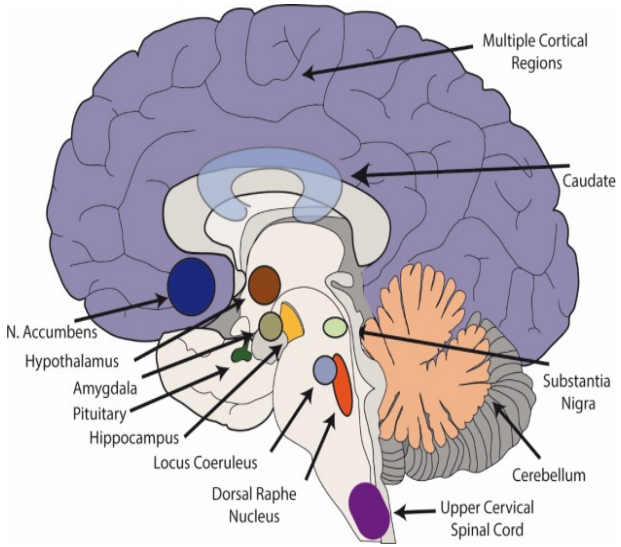


Pain free in 1/3 of patients within 2 hours.

1. Kuca B, et al. *Neurology*. 2018;91:e2222-e2232. 2. Goadsby PJ, et al. *Brain*. 2019;142(7):1894-1904.

Central 5HT-1F Receptor Distribution and Side Effect Profile

	SAMURAI (First Dose)			SPARTAN (First Dose)			
TEAEs[a]	L 200 mg (n=609)	L 100 mg (n=630)	PBO (n=617)	L 200 mg (n=649)	L 100 mg (n=635)	L 50 mg (n=654)	PBO (n=645)
≥1 TEAEs	42.2%	36.3%	16.0%	39.0%	36.1%	25.4%	11.6%
Dizziness	16.3%	12.5%	3.4%	18.0%	18.1%	8.6%	2.5%
Paresthesia	7.9%	5.7%	2.1%	6.6%	5.8%	2.4%	0.9%
Somnolence	5.4%	5.7%	2.3%	6.5%	4.6%	5.4%	2.0%
Fatigue	3.1%	4.1%	0.3%	4.8%	4.1%	2.8%	0.9%
Nausea	5.3%	3.0%	1.9%	2.6%	3.3%	2.8%	1.2%
Lethargy	2.5%	1.9%	0.3%	2.2%	1.3%	1.2%	0.2%



Vila-Pueyo. Neurotherapeutics (2018) 15:291–303,

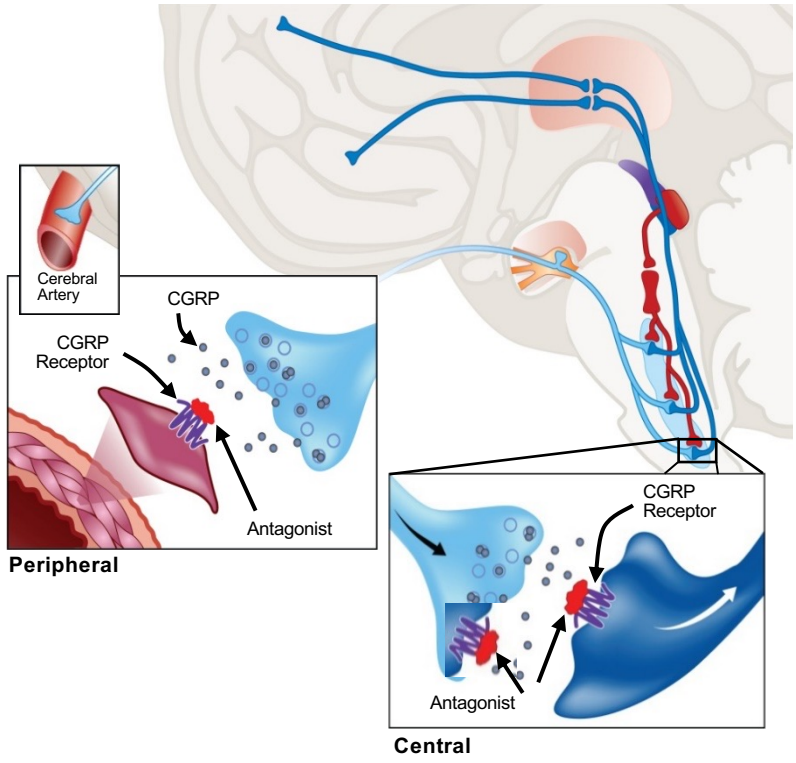
RESEARCH ARTICLE

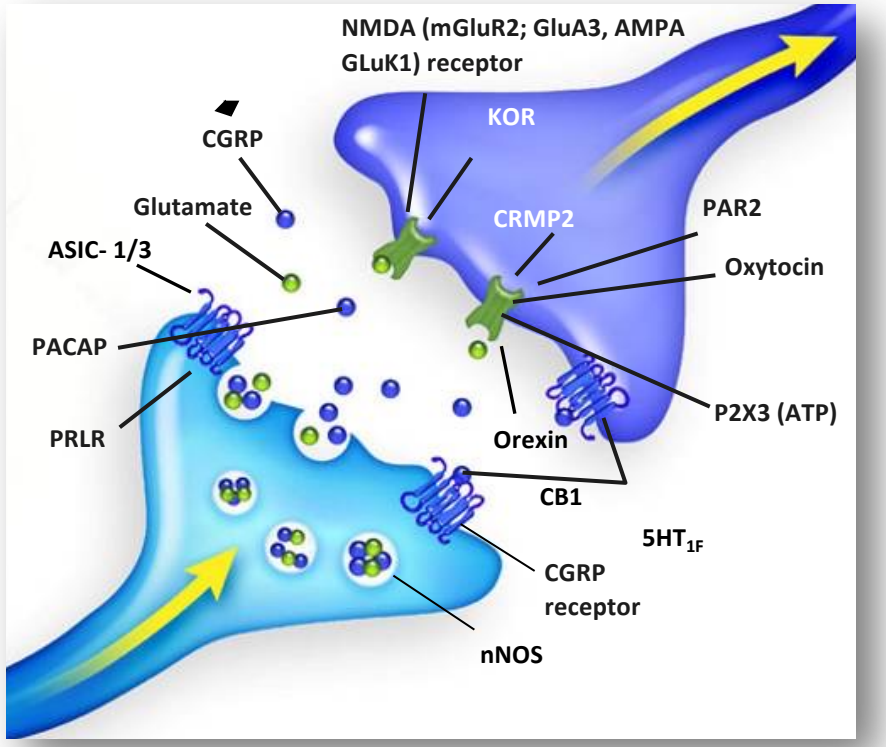
WILEY

Effects of lasmiditan on simulated driving performance: Results of two randomized, blinded, crossover studies with placebo and active controls

Eric M. Pearlman[1] | Darren Wilbraham[1] | Ellen B. Dennehy[1,2] | Paul H. Berg[1] | Max Tsai[1] | Erin G. Doty[1] | Gary G. Kay[3]

OTHER TRIGEMINAL SENSORY TARGETS





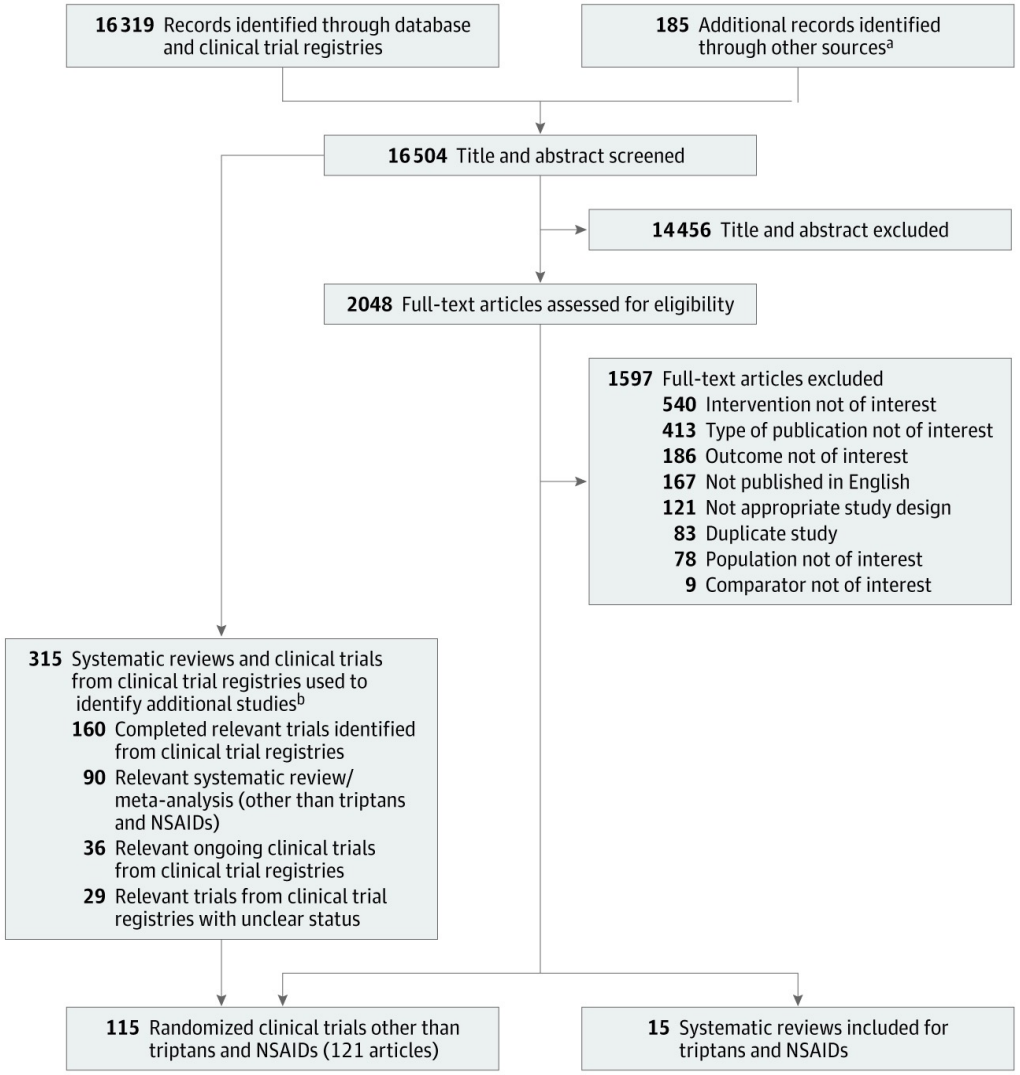
JAMA | Original Investigation

Acute Treatments for Episodic Migraine in Adults
A Systematic Review and Meta-analysis

Juliana H. VanderPluym, MD; Rashmi B. Halker Singh, MD; Meritxell Urtecho, MD; Allison S. Morrow, BA; Tarek Nayfeh, MD; Victor D. Torres Roldan, MD; Magdoleen H. Farah, MBBS; Bashar Hasan, MD; Samer Saadi, MD; Sahrish Shah, MBBS; Rami Abd-Rabu, MBBS; Lubna Daraz, PhD; Larry J. Prokop, MLS; Mohammad Hassan Murad, MD, MPH; Zhen Wang, PhD

JAMA. 2021;325(23):2357-2369. doi:10.1001/jama.2021.7939

- Use of triptans, NSAIDs, acetaminophen, DHE, CGRP antagonists, lasmiditan, & some nonpharm treatments were associated with improved pain and function
- The evidence for opioids in the acute treatment of migraine is limited



MOH: UPDATES IN UNDERSTANDING FROM THE MOTS TRIAL

- **Methods**: 720 participants with migraine & MOH randomized to 1) preventive treatment only or 2) preventive treatment & switching to alternative acute treatment (max 2 days/week)
- **Primary outcome**: Migraine preventive medication without switching of the overused medication *was not inferior* to preventive medication with switching for moderate-to-severe headache day frequency during weeks 9-12
- **Secondary outcome**: Switching group had reduced their consumption of medication by 52% (vs 32% in the non-switching group) at weeks 9-12
- **Conclusion**: For patients with CM and medication overuse, the efficacy of starting or optimizing preventive medication is *not dependent* on whether patients first reduce their use of acute medication

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Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000200117

Patient-Centered Treatment of Chronic Migraine With Medication Overuse: A Prospective, Randomized, Pragmatic Clinical Trial

Author(s):
Todd Schwedt, MD[1]; Joseph Hentz, MS[1]; Soma Sahai-Srivastava, MD[2]; Natalia Murinova, MD[3]; Nicole Spare, DO[4]; Christina Treppendahl, FNP[5]; Vincent T Martin, MD[6]; Marius Birlea, MD[7]; Kathleen Digre, MD[8]; David Watson, MD[9]; Michael Leonard, MDiv[1]; Teri Robert, PhD[10]; David Dodick, MD[1] on behalf of The MOTS Investigators

Ask about **CONTRACEPTION AND PREGNANCY PLANS**…

Many patients are women of childbearing potential – these decisions will impact treatment choices.

EFFECT OF MIGRAINE ON PREGNANCY PLANNING: INSIGHTS FROM THE AMERICAN REGISTRY FOR MIGRAINE RESEARCH (ARMR) DATABASE

- **Almost 20% of women** with migraine in the ARMR database attested to pregnancy avoidance because of migraine
- Those who indicated intent to avoid pregnancy were:
  - predominantly young
  - are more likely to have menstrual migraine
  - are more likely to have never been pregnant since the onset of migraine
- Migraine usually improves during pregnancy, especially in patients who have migraine without aura, migraine that started with menarche, or menstrual migraine.
  - About 1/2 to 3/4 of those with migraine have a marked improvement in migraine during pregnancy, with a significant reduction in attack frequency and intensity, especially during second and third trimesters
- Education is important!

Ishii R et al Mayo Clinic Proc 2020
Halker Singh RB & Sirven JI Mayo Clinic Proc 2020

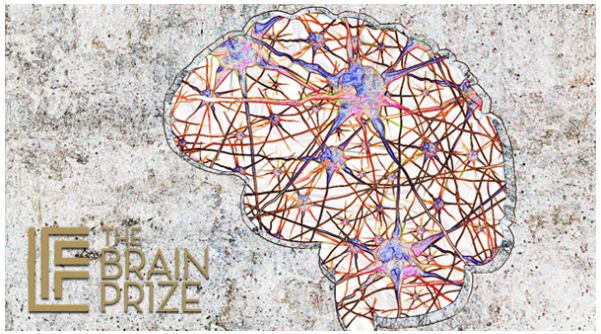
MANAGEMENT OF PRIMARY HEADACHES DURING PREGNANCY, POSTPARTUM, AND BREASTFEEDING: A SYSTEMATIC REVIEW

- *Methods*: 8549 citations for studies and 2788 citations for SRs. Sixteen studies (mostly high risk of bias) comprising 14,185 patients (total) and 26 SRs met the criteria
- *Prevention:* calcium channel blockers and antihistamines may not be associated with fetal/child adverse effects
- *Acute treatment:* combination metoclopramide and diphenhydramine may be more effective than codeine. Triptans and low-dose aspirin may not be associated with fetal/child adverse effects; **notable finding that triptan use for migraine during pregnancy seems to have low risk of adverse effects**
- *Nonpharm*: 6 studies on nonpharmacologic approaches for acute treatment of headache (no preventive studies) – not enough to make conclusions on benefits/harms

Saldanha IJ et al Headache 2021
Hamilton KT Headache 2021

Conclusions

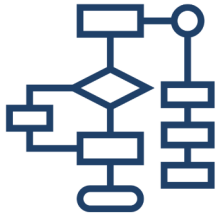
- Advances in our understanding of the molecular biology of migraine has led to:
  - The first migraine-specific therapy developed, approved, and available for prevention
  - Two new acute drug classes since the triptans emerged 30 years ago
  - A move away from drugs that constrict blood vessels to those which act on peripheral trigeminal nerve and/or central brain targets
  - The first acute drug class demonstrated not to produce medication overuse headache (“rebound”)
  - Very important expansion in the treatment options for many patients



71% of patients

consult their primary care practitioner for migraine.

That's why it's essential that you have access to accurate, timely information on migraine and headache disorders. **First Contact – Headache in Primary Care** provides free educational resources to help you identify and treat migraine.



Migraine Management Flowchart

Videos and Podcasts

Research Summaries and Articles

First Contact HEADACHE In Primary Care

BY THE AMERICAN HEADACHE SOCIETY

Learn more and explore our resources here: