Comprehensive Migraine Update

Deena E. Kuruvilla, MD, FAHS
Medical Director
Brain Health Institute
Neurologist and Specialist in Headache & Facial Pain
Westport, CT
Deena@brainhealthct.com

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Disclosure

Consultant: AbbVie Inc.; Cefaly Technologies; Linpharma; Pfizer Pharmaceuticals

Speaker's Bureau: AbbVie Inc.

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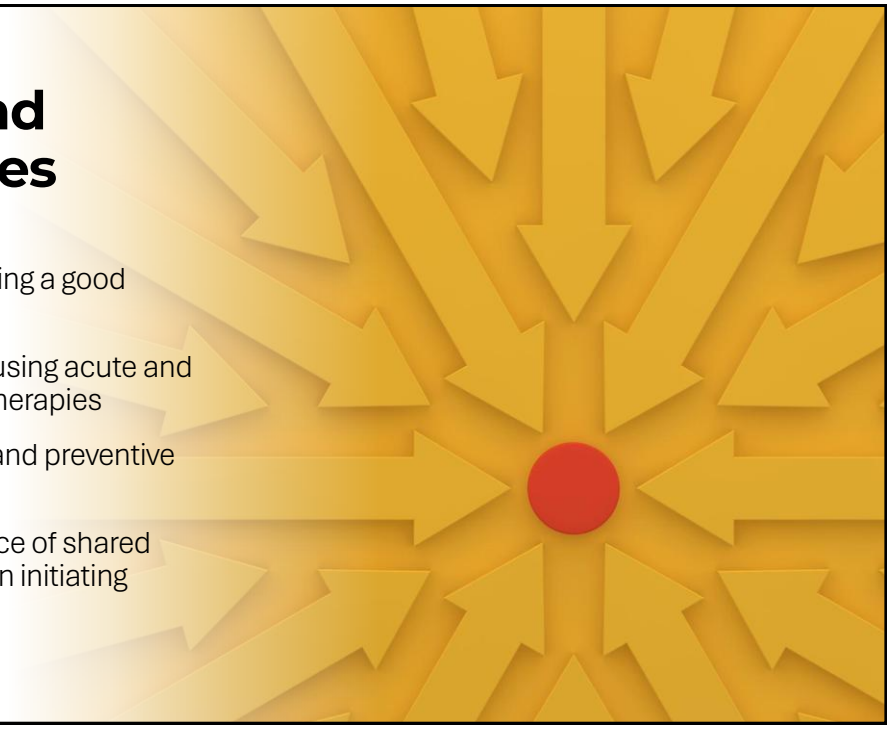
Goals and Objectives

- Discuss pearls to taking a good headache history
- Review approach to using acute and preventive migraine therapies
- Highlight new acute and preventive therapies
- Explain the importance of shared decision making when initiating treatment



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Case 1: Erika's Bad Headaches

Erika is a 38-year-old high school teacher with severe headaches

Recalls headaches in college, would sometimes miss class, especially prior to menses

Recently pain is worse w/ 1 severe attack per week, OTC medications aren't helping

Describes pain as across the front of her head, starts dull and builds to throbbing, nausea when severe

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What Are Some Of Your Pearls for Eliciting an Accurate Headache History?

What's Your Diagnosis?

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Migraine Is..

Real

- Not "just a headache": neurological, sensory, autonomic, vestibular, cognitive, and gastrointestinal symptoms
- Chronic neurologic disease involving disordered sensory processing, influenced by genetics and the environment

Common

- > 47 million Americans
- 10% of school-age children
- 7% have chronic migraine (>15 headache days/month)

Disabling

- Leading cause of years lived with disability in people under the age of 50 worldwide
- Peak prevalence during working years 25-55yo

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Migraine Diagnosis

Migraine

- ≥ 5 attacks lasting 4-72 hours
- 2 out of 4
  - Unilateral location
  - Pulsating quality
  - Moderate or severe intensity
  - Aggravation by or causing avoidance of routine physical activity
- ≥ 1 of the following:
  - Nausea and/or vomiting
  - Photophobia and phonophobia

Chronic migraine

- Migraine or TT headache ≥15 days/month for >3 months
- ≥8 days/month
  - Fulfill criteria for migraine
  - Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

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Lost in Translation?

4 migraine attacks per month, each lasting 2 days = 8 headache days per month

How many days per week/month are you *completely* headache free?

Erika has episodic migraine

Patient Says	Doctor Hears	Patient means
4 migraines	4 days of migraine attack	4 episodes, of 2 days each
Cluster migraines	Diagnostic confusion	Several migraine attacks or days in a row, "clustering" together
Migraine	Migraine	Migraine with aura, not "the other headaches" (migraine without aura)

Semantics matter.

Asthma : Asthma Attack : Migraine : Migraine Attack

Language communicates it's a chronic neurologic disease

Parikh SK, Young WB. 2019 Feb 9;23(1):8.

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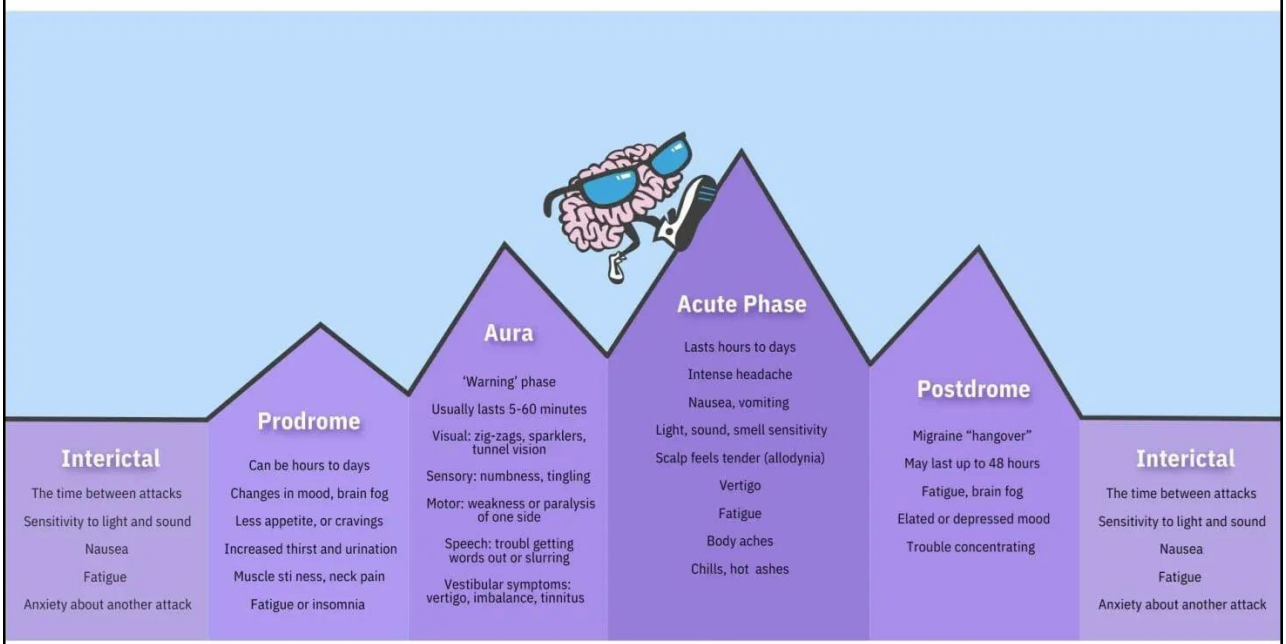

https://www.milesformigraine.org/phases-of-migraine-attack/

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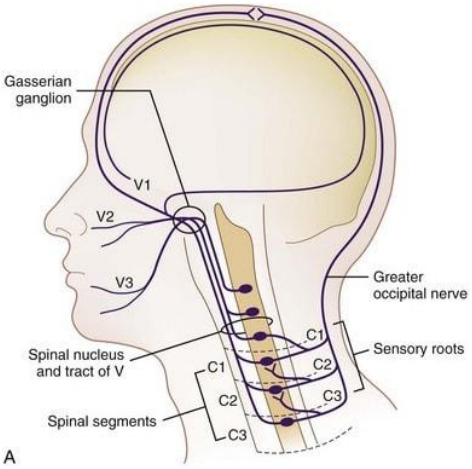
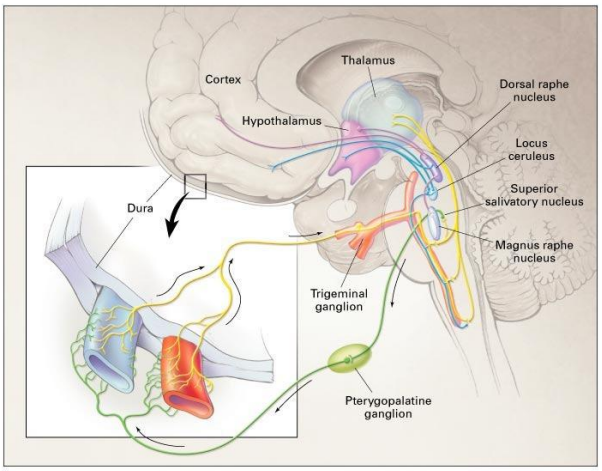
Explaining the Diagnosis



Anthony M. Clin Neurol Neurosurg 94(4):297-301, 1992



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

my.clevelandclinic.org/health/diseases/5005-migraine-headaches

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Diagnostic Pitfalls

- "Sinus" Headache: Facial/periorbital pain, ?autonomic features
- Cervicogenic: Often related to peripheral/central sensitization, though can be caused by high radiculopathy, facet arthropathy, etc.
- Tension: Mild to moderate in intensity; although it's the most common headache type, I don't often see this!

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Challenge the Utility of "Triggers"

Patients may feel "blamed" or stigmatized for having a migraine

Triggers may be impossible to figure out

Triggers may not be avoidable

Can increase anxiety or lead to anticipation of attacks

Do not address the underlying cause of the disorder

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Turner DP, Houle TT. Influences on headache trigger beliefs and perceptions. Cephalalgia. 2017;38(9):1545-1553.

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Case 2: Sheila with Acute Migraine Needs

24-year-old woman with episodes of unilateral moderate to severe attacks of pulsating head pain with associated light sensitivity.

Nausea and sometimes vomiting if pain is more intense.

Symptoms worse with movement and can last 6 hours or so if untreated.

Ibuprofen used to get rid of symptoms within one hour but has been less helpful over last few months.

She has about 2-3 of these a month, associated with poor sleep and stress.

She has never been given prescription medication in the past.

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Now What?

What Treatment Gaps Exist for Her?

What Would You Prescribe?

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Level of Evidence for Acute Migraine Treatment

Level A

Triptans: all triptans, all formulations

Ditans: Lasmiditan

Gepants: Rimegepant, Ubrogepant, Zavegepant

Dihydroergotamine NS

NSAIDs: Diclofenac, aspirin, naproxen, ibuprofen, celecoxib liquid, rizatriptan/meloxicam combination

Acetaminophen/aspirin/caffeine 500/500/130 mg

Acetaminophen 1000 mg (for non-incapacitating attacks)

Level B

Antiemetics: IV Metoclopramide & Prochlorperazine

Anti-dopamine: IV Chlorpromazine & Droperidol IV

Ergots: IM/IV Dihydroergotamine

NSAIDS: Ketorolac

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Ailani J, Burch R, Robbins M Headache. 2021 Jul;61(7):1021-1039.

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Next Generation Oral Acute Treatments

Gepants

- Rimegepant 75 mg orally dissolving tablet, no repeat dose recommended
- Ubrogepant 50, 100 mg PO, second dose allowed per 24-hour period
- Zavegepant 10 mg nasal spray, no repeat dose recommended

Ditans

- Lasmiditan

When to consider?

- Nonresponse or side effects with 2 triptans
- Contraindications to other acute treatments including triptans

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

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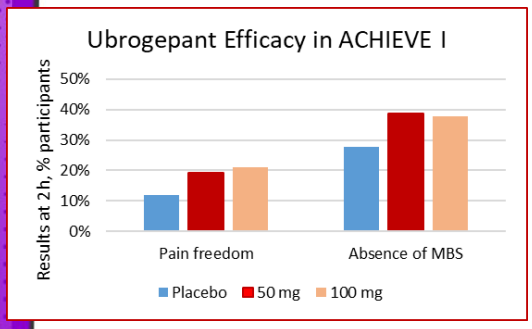
Gepants in Clinical Practice



- Adverse events
  - Nausea, somnolence, (low rates), dysgeusia (nasal spray only)
- Gepant contraindications:
  - Pregnancy
  - Use with strong CYP3A4 inducers (ketoconazole, clarithromycin)
  - Ubrogepant dose should be limited to 50 mg in patients taking verapamil and in hepatic disease; avoid rimegepant
- Not believed to cause medication overuse headache
  - Rimegepant is FDA approved for prevention with every other day dosing

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Dodick DW, et al. N Engl J Med. 2019 Dec 5;381(23):2230-2241; Lipton RB et al. JAMA. 2019 Nov 19;322(19):1887-1898; Lipton RB et al Lancet Neurol. 2023. Mar;22(3):209-217.

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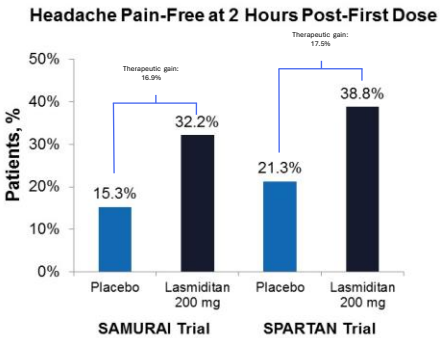
Lasmiditan in Clinical Practice

Receptor	Location	Primary Activity
5-HT_{1D}/5-HT_{1F}	Trigeminal terminals	Inhibit CGRP release
5-HT_{1B}	Blood vessels	Vasoconstrictor
5-HT_{1F}/5-HT_{1B}	CNS	Inhibit 5-HT, NE, ACh release



- Targets 5-HT1F receptors (nociception without vasoconstriction)
- AEs: Dizziness, paresthesia, somnolence, fatigue, nausea, and lethargy
- Major caveat: no driving for 8 hours after taking, even if patient feels fine
- Clinical usage: Probably best for nighttime or end of day rescue
  - 100, 200 mg doses
- Avoid during pregnancy

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Moreno-Ajona D et al, Headache. 2019 Jul;59 Suppl 2:3-19.

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Rescue Therapy

- Consider in any patient with
  - Significant nausea/vomiting
  - Rapid onset headache
  - Intermittent treatment failure
  - At least one ED visit for migraine
- Strategy: Non-oral formulations helpful
  - Injections
  - Nasal sprays
  - Phenothiazine suppositories
  - Indomethacin suppositories
- What about butalbital combination medications and opiates?
  - Level C evidence
  - High risk of medication overuse headache
  - Butalbital and opiate withdrawal syndromes with high daily dosing
  - Never first line, maybe as rare rescue
- Other:
  - Sedatives
  - Steroids – especially for prolonged refractory migraine (status migrainosus)

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Non-Oral Options

Ergot	• Nasal • SQ/IM injection (drawn up and injected by patient)
Triptans	• Nasal sumatriptan, zolmitriptan • SQ sumatriptan auto injector
NSAIDs	• Ketorolac nasal vs. SQ/IM injection (drawn up and injected by patient)
Neuromodulation	• Many options for acute/preventive… More to come!
Gepant	• Zavegepant

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Decision Making

Choosing the right option for your patient

- Speed of onset of attack (fast onset may benefit from non-oral route)
- Severity of attack (migraine specific)
- Associated GI symptoms (non-oral route of administration)

When to choose new treatments

- Inadequate response or inability to tolerate two or more oral triptans
- Contraindications (CV/Safety concerns/Age)

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Patient Satisfaction

- Make sure to follow up next visit if the medication is effective
- Fast pain relief?
  - Most patients will rate this as most important feature, but will consider fast to be minutes and still prefer oral medication
- Return to normal function?
  - Most patients will tolerate mild headache if able to function!
- Side effects?
  - Enough to delay care?
  - Enough to prefer to use OTC medication instead?
- Cost?
  - Newer medications/devices; patients will often save medication or device use due to small quantity given

Lipton RB. Headache 1999
Lipton RB. Headache 2002

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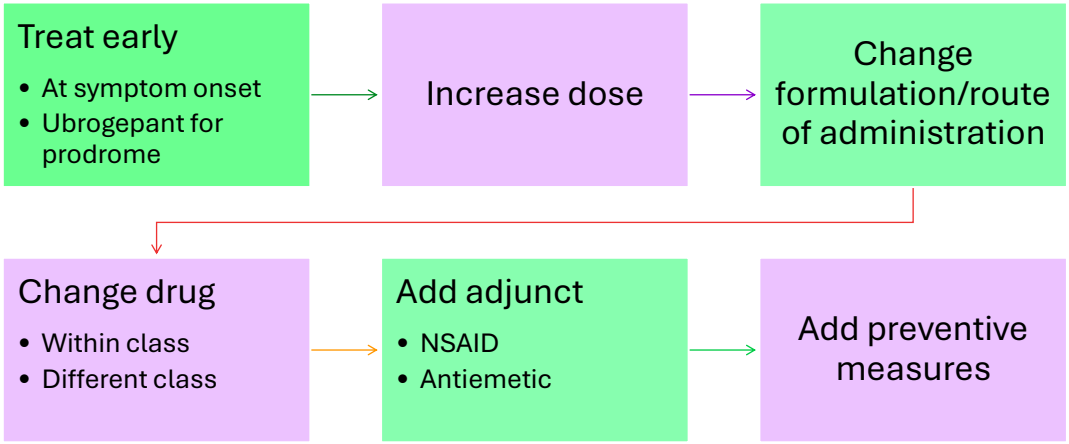
Optimizing Treatment with Treatment Failure



Gao L, Zhao F, Tu Y, Liu K. The prodrome of migraine: mechanistic insights and emerging therapeutic strategies. Front Neurol. 2024 Nov 29;15:1496401.

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Pearls

- Every person with migraine needs reliable acute treatment
- Consider migraine specific treatment in those with moderate to severe attacks
- Consider non-oral in those with associated nausea, fast onset/fast build up attacks, or those who want fast relief
- Consider neuromodulation or gepants when concerned about overuse of acute treatment in addition to starting prevention

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Case 3: Patient Who Prefers Non-drug Treatments

- 49-year-old woman with a history of migraine with aura since her 20s, presents with 4 headache days/month
- 2 of these days are severe
- She experienced intolerable side effects on nortriptyline and topiramate
- Sumatriptan works within 2 hours, but it makes her feel awful
- She would like to avoid taking prescription medications, if possible

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Non-Drug Treatments in Practice

When Do You Think About Them?

Do You Ask Patients About Non-drug Treatment Experience?

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Evidence-based, Non-Pharmacologic Treatments

Body-Based Approaches

- PT/Craniosacral/Acupuncture

Neuromodulation

Mind-Body Approaches

- Cognitive Behavioral Therapy
- Biofeedback
- Relaxation Training
- Acceptance and Commitment Therapy
- Mindfulness Based Stress Reduction

Nutriceuticals

Kuruvilla, D. E., Mehta, A., Ravishankar, N. & Cowan, R. P. A patient perspective of complementary and integrative medicine (CIM) for migraine treatment: a social media survey. *BMC Complement Med Ther* 21, 58 (2021).

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Evidence-Based Lifestyle Modifications for Migraine Prevention

Exercise: Regular, aerobic exercise reduces headache frequency, severity, and duration[1]

Sleep: Treat underlying sleep disorders.

Healthy sleep practices such as sleeping at regular intervals can decrease headache frequency[2]

Nutrition and Hydration:

Keep a consistent meal schedule, avoid fasting or skipping meals.[3]

Maintain adequate hydration[4]

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Nutraceuticals for Migraine Prevention

- Magnesium - 600 mg daily
- Riboflavin (Vitamin B2) - 400mg daily
- Butterbur (*Petasites hybridus*)- 50-75mg twice daily
  - Use with caution due to hepatotoxicity
  - Removed from treatment AHS/AAN guidelines
- Feverfew - 100 mg-300 mg up to 4 times a day with 0.2-0.4% parthenolide content.
  - Contraindicated in pregnancy: uterine contractions/miscarriage
- Coenzyme Q10 - 150 mg daily
- Melatonin – 3 mg daily
- Vit D - 4000 IU daily

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Kuruvilla, D. & Wells, R. E. Evidence-Based Integrative Treatments for Headache. *Headache* 59, 971–972 (2019).

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"Paying attention in a particular way, on purpose, in the present moment, non-judgmentally"

- Jon Kabat-Zinn

TABLE 2. EVIDENCE-BASED BEHAVIORAL TREATMENTS FOR HEADACHE

Treatment (Evidence)[a]	Treatment goals	Example interventions	Evidence-based results
Relaxation training[3,24] (Grade A)	Modify headache-related responses and reduce stress-related arousal Decrease muscular tension, particularly beneficial for somatic symptoms	Progressive muscle relaxation Diaphragmatic breathing Autogenic training Self-hypnosis	Reduced headache frequency and missed work days More effective when combined with CBT
Biofeedback[25] (Grade A)	Self-regulate typically nonvoluntary responses (eg, body temperature) Use devices to monitor headache-related responses to view and control	Thermal biofeedback to raise body temperature reduces sympathetic arousal and EMG biofeedback to reduce muscle tension	Thermal feedback most effective when combined with relaxation training
CBT[26,27] (Grade A)	Recognize and cope more effectively with stressful situations Target thoughts/emotions not directly addressed in relaxation and biofeedback Reduce perceived trigger avoidance Target comorbid mood/anxiety disorders	Monitoring of stressful situations/responses Modification of unhelpful thoughts ("I can cope" vs "I will be disabled") Coping skills/problem-solving Trigger management	Reduced headache frequency, severity, and disability Reduced depression/anxiety Improved quality of life Reduced catastrophizing and increased positive coping
Mindfulness therapies[2,28,29] (Emerging evidence from small trials)	Accept pain while distancing from pain-related thoughts Reduce emotional suffering and magnification of pain sensations Pay attention moment-to-moment experience with acceptance of change	MBSR (8 weeks) emphasizing formal mindfulness meditation and movement-based practices Mindfulness-based cognitive therapy, adapted from MBSR, emphasizing identifying negative thinking patterns Acceptance and commitment therapy for mindfulness with emphasis on engaging in valued behaviors	Reduced headache frequency and duration Reduced disability Improved self-efficacy Reduced catastrophizing and increased acceptance
CBT-I[30] (Small, growing evidence)	Change underlying behaviors and thoughts that maintain insomnia	Strategies for reducing conditioned arousal and racing thoughts at night	Reduced headache frequency Typically, effective in 4-6 sessions

[a]Grade A = strongest research support as per 2000 US Headache Consortium Guidelines[31]; may consider as front-line treatment.
Abbreviations: CBT, cognitive-behavioral therapy; CBT-I, cognitive-behavioral therapy-insomnia; MBSR, mindfulness-based stress reduction

Motwani, M, Kuruvilla, D. Practical Neurology 2019

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Mind-Body Therapies

Particularly well suited for patients who:

- Have inadequate response, poor tolerance, or medical contraindication to specific pharmacologic treatments.
- Are pregnant, lactating, or planning pregnancy
- Have a history of MOH
- Exhibit significant stress or deficient stress coping skills
- Have high migraine-related disability, significant medical co-morbidities

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Ailani J, et al. Headache. 2021;61(7)1021-1039

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Cognitive Behavioral Therapy

Skills-based psychotherapy built on the interrelationships among thoughts, emotions, behaviors, and physiologic responses.

Patients learn cognitive skills

- Identify and challenge negative self-talk
- Develop helpful coping thoughts

Patients learn behavioral strategies

- Problem-solving skills to adaptively manage stressors
- Relaxation strategies

Improves patient's self-efficacy

- Manage headache pain and disability
- Respond more effectively to stress/symptoms

Heterogeneity in studies, but does reduce headache frequency and MIDAS/disability

Seng, E. K. *et al.* Does Mindfulness-Based Cognitive Therapy for Migraine Reduce Migraine-Related Disability in People with Episodic and Chronic Migraine? A Phase 2b Pilot Randomized Clinical Trial. *Headache* **59**, 1448–1467 (2019).
Bae JY, et al. Medicina (Kaunas). 2021 Dec 28;58(1):44

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Biofeedback

Courtesy of Dr. Niushen Zhang at Stanford! ☺

- Electronic sensory feedback and monitoring to help patients learn voluntary control over their bodily reactions
- $$$/Access
- Frequently used modalities for migraine:
  - Peripheral skin temperature
  - Blood-volume pulse
  - Electromyography

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Relaxation Training

- Helps patients learn to differentiate between tension and relaxation in the body and decrease sympathetic arousal in response to pain and stress.
- Patients learn a variety of relaxation techniques :
  - Diaphragmatic breathing
  - Progressive muscle relaxation*
  - Guided imagery
- Encourage practice daily as a preventive strategy, and as needed as an acute strategy
- Some examples of apps helping in our practice
  - Juva, Calm, Headspace

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*Minen, M.T., et al. (2020) Headache; 60: 2232-2246.

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Neuromodulation

All are FDA cleared for acute and preventive treatment except one

- Supraorbital transcutaneous nerve stimulation- up to 1 hour during attack
- Single pulse transcranial magnetic stimulation- 3 pulses as needed up to 3 times during an attack [cleared in age 12+]
- Non-invasive vagal nerve stimulation- bilateral application, 2 minutes each side [cleared in age 12+]
- Remote electrical neuromodulation - application to arm 45 minutes during attack [cleared in age 12+ migraine/chronic migraine]
- External combined occipital and trigeminal neurostimulation – up to 1 hour during attack **(acute indication only)**

Singh RH. Headache 2019
Yarnitsky D. Headache 2019
Ailani J Headache 2021
Tepper SJ Headache 2022

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The Treatment Plan for This Patient

Preventive Treatment

- Lifestyle modification: Avoid skipping meals, increase frequency of aerobic exercise
- Started magnesium, riboflavin, coenzyme Q10
- Referral to pain psychology and biofeedback

Acute Treatment

- Switch sumatriptan to almotriptan

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PART II

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Case 4: Deven with Frequent Migraine Attacks

- Deven is 36-year-old lawyer with a 16-year history of migraine
- Over the last 2 years, he has seen a gradual worsening of migraine and is now having 2-3 headaches per week
- His triptan is not consistently effective and ends up missing work about once per month

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When to Consider Preventive Treatment

- Significant interference with activities despite acute treatment
- Attack frequency > 1 per week
- Elevated risk: medication overuse or daily headache
- Acute meds: ineffective, contraindicated, used >2x/week
- Patient preference
- Uncommon migraine types (brainstem, hemiplegic, prolonged aura, migrainous infarct)

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Important to Consider Attack-related Disability

Prevention should be…	Headache days/month	Degree of disability*
Offered	≥ 6	None
	≥ 4	Some
	≥ 3	Severe
Considered	4 or 5	None
	3	Some
	2	Moderate

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Ailani J, Burch RC, Robbins MS; Headache. 2021 Jul;61(7):1021-1039.

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Goals of Preventive Treatment

Reduce headache-related disability

Reduce by at least 50%:

- Frequency
- Duration
- Intensity

Improve response to acute medications

Reduce acute medication requirements

Can't promise "no headaches"

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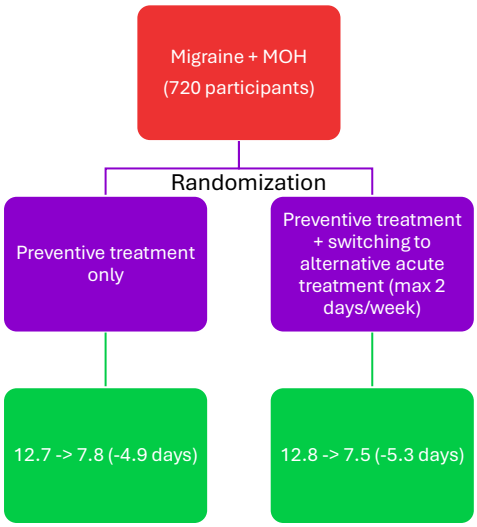
Medication Overuse Headache: The MOTS Trial



Moderate-severe headache days at 9-12 weeks

- **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 chronic migraine and medication overuse, the efficacy of starting or optimizing preventive medication is ***not dependent*** on whether patients first reduce their use of acute medication

Todd J. Schwedt et al. Neurology 2022;98:e1409-e1421

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Slide courtesy of AHS Reach Program

Preventive Treatments for Migraine

Established Efficacy		Probably Effective	
Oral	Parenteral	Oral	Parenteral
Atogepant		Amitriptyline	OnabotulinumtoxinA + CGRP mAb
Candesartan	Eptinezumab	Atenolol	
Divalproex sodium	Erenumab	Lisinopril	
Frovatriptan (menstrual migraine)	Fremanezumab	Memantine	
Metoprolol	Galcanezumab	Nadolol	
Propranolol	OnabotulinumtoxinA	Venlafaxine	
Rimegepant			
Timolol			
Topiramate			
Valproate sodium			

Ailani J et al. *Headache*. 2021;59:1-19.

Conclusion

The CGRP-targeting therapies should be considered as a first-line approach for migraine prevention along with previous first-line treatments without a requirement for prior failure of other classes of migraine preventive treatment.

Charles AC et al. *Headache*. 2024 Mar 11

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Disease-specific Preventive Treatments: *CGRP mAbs*

	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
CGRP target	Receptor	Peptide	Peptide	Peptide
Side effects	Constipation, worsened HTN, Hypersensitivity	Injection site reactions, Hypersensitivity	Injection site reactions, Hypersensitivity	Hypersensitivity
Indication approved	EM, CM	EM, CM, eCH	EM, CM	EM, CM
Formulation	SQ	SQ	SQ	IV
Frequency	Monthly	Monthly	Monthly, Quarterly	Quarterly
Dosing	70mg, 140mg	240mg loading dose, 120mg maintenance dose	225mg (monthly) or 675mg (quarterly)	100mg, 300mg

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CGRP Monoclonal Antibodies: FAQs

- Can I use these in people with episodic migraine?
  - Approved and effective for all migraine
- Can I use with Onabotulinum Toxin?
  - Evidence for improved efficacy with combination treatment
- Do they work in patients with refractory migraine?
  - Similar efficacy:
    - Even if other treatments have failed
    - Even with medication overuse
    - Even with significant comorbidity
- How quickly do they start working?
  - Onset can be within first week or first day
- How long should I wait to determine efficacy?
  - Efficacy can increase over time
- How do real world results compare to clinical trial results:
  - Similar efficacy, maybe higher rates of constipation/HTN with erenumab

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Real-world Experience with mAbs: What Can Patients Expect?

- How do you switch from one mAb to the other?
- What are your patients telling you about effectiveness and tolerability?
- New AEs (dizziness, fatigue, cramps, joint pain, fatigue, nausea, worsening headache)
  - HAIR LOSS AND ORAL ULCERS added to erenumab warnings*
- Early wearing off (before next dose, over time)
- All CGRP mAbs are ineffective for some

* https://www.medsafe.govt.nz/consumers/cmi/a/aimovig.pdf

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

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Consider Comorbidities When Personalizing Treatment

- Comorbidity may complicate diagnosis
  - Having diagnosed migraine or depression the other condition becomes more likely
  - Parsimony is a mistake
- Comorbidity informs and limits treatment
  - Multiple comorbidities and contraindications
  - Key to good outcome is recognizing
- Insights into mechanisms
- Some comorbidities are risk factors for progression
- Comorbidity contributes to disease burden
  - HRQoL
  - Economic impact

Lipton RB, et al. *Neurology*. 2000;55(5):629-635.
Lafata et al, *AGIM*, 2003

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How to Choose?: Patient Preferences

- Ask patients about priorities and preferences
  - Urgency of preventive treatment benefits
- Accurately determine HA frequency and burden of illness
- Ask patients about what symptoms bother them the most
- Determine the most appropriate kind of treatment (one patient may need multiple treatments)
  - Preventive vs acute treatments (denial of chronicity is a barrier to prevention)
  - Natural products, neuromodulation, and/or drugs
- Nature of administration for preventives
  - Oral vs injectable; at home vs in office
- Tolerability vs efficacy

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Guidelines for Starting CGRP Meds

American College of Physicians Guideline 2/2025

Rec #1: Either metoprolol or propranolol; valproate; venlafaxine; or amitriptyline.

Rec #2: If they do not tolerate or respond to treatments in #1, then CGRP antagonist or a CGRP monoclonal antibody

Rec #3: If they do not tolerate or respond to treatments in #1 or #2, then topiramate

American Headache Society 4/2024 Position Statement

- The CGRP-targeting therapies should be considered as **a first-line approach** for migraine prevention along with previous first-line treatments without a requirement for prior failure of other classes of migraine preventive treatment.

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Pearls

- Disabling attacks, poor response to acute treatment, frequent use of acute treatment are all good reasons to start prevention
- Per the MOTS trial, in 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
- Dosing strategy: starting low vs quickly maximizing effectiveness
- Shared decision making should be used when starting treatment with patients

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If You Could Only Bring One Preventive, Which Would You Choose?

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Case 5: Pregnant Patient with Migraine

35-year-old woman with a history of episodic migraine without aura, who is now 14 weeks pregnant and experiencing increase in migraine frequency in the past month.

Prior to pregnancy, she had 1-2 migraine days/month that were effectively treated with rizatriptan

In the past month, she has been having 3-4 migraine days/week.

No change in character of the headaches, normal neurological exam

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Now What?

How Do You Talk About Options Even Before Pregnancy?

What Do You Tell Patients to Expect During Pregnancy?

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Case 5: Pregnant Patient with Migraine

35-year-old woman with a history of episodic migraine without aura, who is now 14 weeks pregnant and experiencing increase in migraine frequency in the past month.

Prior to pregnancy, she had 1-2 migraine days/month that were effectively treated with rizatriptan

In the past month, she has been having 3-4 migraine days/week.

No change in character of the headaches, normal neurological exam

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Migraine Treatment During Pregnancy

- Preventive Treatments to Consider:
  - Lifestyle modifications
  - Nutraceuticals
  - Behavioral therapies
  - Oral preventives
  - OnabotulinumtoxinA
  - Peripheral nerve block
  - Neuromodulatory Devices
- Acute Treatments to Consider:
  - Acetaminophen
  - Metoclopramide
  - Triptans
  - Peripheral nerve block
  - Neuromodulatory Devices

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Systematic Review on Headache Treatment in Pregnancy and Lactation

Preventive		Acute	
May be associated with fetal/child adverse events	**May NOT be associated with fetal/child adverse events**	**May be associated with fetal/child adverse events**	**May NOT be associated with fetal/child adverse events**
Antiseizure Meds Venlafaxine Tricyclics Benzodiazepines Beta blockers Prednisolone Oral magnesium	Calcium channel blockers Antihistamines	Acetaminophen Prednisolone Indomethacin Ondansetron Antipsychotics IV Magnesium	Triptans Low dose aspirin

Saldana IJ, et al. Headache 2021.

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CLINICAL PRACTICE GUIDELINE

NUMBER 3

ACOG
The American College of Obstetricians and Gynecologists

Headaches in Pregnancy and Postpartum

Committee on Clinical Practice Guidelines–Obstetrics. This Clinical Practice Guideline was developed by the ACOG Committee on Clinical Practice Guidelines–Obstetrics in collaboration with Catherine S. Stika, MD; Kathleen Brookfield, MD, PhD, MPH; and Laura Mercer, MD, MBA, MPH, with consultation from Nina Riggins, MD, PhD and Huma U. Sheikh, MD.

PURPOSE: To provide updated evidence-based recommendations for the evaluation and treatment of primary and secondary headaches in pregnancy and postpartum.

TARGET POPULATION: Pregnant and postpartum patients with a history of or experiencing primary or new secondary headaches.

Headaches in Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 3. Obstet Gynecol. 2022 May 1;139(5):944-972. Erratum in: Obstet Gynecol. 2022 Aug 1;140(2):344.

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ACOG Recommended Acute Therapy

Table 3. Interventions for Treatment of Primary Headaches in Pregnancy*

Drug	Class	Recommendation	Potential Associated Risks
Acetaminophen[1]	Analgesic	Recommended	Maternal and fetal hepatic toxicity with overdosage
Caffeine[1–4]	Methylxanthine, dietary supplement	Recommended at less than 200 mg per day	Neonatal cardiac arrhythmias at greater than 200 mg per day
Diphenhydramine[1]	Antihistamine	Recommended	Maternal drowsiness
Metoclopramide[1]	Antiemetic – dopamine antagonist	Recommended	Maternal fatigue, dizziness, agitation, nausea; combine with diphenhydramine to reduce metoclopramide-associated akinesia

Headaches in Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 3. Obstet Gynecol. 2022 May 1;139(5):944-972. Erratum in: Obstet Gynecol. 2022 Aug 1;140(2):344.

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TABLE 4-4 Safety and Effectiveness of Acute Medications in Pregnancy

Medication	Safety[a]	Effectiveness[a]
Metoclopramide	More safe	Moderately effective
Lidocaine (subcutaneous, intranasal)	More safe	Moderately effective
Acetaminophen	More safe	Moderately effective
Cyclobenzaprine	More safe	Moderately effective
Diphenhydramine (adjunct for sedation)	More safe	Least effective
Ondansetron (adjunct for nausea)	Between safest and moderate safety categories	Most effective
Triptans	Between safest and moderate safety categories	Most effective
Ibuprofen (only for use during second trimester)	Moderate safety	Moderately effective
Prednisone	Moderate safety	Moderately effective
Prochlorperazine	Moderate safety	Moderately effective
Oxycodone (generally not recommended for migraine)	Moderate safety	Least effective
Butalbital (generally not recommended for migraine)	Moderate safety	Least effective
Lasmiditan	Least safe	Most effective
Gepants (rimegepant, ubrogepant)	Least safe	Most effective
Magnesium sulfate (IV)	Least safe	Least effective
Ergots	Least safe	Moderately effective

[a] Relative safety and effectiveness judged by the opinion of the author of this article combining tolerability in clinical practice and review of the available evidence[29,33] and expert consensus,[34] not based on direct comparisons among therapies in clinical trials.

Rayhill M. Headache in Pregnancy and Lactation. Continuum (Minneap Minn). 2022 Feb 1;28(1):72-92.

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Triptans and Pregnancy

Recent systematic review and meta-analysis of 6 acute studies

Triptans do not appear to increase the risk of pregnancy outcomes when compared to the general population

Dudman DC et al. J Neurology 2021

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ACOG Recommended Prevention

IS ANYTHING MISSING??

Table 2. Interventions for Prevention of Headaches in Pregnancy*

Drug or Therapy	Class	Recommendation	Potential Associated Risks
Amlodipine[1,2]	Calcium channel blocker	Consider as first line use for prevention	None
Cyproheptadine[1]	Antihistamine	Consider as first line use for prevention	None
Diphenhydramine[1]	Antihistamine	Consider as first line use for prevention	None
Nifedipine[1,2]	Calcium channel blocker	Consider as first line use for prevention	None
Verapamil[1,2]	Calcium channel blocker	Consider as first line use for prevention	None

Headaches in Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 3. Obstet Gynecol. 2022 May 1;139(5):944-972. Erratum in: Obstet Gynecol. 2022 Aug 1;140(2):344.

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What Do We Know About Onabotulinum Toxin Safety in Pregnancy?

- ~500 cases of onabotulinum toxin A use during pregnancy have now been reported
- Recent cumulative update from Allergan safety database (29 years of data)
  - 397 eligible pregnancies
  - 30% for migraine; 35% aesthetic
  - 95% *prior to conception or in the first trimester*
  - No increased signal of teratogenicity
- Case series of ~55 patients treated with onabotulinum toxin A for chronic migraine *throughout pregnancy*
  - Live full-term births of healthy babies with no organ malformations

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Brin MF et al. *Neurology*. 2023 Jul 11;101(2):e103-e113.
Summers JE et al. Safety of using onabotulinumtoxinA for the treatment of chronic migraine in pregnancy. Presented at: Virtual Annual Scientific Meeting; AHS

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CGRP Monoclonal Antibodies

- IgG cross the placenta through the neonatal Fc receptor at 20-22 weeks of pregnancy and allows for placental transport
- CGRP regulates utero-placental blood flow and uterine relaxation
- May regular gestational blood pressure: preventing eclampsia and hypertension
- Animal studies did not identify reproductive toxicity
- Long half-lives; pre-pregnancy counseling is key and should stop 5-6 months prior to conception

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Are CGRP Antagonists Safe to Use During Pregnancy?

- Objective: Assessed the safety profile of erenumab, galcanezumab, and fremanezumab in pregnancy and lactation
- Methods: Safety reports of suspected adverse drug reactions were retrieved from VigiBase as of 2019, for case-by-case assessment and disproportionality analysis using the reporting odds ratio
- Results: 94 safety reports (50 erenumab, 31 galcanezumab, 13 fremanezumab). No specific maternal toxicities, patterns of major birth defects, or increased reporting of spontaneous abortion were found
- Because of relatively limited number of adverse drug reactions reported and the lack of long-term safety data, continuous surveillance is required in pregnant and lactating women exposed to these drugs

Noseda R, et al. Safety profile of erenumab, galcanezumab and fremanezumab in pregnancy and lactation: Analysis of the WHO pharmacovigilance database. Cephalalgia. 2021 Jun;41(7):789-798.

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Pregnancy Registries

- Rimegepant registry: https://nurtecpregnancyregistry.com/
- Erenumab: https://www.genesispregnancyregistry.com/
- Ubrogepant and Atogepant: https://www.empresspregnancyregistry.com/
- Galcanezumab: https://pregnancyregistry.lilly.com/emgality#patients
- Fremanezumab: https://tevamigrainepregnancyregistry.com/
- LIST OF EXPOSURE REGISTRIES FDA:
- https://www.fda.gov/consumers/pregnancy-exposure-registries/list-pregnancy-exposure-registries

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TABLE 4-3 Safety and Effectiveness of Preventive Treatments in Pregnancy

Medication	Safety[a]	Effectiveness[a]
Propranolol	More safe	Most effective
Magnesium	More safe	Least effective
Memantine	More safe	Moderately effective
Coenzyme Q_{10}	More safe	Least effective
Venlafaxine	Moderate safety	Moderately effective
OnabotulinumtoxinA	Moderate safety	Most effective
Amitriptyline/nortriptyline	Moderate safety	Most effective
Riboflavin	Moderate safety	Least effective
Verapamil	Moderate safety	Least effective[b]
Gabapentin	Moderate safety	Least effective
Calcitonin gene-related peptide targeting treatments (erenumab, fremanezumab, galcanezumab, eptinezumab, rimegepant, atogepant)	Least safe	Most effective
Topiramate	Least safe	Most effective
Lisinopril	Least safe	Moderately effective
Candesartan	Least safe	Moderately effective
Valproic acid	Least safe	Most effective
Feverfew	Least safe	Least effective

[a] Relative safety and effectiveness judged by the opinion of the author of this article combining tolerability in clinical practice and review of the available evidence[29,33] and expert consensus,[34] not based on direct comparisons among therapies in clinical trials.
[b] May have a specific role in the prevention of migraine with aura.

Stay Tuned for More Changes Given ACOG Guidelines; A Statement from Neurology Is Forthcoming!

Rayhill M. Headache in Pregnancy and Lactation. Continuum (Minneap Minn). 2022 Feb 1;28(1):72-92.

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Devices in Pregnancy

- External Trigeminal Neurostimulation (Cefaly) Registry: https://clinicaltrials.gov/study/NCT06788977
- Remote Electrical Neuromodulation (REN/Nerivio migra):
  - Peretz A, Stark-Inbar A, Harris D, et al. Safety of remote electrical neuromodulation for acute migraine treatment in pregnant women: A retrospective controlled survey-study. *Headache*. 2023; 63: 968-970.

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Treatment Plan for This Patient

Preventive Treatment	Acute Treatment
• Rule out secondary causes • Lifestyle modification: more regular sleep schedule, devoted time to walks • Started magnesium • Peripheral nerve block with lidocaine	• Metoclopramide/ acetaminophen • Occasional rizatriptan • Remote Electrical Neuromodulation (REN) device

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Case 6: Sadia's Chronic Migraine Is Still Disabling

- Sadia is a 48-year-old woman with chronic migraine
- Reduced severity and frequency with onabotA and topiramate
- Still experiences near daily headache, with 8 severe days per month
- Uses PO triptan for severe days, NSAID for moderate and REN device for her milder days
- Missing work 2-3 days each month when her rescue of IM Ketorolac doesn't work
- She asks about whether she is a candidate the new medications?

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How Do Migraine Attacks Affect Your Life?

Migraine affects everything. I can't make plans because what if I have a migraine and have to cancel. I used to go to yoga with my friends, but I kept missing, so this season I just didn't sign up. What's the point?

At work I've had to call out a couple times, one day I almost threw up in the classroom.

Can you imagine?

I try to hide it and just power through. But my family knows. My kids can see it on my face. Mom has a migraine again. They're so disappointed.

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Definition of Refractory?

Intractable migraine-Goadsby[2]
- Migraine
- Contraindication or failure of 4 preventative classes (adequate trial)

Refractory migraine-EHF[5]
- Chronic Migraine (ICHD3 beta)
- No MO
- Contraindication or failure of 3 preventative classes (minimum 3-month trial)

Refractory migraine-D'Antona[6]
- Chronic Migraine (ICHD3)
- No MO
- Contraindication or failure of 5 preventative classes (minimum 2-month trial)

2006 2008 2014 2019 2020

Refractory migraine-AHS[3]
- Migraine (ICHD2)
- Failure of 2 preventative classes (minimum 2-month trial)
- MIDAS≥11
- Contraindication or failure of acute treatments

Refractory migraine-Austrian consensus[4]
- Migraine (ICHD3 beta)
- Detoxification if MO
- Contraindication or failure of 3 preventative classes (minimum 3-month trial)

EHF consensus[7]

Resistant migraine	Refractory migraine
• Migraine (ICHD3) • Debilitating headache for **≥ 8 days/month for at least 3 months** • Contraindication or failure of **3 preventative classes** • MO can be present	• Migraine (ICHD3) • Debilitating headache for **≥ 8 days/month for at least 6 months** • Contraindication or failure of **all preventative classes** • Medication withdrawal attempts if MO

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Ornello, R. *et al*. Resistant and refractory migraine: clinical presentation, pathophysiology, and management. *EBioMedicine* **99**, 104943 (2024).

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Neurol Ther (2023) 12:1533–1551
https://doi.org/10.1007/s40120-023-00529-x

REVIEW

Multimodal Migraine Management and the Pursuit of Migraine Freedom: A Narrative Review

Andrew M. Blumenfeld · Richard B. Lipton · Stephen Silberstein · Stewart J. Tepper · Larry Charleston IV · Stephen Landy · Deena E. Kuruvilla · Aubrey Manack Adams

- **Layer preventive therapies**
- **Provide backup plans for acute treatment once preventives are optimized**
- **Address risk factors for progression – anxiety, depression, sleep disturbance (OSA), medication overuse**

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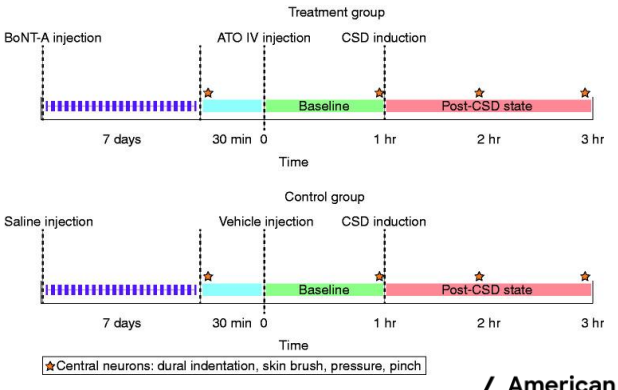
Combination Therapy

- OnabotulinumtoxinA and atogepant can produce attenuation of C- and Aδ-meningeal nociceptors
- Simultaneous use of both can block CSD-induced activation and sensitization of trigeminovascular HT and WDR neurons in the spinal trigeminal nucleus

CSD – cortical spreading depression
HT – high-threshold
WDR – wide-dynamic neurons



Melo-Carrillo, A. *et al*. Combined onabotulinumtoxinA/atogepant treatment blocks activation/sensitization of high-threshold and wide-dynamic range neurons. *Cephalalgia* 41, 17–32 (2021).

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Does Adding CGRP mAb to Onabotulinum Toxin A Help?

- CM pts on onabotA added CGRP mAb
- 15-25 ⟹ 6-11 migraine days/month
- Improvement by 3-4 days less migraine with addition of mAb
- Reduced wear-off of onabotA with addition of erenumab

Cohen F et al. Headache 2020;60(S1).
Suri H et al. Headache 2020;60 (S1).
Blumenfeld AM, et al. Pain Ther 2021
Ozudogru S et al. Headache 2020

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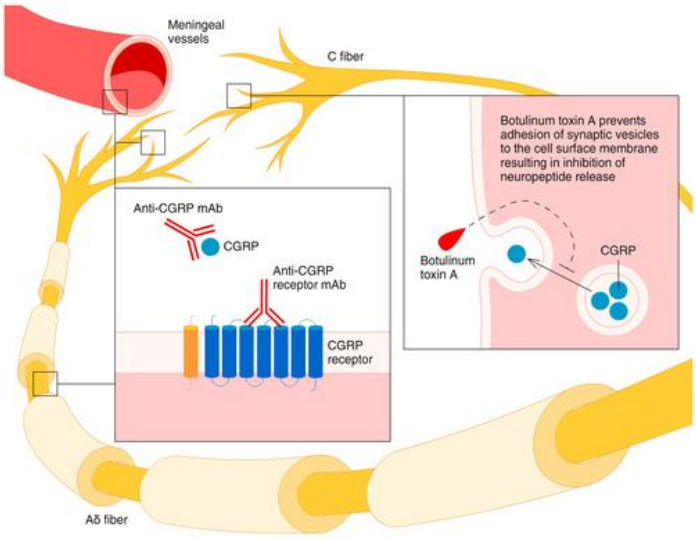
Rationale for OnabotA and CGRP mAb

- Preclinical data suggest synergistic effects within trigeminovascular system
- Fremanezumab prevents activation of Aδ-fibers
- OnabotA prevents activation of C-fibers



Pallesi L et al. Headache 2020; 60:1056

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Would Using a CGRP mAb + Gepant Work?

1. Mullin K et al. Potenial for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy. Neurology 2020.
2. Berman G et al. Safety of Rimegepant, an Oral CGRP Receptor Antagonist, Plus CGRP Monoclonal Antibodies for Migraine. Headache 2020.
3. Jakate A et al. Safety and tolerability of Ubrogepant for the acute treatment of migraine following co-administration with preventive monoclonal antibody treatment. Headache 2020. 60(S1).

Rimegepant prn + CGRP mAb was possibly effective and well tolerated.

- 2 patients using rimegepant for acute added erenumab and had preventive benefit[1].
- Case series of 13 patients (7 erenumab, 4 fremanezumab, 2 galcanezumab) showing combo well tolerated[2].

Ubrogepant following CGRP mAb safe and tolerated[3]

- No change in PK of ubrogepant when co-admin with erenumab or galcanezumab
- No safety concerns identified

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CGRP mAb + Gepant

- Real-world efficacy of ubrogepant
  - Prior treatment responders to CGRP mAb predicted response to ubrogepant
  - Patients concurrently using CGRP mAb + gepants had no difference in good responder rate or adverse event rate compared to non CGRP mAb user
  - Those on concurrent CGRP mAb with AE reported more moderate than mild AE

Chiang CC et al. Headache 2021

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Combining -Gepant for Acute AND Preventive?

- Phase Ib open label of atogepant 60mg daily for preventive and ubrogepant 100mg q3 days
- 31 enrolled, 26 completed
- Co-administration resulted in
  - 19% increase in ubro AUC plasma concentration time curve
  - 26% increase in ubro max plasma concentration
  - Not clinically meaningful, no new safety concerns
- Most frequently reported TEAEs (>10% of participants) were constipation, nausea, fatigue, back pain, abdominal pain, and neck pain

Blumenfeld AM et al. Headache 2023

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Rx: Gepant But Sadia Has Questions...

Which medication is stronger: triptan vs gepant?

Can I take the triptan and gepant together?

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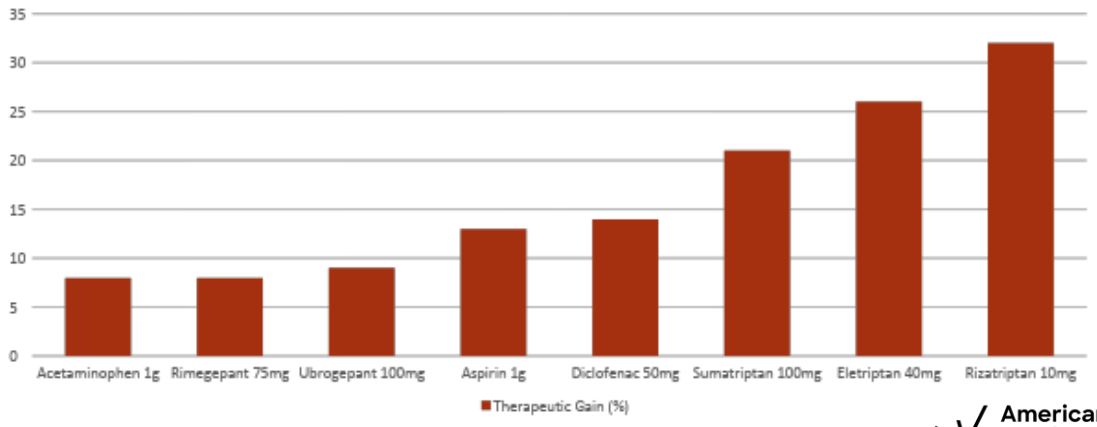
2hr Pain Freedom Rates



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Combining Acute Treatment

- GTN mouse model
  - Gepant vs. Triptan vs. Combination
  - Gepant x 9 days then triptan day 10 (rescue)
  - Triptan x 9 days then gepant day 10 (rescue)
- Combo was <u>not</u> more effective than single agent
- Rescue with either agent on day 10 not effective for pain reduction
- Why?
  - Perhaps both work on similar mechanism
  - Perhaps you need to add central agent (Ditan/NSAID)
- Take home: Tell your patient to save their triptans/gepants, if one does not work, layer in a ditan or NSAID

Ernststen C et al. Cephalalgia 2021;41:329-339

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Headache
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Research Submission

Discontinuation of Acute Prescription Medication for Migraine: Results From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study

Richard B. Lipton, MD; Susan Hutchinson, MD; Jessica Ailani, MD; Michael L. Reed, PhD; Kristina M. Fanning, PhD; Aubrey Manack Adams, PhD; Dawn C. Buse, PhD

Treatment Satisfaction

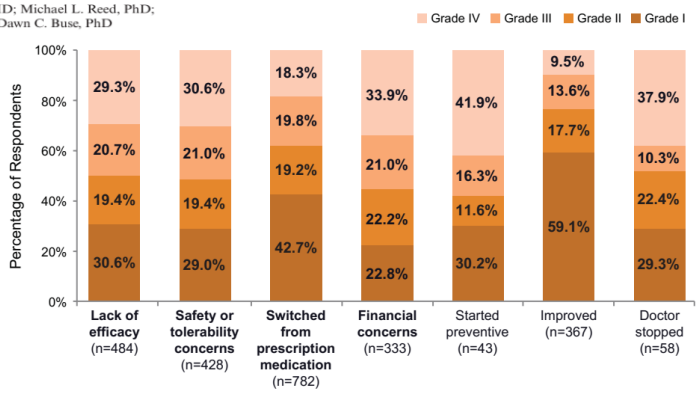

Fig. 2.—Migraine-related disability[a] among users who discontinued medication use by domains associated with discontinuation. [a]As determined by the Migraine Disability Assessment (MIDAS), where score 0-5 = grade I (little or no disability), 6-10 = grade II (mild disability), 11-20 = grade III (moderate disability), ≥21 = grade IV (severe disability). [Color figure can be viewed at wileyonlinelibrary.com]

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Risk Factors for Migraine Disease Progression

Table 1 Summary of key risk factors of migraine disease progression and possible protective actions

	Risk factors	Evidence for the risk factor association with progression	Possible protective actions	Evidence that addressing risk factors reduces progression risk
Migraine disease characteristics	*Any migraine disease characteristic risk factor*		Track attack frequency, severity, and treatment use through a diary or app	O
			Optimize acute and preventive treatment using both pharmacologic and non-pharmacologic options [1, 95–101]	↑
			Educate patients on healthy lifestyle choices and how to implement change	O
	≥5 MHDs (moderate risk) or ≥10 MHDs (high risk) [43]	↔	Progressive muscle relaxation [115]	↔
	Cutaneous allodynia [45–47]	↑		
	Persistent, frequent nausea [48]	↔		
Suboptimal treatment	*Any treatment-related factor*		Use non-pharmacologic approaches such as neuromodulation and biobehavioral therapies [1, 95]	↔
			Change dose or route of administration	O
			Add or switch to another acute or preventive medication	O
			Add preventive therapies	O
			Optimize adherence	O
	Suboptimal acute treatment [21, 24, 49, 50, 102]	↑	Optimize acute migraine medication	O
			Educate patients about their acute migraine medication [103]	O
	Acute medication overuse [22, 47, 52, 91]	↑	Educate patients about appropriate exposure to acute migraine medication and risks of high use	O
			Limit acute medication use to < 8 days/month	O
	Preventive medication not satisfactorily effective/tolerated	O	Optimize preventive medication [5, 104–111]	↑
			Aim for treatment to reduce days of moderate or severe pain to < 4 days per month	O
			Take preventive medication as prescribed	O
			Consider adding non-pharmacologic preventive options	O

Lipton, R. B. *et al.* Risk factors for migraine disease progression: a narrative review for a patient-centered approach. *J. Neurol.* 270, 5692–5710 (2023).

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Risk Factors for Migraine Disease Progression

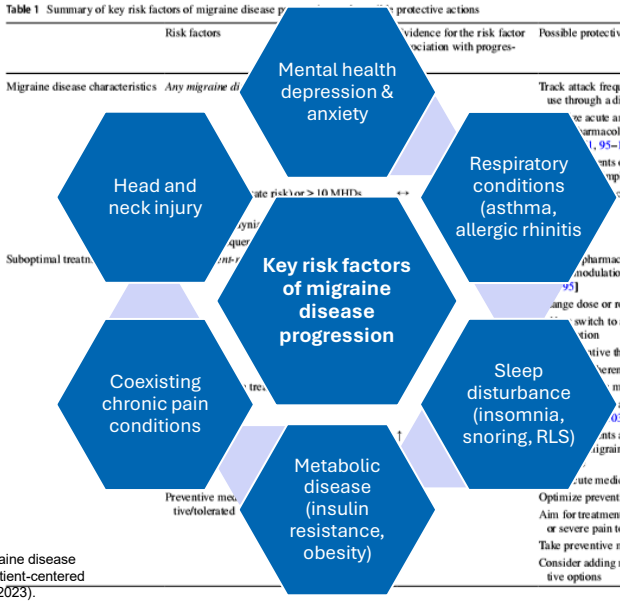

Table 1 Summary of key risk factors of migraine disease p protective actions

Risk factors	vidence for the risk factor sociation with progres-	Possible protective actions	Evidence that addressing risk factors reduces progression risk
Migraine disease characteristics *Any migraine di*		Track attack frequency, severity, and treatment use through a diary or app	O
		e acute and preventive treatment using armacologic and non-pharmacologic 1, 95–101]	↑
		nts on healthy lifestyle choices mplement change	O
	ate risk) or > 10 MHDs ↔	cle relaxation [115]	↔
Suboptimal treatn		pharmacologic approaches such as modulation and biobehavioral therapies 95]	↔
		ange dose or route of administration	O
		switch to another acute or preventive tion	O
		tive therapies	O
		erence	O
		migraine medication	O
		about their acute migraine 03]	O
		nts about appropriate exposure migraine medication and risks of	O
		cute medication use to < 8 days/month	O
Preventive me tive/tolerated		Optimize preventive medication [5, 104–111]	↑
		Aim for treatment to reduce days of moderate or severe pain to < 4 days per month	O
		Take preventive medication as prescribed	O
		Consider adding non-pharmacologic preventive options	O

Lipton, R. B. *et al*. Risk factors for migraine disease progression: a narrative review for a patient-centered approach. *J. Neurol.* 270, 5692–5710 (2023).

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One Step Forward, Two Steps Back

Prior auth win! Add Fremanazumab 225mg monthly

At three month follow up, Sadia reports a reduction to 15 headache days a month

No longer calling her pharmacy at the end of each month asking when she can refill her triptan

However, had an EGD for some stomach pain last month and now diagnosed with gastritis

GI says no more NSAIDs

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