State of the Art 2023 Patient-Centered Migraine Care: Implications for Clinical Practice

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Disclosures

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Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Distinguish current and emerging migraine therapies by their efficacy and safety profiles, pharmacologic properties, indications, and administration.
2. Apply current clinical evidence and patient factors to ensure appropriate and timely treatment decisions for patients with migraines.
3. Develop advanced collaborative strategies and communication methods to facilitate effective shared decision-making and patient-centered migraine care.

Acute Treatment

26-year-old woman presents with 2 days a month of disabling unilateral head pain with associated nausea, photophobia, dizziness, and poor concentration.

What do you offer her?

(Getty Images, n.d.)

Poll Instructions

Join by Web

1. Go to **PollEv.com**
2. Enter **CEPO**
3. Respond to activity

Join by Text

1. Text **CEPO** to **22333**
2. Text in your message

What Do You Offer Her?

A. Ibuprofen 800mg
B. Sumatriptan 100mg
C. Butalbital /Acetaminophen/Caffeine
D. Meclizine 25mg

Acute Treatment

- Acute medications should be offered to EVERY patient with migraine

- Fewer than 1 in 5 persons with migraine use migraine-specific acute medications
  - 37% ever used a triptan (82% oral, 21% nasal, 19% injection)
  - 15% currently use a triptan
  - 38-66% patients never refill initial triptan

- Many persons with migraine are dissatisfied with their current acute treatment
  - Lack of efficacy, Safety concerns, Poor tolerability

- 95.8% of persons with migraine have 1 unmet acute treatment need

(Digre, K., 2018)
(Bigal , ME, 2009)
(Rahimtoola, H, 2003)
(Bigal, M, 2007)
(Lipton, RB., 2018)
(Katic, BJ, 2011)

Goals of Acute Treatment

Rapidly treat attack with minimal recurrence

Reduce use of additional rescue medications

Restore function

Reduce subsequent resource use (office visit/urgent care/emergency room)

Cost effective/Minimum adverse effects

(Silberstein, SD, 2000)

American Headache Society (AHS) 2021 Consensus Statement Medications with Evidence for Acute Treatment Migraine

Established efficacy	
Migraine Specific	**Nonspecific**
Triptans 5HT 1B,D R-A	NSAIDs (ASA, Celecoxib oral solution, diclofenac, ibuprofen, naproxen)
Ergotamine Derivatives α-adrenergic activity + 5HT1B/D	Combination analgesic (acetaminophen/asa/ caffeine)
Gepants CGRP R-Ant	
Lasmiditan 5HT1F R-A	

Probably effective	
Migraine Specific	**Nonspecific**
Ergotamine	NSAIDs (flurbiprofen, ketoprofen, IV and IM ketorolac)
Other forms of DHE	IV magnesium (MA)
	Isometheptene-containing compounds
	Antiemetics: metoclopramide, prochlorperazine, promethazine, chlorpromazine, droperidol

CGRP- Calcitonin gene-related peptide
NSAIDs - Non-steroidal anti-inflammatory drugs
IV – intravenous
IM - intramuscular

DHE - dihyrdroergotamine

(Ailani, et al. 2021)

Triptans: 5HT1B/D Receptor Agonist

Fast Onset

Half life between 1.8 (suma nasal)-5hrs (eletriptan)

- Oral: Sumatriptan 25mg/50mg/100mg, Sumatriptan 85mg/naproxen 500mg, Rizatriptan 5mg/10mg/MLT, Zolmitriptan 2.5mg/5mg/ODT, Almotriptan 6.25mg/12.5mg, Eletriptan 20mg/40mg

Long Lasting

Half life between 6 (Naratriptan) to 26 hours (Frovatriptan)

- Oral: Naratriptan 1mg/2.5mg, Frovatriptan 2.5mg

ODT - Orally Disintegrating Tablets

Ditans: Selective 5HT-1F Agonist

- Lasmiditan, 3 doses (50mg, 100mg, 200mg)
  - One tablet as needed for migraine
  - NO repeat dose as not found to be effective
  - Max daily dose is 200mg
- SE: dizziness (more at higher doses 12-16%), sedation/fatigue, nausea, paresthesia
- Studied in those with CV risk (mostly FH)
- Precautions
  - Driving Caution x 8 hours
  - Controlled substance
  - Discuss potential for Serotonin Syndrome
  - Medication Overuse headache discussion
  - Avoid in pregnancy/lactation

(Kuca, B,2018)
(Goadsby, PJ,2019)
(Shapiro, RE, 2019)
(Loo, LS, 2019)

Gepants: CGRP receptor antagonist

Ubrogepant, Rimegepant

- Ubrogepant with 2 doses, can be repeated once in 2 hours (half life 5-7 hours)
- Rimegepant with 1 dose, ODT (half life 11 hours)

SE- Nausea (~4%), Somnolence (3% for 100mg ubrogepant), Dry mouth (2% at 100mg ubrogepant)

No MOH warning, no driving warnings, no risk of serotonin syndrome

Use with CYP3A4 strong inducers should be avoided

- Ubrogepant: dose modify with moderate or weak CYP3A4 inhibitors or inducers/BCRP/P-gp inhibitors
- Rimegepant: avoid dose in 48 hours with moderate CYP3A4 inhibitors or inducers

(Dodick, DW, 2019)
(Lipton, RB, 2019)
(Croop, R., 2019)

Celecoxib Oral Solution

- Pooled Efficacy of 2 randomized controlled trials (RCTs) for Acute Treatment of Migraine
- 2-8 migraine attacks per month, treated mod-severe pain with celecoxib 120mg oral solution vs. placebo within 1 hour of onset of migraine
- 2-hour pain freedom 34% celecoxib vs. 24% placebo (p=0.0002)
  - 1 hour pain freedom 18% celecoxib vs. 13% placebo (p=0.0095)
- 2 hour most bothersome symptom (MBS) freedom 57% celecoxib vs. 44% placebo (P<0.0001)
  - 1 hour MBS freedom 38% celecoxib vs. 26% placebo (P<0.0001)
- TEAE Dysguesia, Nausea

(Tepper, S, et al. 2022)

When to use newer acute treatments?

Contraindications or Intolerance to triptans	Inadequate response to 2 or more oral triptans determined by EITHER of the following
• Vascular disease • Side Effects	• Validated acute treatment patient-reported outcome questionnaire (mTOQ, Migraine-ACT, PPMQ-R, FIS, PGIC) • Clinician attestation

Migraine Treatment Optimization Questionnaire (mTOQ)
Migraine Acceptance Commitment Therapy (ACT)
Patient Perception of Migraine Questionnaire (PPMQ)
Functional Impairment Scale (FIS)
Patient Global Impression of Change (PGIC)

(Ailani, et al, 2021)

Are Triptans "Better" Than Newer Treatments?

- Primary outcome OR for pain freedom at 2 hours
  - **Most triptans higher ORs pain freedom at 2 hours vs. Lasmiditan, rimegepant,and ubrogepant**
- Secondary outcomes ORs pain relief at 2 hours and any adverse events (AE)
  - **Most triptans were associated with higher ORs for pain relief at 2 hours vs. lasmiditan, rimegepant and ubrogepant**
  - **Lasmiditan was associated with the highest risk of any adverse events, and certain triptans** (rizatriptan, sumatriptan, and zolmitriptan) **were also associated with a higher risk of any adverse events than the calcitonin gene-related peptide antagonists**

(Yang, CP, et al., 2021)

Real-World Effectiveness of Ubrogepant Among Participants with Prior Treatment Failure: UNIVERSE Study

- Observational cross-sectional study US adult users of Migraine Buddy
- Self-report use of Ubrogepant for >4 prior migraine headaches
  - At least 1 dose in the preceding 14 days
- 302 respondents
  - 87.4% switched to Ubrogepant due to prior treatment lack of efficacy
  - 76% satisfied with pain relief at 2 hours
  - 85.2% satisfied for ability to think clearly
  - 85% satisfied to return to normal function after treatment
  - 92% likely to continue Ubrogepant treatment
- Reduced use of opioids (-28%), barbiturates (-25%), ergots (-15%), triptans (-55%), NSAIDS (-38%), and other acute medications (-37%)

(Shewale, AR, et al, 2022)

Rimegepant PRN Use Reduces Migraine Frequency

Post hoc analysis of LT OL 52-week study

1066 participants 6+ MMD at baseline prn use of rimegepant

Mean MMD 10.9

15.6% on concomitant preventive medication

Mean time to reduction of Migraine Days by at least 30% is 12 weeks

Mean time to reduction of 50% is 32 weeks

Lower the baseline number of migraine days, faster reduction of migraine days with prn use of rimegepant

(L'Italien, G, et al, 2022)

Non-Oral Acute Case

(Getty Images, n.d.)

Mithal is a 44-year-old woman with chronic migraine

She is on topiramate and erenumab for prevention and has 6 migraine days a month and 3 -4 tension type headaches a month

Her migraines are associated with nausea and sometimes vomiting

She has been using oral rizatriptan which can be effective if she does not vomit

She wonders what she should do if she vomits after taking her medication?

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	• STNS, sTMS, nVNS, RENS

Subcutaneous (SQ)
Subthalamic nucleus (STN)
Single pulse transcranial magnetic stimulation for migraine (sTMS)
Non-invasive Vagus nerve stimulation (nVNS)
Remote electrical neuromodulation (REN)

DHE: 5HTB/D receptor agonist

- α-adrenergic activity in addition to 5HT1B/D activity
- More nausea than triptans
- Vasoconstrictive
- May increase blood pressure
- Can work later in attack
  - Status migranosus, infusion therapy
- Minimal oral absorption
  - Available as Normal Saline (NS), IM, IV

DHE POD Device: Study Design

- STOP 301: Phase 3 Open-label Study
  - 24-wk safety study (N=354), with 28-week extension period (N=73)
- "Best usual care" during 28-day screening: automatic positive airway pressure (APAP), NSAIDs, triptans, combination analgesics
- Patients self-administered INP104 1.45 mg when they experienced recognizable migraine pain
- 68.1% of patients reported treatment-emergent adverse events (AEs)
  - Nasal congestion, nausea, nasal discomfort, abnormal taste
- 2 hours after single dose of INP104 - 1st treated attack
  - 38% of patients self-reported freedom from pain
  - 52.1% of patients self-reported freedom from MBS

(Smith, TR et al, 2021)

Zavegepant Nasal Spray

- Single dose acute migraine study in adults with EM
- 2-hour pain freedom with zavegepant 24% vs. 15% placebo ($p<0{\cdot}0001$)
- 2-hour MBS freedom with zavegepant 40% *vs.* 31% placebo ($p=0{\cdot}0012$)
- Common AE dysgeusia (21%), nasal discomfort (4%), and nausea (3%)

When to consider: Associated nausea/vomiting, desire of (slightly) faster onset of efficacy and does not mind nasal side effects

(Lipton, 2023)

Neuromodulation

The Food and Drug Administration (FDA) cleared for acute treatment	Supraorbital transcutaneous nerve stimulation- 1 hour during attack
	*Single pulse transcranial magnetic stimulation- 3 pulses as needed up to 3 times during an attack
	*Non-invasive vagal nerve stimulation- bilateral application, 2 minutes each side
	*Remote electrical neuromodulation - application to arm 45 minutes during attack
	Non-invasive combined occipital and trigeminal nerve stimulation- 40 minutes during attack
Consider in those who have (any of the following)	Failed 2 triptans
	Contraindications to standard therapy
	Overusing standard treatment
	Prefer nondrug therapy

*Expanded use in adolescents 12 to 17 years of age

(Sing, RH, 2019)
(Yarnitsky, D., 2019)
(Ailani, 2021)

Frequent Medication Use

Medication overuse

- May be related to anxiety
- Risk of significant negative unintended effects
  - Gastrointestinal bleed, Renal insufficiency/failure, liver failure, Cardiovascular, dependence, addiction

Medication overuse headache

- Due to overuse of medication headache worsens
- Not as frequent as we may think
- Ongoing debate how to treat

(Scher, A, 2017)

Building an Attack Toolbox

Mild attack

- Nonspecific analgesics
- Neuromodulation

Moderate to Severe attack

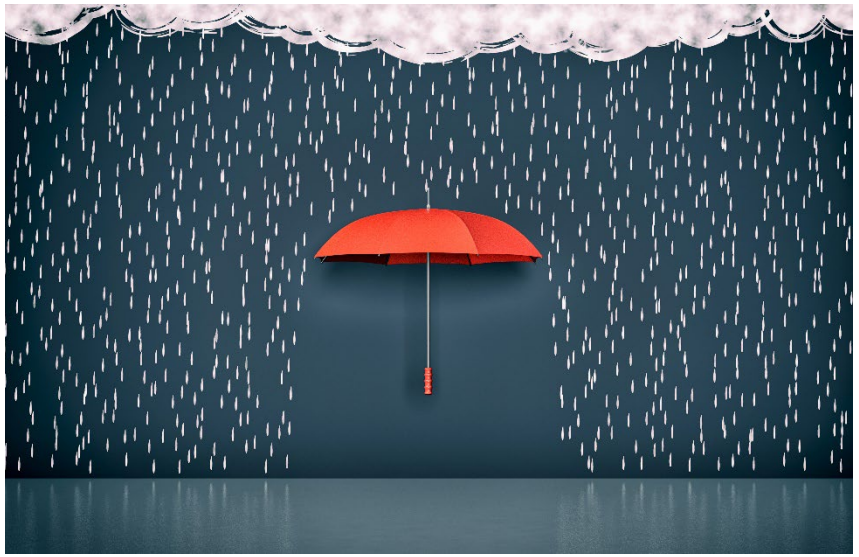
- Triptan
- Gepant (incomplete triptan response/contraindications/side effects)
- Ditan (incomplete triptan response/contraindications/side effects)
- + NSAID (incomplete response/inconsistent response to triptan alone)
- + Anti-emetic (incomplete response to treatment alone/significant nausea)
- Neuromodulation (incomplete triptan response/contraindications/side effects)
- DHE (incomplete triptan response, longer attack, delayed treatment)

Sudden onset/Severe at onset/Nausea/Vomiting

- Non-oral

(Ailani, J, 2021)

Prevention



(Adobe Stock Image, n.d.)

42 yo woman with migraine attacks from 5 to 7 days a month presents to your office for management. She is missing work 2 days a month, missing social events 2 days a month, and recently arrived late to her sister's baby shower due to a disabling attack.

What do you offer her?

What is Prevention

Using treatment to

- Reducing frequency of Migraine
- Increasing functionality of patient
  - Improve Quality of Life
- Modify Disease by reducing attack frequency we can reduce headache progression
  - Reduce medication overuse

Prevention is not a cure

When to Offer Prevention

- Attacks significantly interfere with patients' daily routines despite acute treatment
- Frequent attacks* (6 MHD/month and no disability or 3MHD/month and severe disability)
- Contraindication to, failure, or overuse of acute treatments, with overuse defined as:
  - 10 or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused
  - 15 or more days per month for non-opioid analgesics, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs)
- AEs with acute treatments
- Patient preference

*Offer if 6 or more days and no disability, 4 or more days and some disability, 3 or more days and severe disability
Consider if 4 or more days and no disability, 3 days and some disability, 2 days and severe disability

(Ailani, et al, 2021)

Lifestyle Modifications

(Adobe Stock Image, n.d.)

- Regular Moderate Cardiovascular Exercise
- Regular Sleep/Wake Time
- Regular Eating times
- Keeping hydrated
- Stress Management

Poll Instructions

Join by Web

1. Go to **PollEv.com**
2. Enter **CEPO**
3. Respond to activity

Join by Text

1. Text **CEPO** to **22333**
2. Text in your message

What Diet Recommendation Should Be Made For Patients With Migraine?

A. No Caffeine or Alcohol
B. No MSG or Tyramine containing foods
C. Regular Eating Times
D. A and B

Neutraceuticals for Migraine Prevention

Supplement	Dose	Special considerations/AEs
Riboflavin	400mg/day (p=0.0001) in adults	Urine discoloration; degraded by light (avoid placing in exposed glass container)
Coenzyme Q10	150mg/day (open-label study in 32 patients was significant)	No AE, low risk
Magnesium	360mg/day in cohort of women with MRM; mag citrate 295.7mg BID; mag 400mg/day in children & adolescents; mag citrate 600mg	Mild GI upset Magnesium deficiency may correlate to migraine susceptibility, can consider checking mag deficiency prior to starting mag
Vit D	50,000 IU weekly x 10 weeks (p=NS) 4000 IU daily (p<0.001 with attack frequency; no change in MAS or disability)	No AE
Melatonin	3-40mg (both children & adult studies)	Daytime somnolence (dose dependent)

(Barmherzig & Rajapakse, 2021)

Behavioral Therapy

- Cognitive Behavioral Therapy (Level A)
- Biofeedback (Level A)
- Relaxation Therapy (Level A)
- Mindfulness-Based Stress Reduction (MBSR)
- Acceptance and Commitment Therapy (ACT)

Acupuncture

(Adobe Stock Image, n.d.)

(Barmherzig & Rajapakse, 2021)
(Halker Singh, et al, 2019)
(Wells, et al, 2020)
(Grazi, L, et al, 2021)

Developing a Treatment Plan to Integrate Behavioral Therapy

Consider using alone in patients who	Consider adding in for patients who	Combination behavioral therapy + pharmacological/interventional treatment
• Prefer non-pharmacotherapy • Are pregnant/lactating/family planning	• Have inadequate response, poor tolerance, or medical contraindications to pharmacological therapies • Medication overuse • Exhibit significant stress or deficient stress-coping skills	• Can have improved outcomes

(Ailani, J, et al, 2021)

American Headache Society 2021 Consensus Statement Medications with Evidence for Migraine Prevention

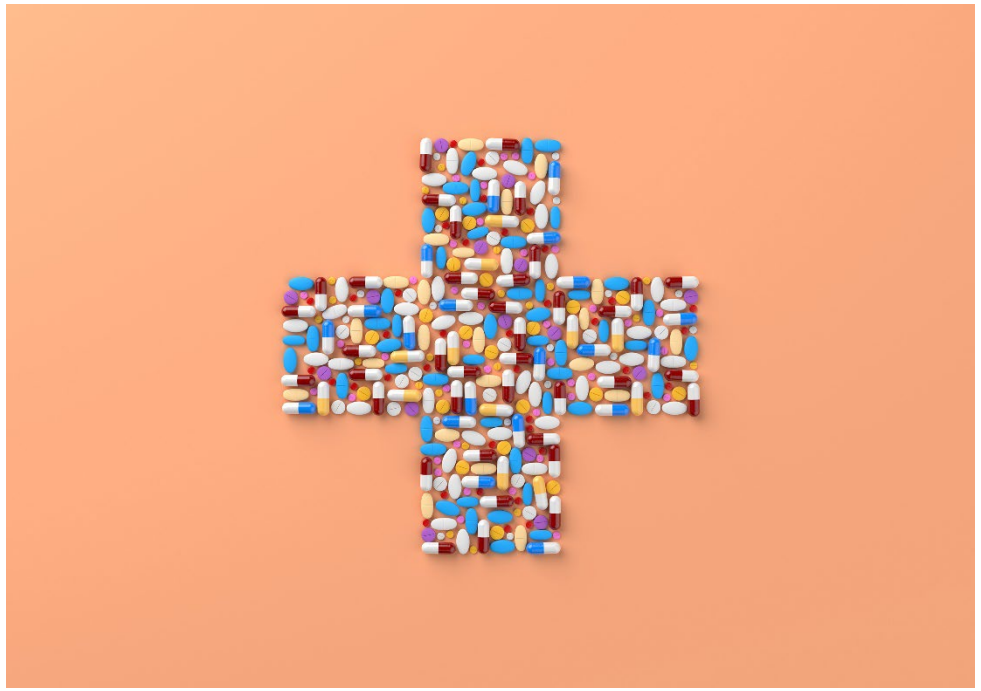
Established efficacy	
Oral	**Parenteral**
Candesartan	Eptinezumab
Divalproex sodium	Erenumab
Frovatriptan*	Fremanezumab
Metoprolol	Galcanezumab
Propranolol	Onabotulinum toxin A
Timolol	
Topiramate	
Sodium valproate	

Probably effective	
Oral	**Parenteral**
Amitriptyline	Onabotulinum toxin A + CGRP mAb
Atenolol	
Lisinopril	
Memantine	
Nadolol	
Venlafaxine	

*= indicated for menstrual migraine

(Ailani, J, 2021)

Utilization of Prevention in Migraine



(Getty Images, n.d.)

Prevention Underutilized

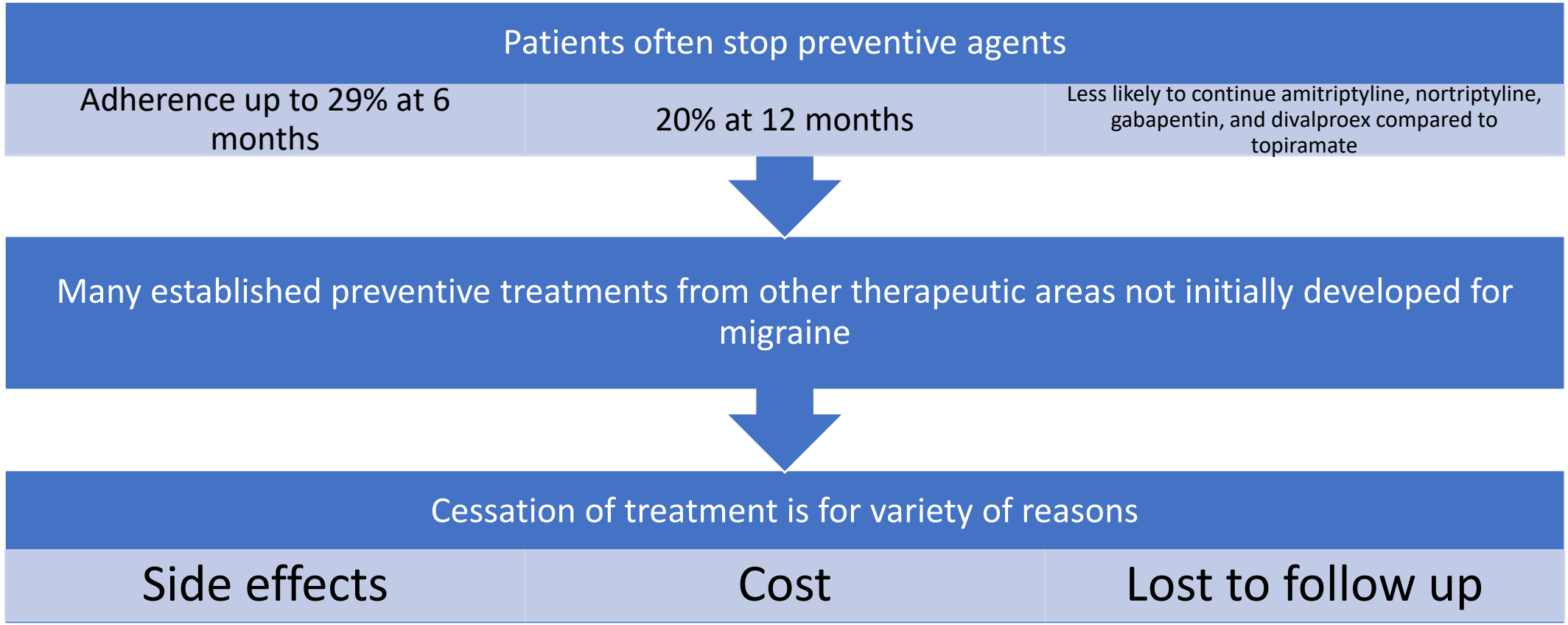
- 43% of people with migraine have never used preventive
  - 32.4% met guidelines for being offered prevention
  - 25% were previous users
  - 13% current users of prevention
- Women are more likely to meet guidelines for prevention compared to men with migraine
  - 34% of women and 28% of men with migraine met guidelines for being offered preventive

Barriers to Prevention

- Lack of awareness by providers
- Lack of confidence in quality of guidelines
- Patient's prior history of side effects or tolerance

(Lipton, RB, 2007)
(Diamond, S, 2007)
(Loder, E, 2012)

Limitations of Traditional Migraine Preventives



(Hepp, Z, 2015)
(Evers, S, 2009)
(Blumenfeld, AM, 2013)
(Berger, A, et al, 2012)
(Buse, DC, et al, 2010)

CGRP Monoclonal Antibodies For Migraine Prevention

	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
Antibody vs	IgG2	IgG4	IgG2a	IgG1
Derivation	Human	Fully humanized	Fully humanized	Fully humanized
Binding site	Receptor	Ligand	Ligand	Ligand
Administration	SC	SC	SC	IV
Dosing interval	Q month	Q month	Q month /Q3 months	Q3 months
T max	6 days	5 days	5 days	3 hours
Half Life	27 days	27 days	31 days	27 days
EM Reduction days/month	-3.2/-3.7 vs. -1.8	-4.7 vs. -2.8	-4.3 vs. -3.1 M -4.2 vs. -3.1 Q	-3.9/-4.3 vs. -3.2
CM Reduction days/month	-6.6/-6.6 vs. -4.2	-4.1 vs. -1.8	-5.1 vs. -3.3 M -4.7 vs. -3.3 Q	-7.7/-8.2 vs. -5/2

(Silberstein, SD, et al, 2017) (Goadsby, PJ, et al, 2017) (Tepper, S, et al, 2017) (Skljarevski, V, et al, 2018) (Stauffer, VL, et al, 2018) (Dodick, DW, et al, 2018) (Ashina, M, et al, 2020) (Lipton, RB, et al, 2020)

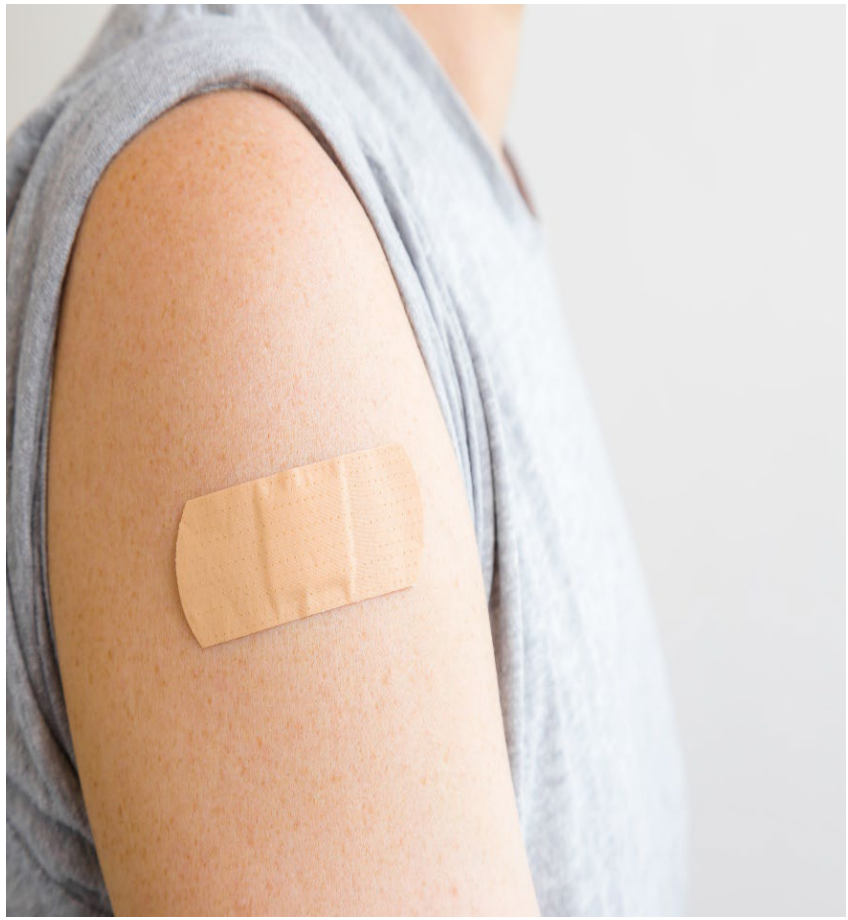
Criteria for Initiating Treatment with Monoclonal Antibodies to CGRP for Migraine

Adult Patient has migraine with or without aura or chronic migraine

Has inability to tolerate or inadequate response to an 8-week trial at a dose established to be potentially effective to 2 or more Level A or B migraine preventives as established by American Academy of Neurology guidelines

- For Onabotulinum toxin A, trial should be 2 quarterly injections

With attestation by the prescribing clinician about medical risk, a trial of two established therapies may not be required before initiating treatment with a monoclonal antibody



(Getty Image, n.d.)

(Ailani, J,. 2021)

Gepants for Prevention

Rimegepant FDA approved for prevention of episodic migraine (average 9-10d/mo)

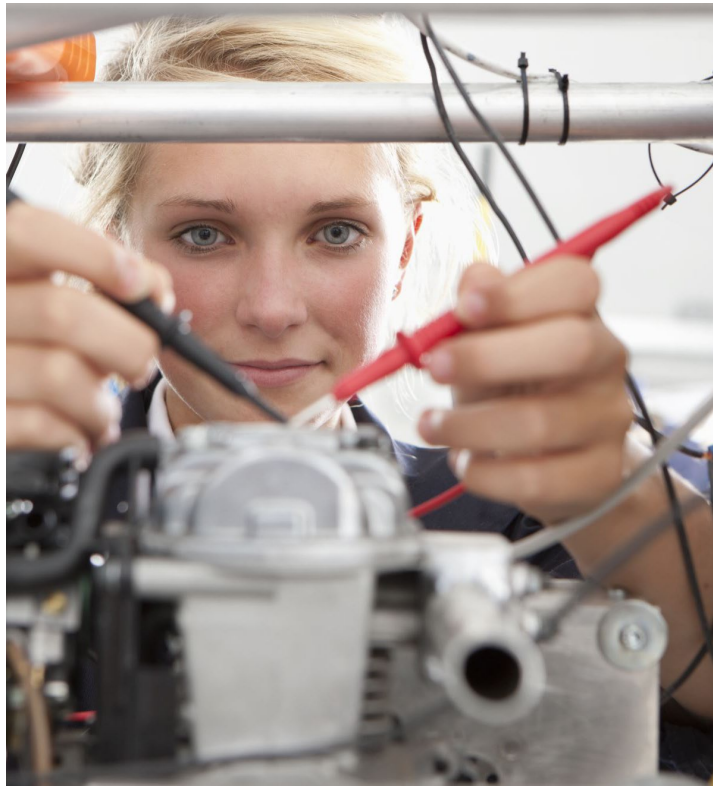
- 75mg ODT every other day
- At month 3, -4.3 days less with treatment vs. -3.5 days less/mo with placebo (p=0.0099)
- AE: Nausea (3%), Nasopharyngitis (4%)

Atogepant for prevention of episodic migraine (average 7-8 d/mo)

- 10mg vs. 30mg vs. 60mg vs. placebo daily
- At month 3, -3.7 to -4.2 days less/mo with treatment vs. -2.5 days less/month with placebo (p<0.001)
- AE: Constipation (7%), Nausea (6%), Reduction in appetite (2%)

Neuromodulation

FDA cleared for preventive treatment	*Supraorbital transcutaneous nerve stimulation- 20 minutes daily
	*Single pulse transcranial magnetic stimulation- 4 pulses to the occiput twice daily
	*Non-invasive vagal nerve stimulation- right neck application for 2 minutes, twice separated by 5 minutes, three times a day
Consider in those who have (any of the following)	Contraindications to standard therapy
	Combination (layered) therapy to aim for greater reduction of migraine days
	Prefer nondrug therapy



*Expanded Indication in Adolescents 12-17 years of age

(Schoenen, J. et al, 2013)
(Diener, HC, et al, 2019)
(Starling, AJ, et al, 2018)
(Halker Singh, et al, 2019)

Procedures Performed in Headache Clinic

- Peripheral Nerve Blocks
- Trigger Point Injections
- Sphenopalatine Ganglion Block
- Onabotulinum Toxin A

Systematic Review and Practice Guideline

- Onabotulinumtoxin A (OnabotA) strong recommendation for use in chronic migraine prevention
  - OnabotA weak recommendation AGAINST use for episodic migraine prevention
- Greater occipital nerve blocks with local anesthetic alone weak recommendations for use for chronic migraine prevention
  - GONB with steroid weak recommendation AGAINST use
- Sphenopalatine ganglion blocks weak recommendation for use for chronic migraine prevention
- Supraorbital nerve blocks weak recommendation for use for chronic migraine prevention
- Trigger Point Injections for migraine prevention had insufficient evidence

(Barad, M, et al, 2021)

Key Takeaways

Unmet treatment needs create greater burden for people with migraine

Addressing acute treatment needs is imperative for every person with migraine

For those with a greater degree of disability, prevention may be considered to reduce disease burden

With newer disease specific treatment options available, the migraine toolbox can be optimized for the patient in front of you

Questions?

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