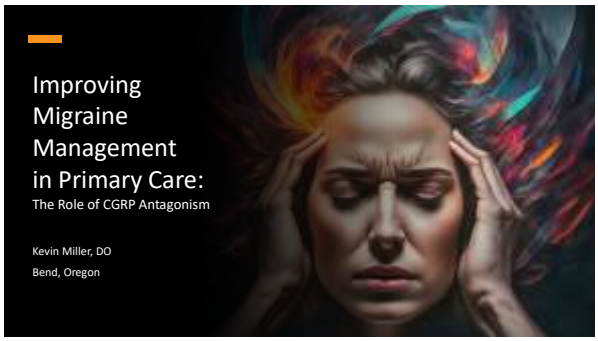


Improving Migraine Management in Primary Care:

The Role of CGRP Antagonism

Kevin Miller, DO
Bend, Oregon

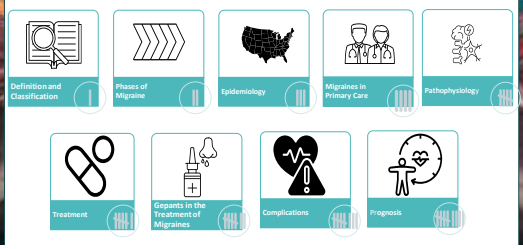
Disclosures

- Kevin Miller, DO, faculty for this educational event, has no relevant relationships with ineligible companies to disclose.
- The remaining Faculty, CME Planning Committee, Reviewer and Moderator have no relevant financial relationships with ineligible companies to disclose.
- The OSMA CME Manager has mitigated all information with ineligible companies listed for these individuals and has resolved all conflicts of interest if applicable.

Learning Objectives

Participants in this presentation should be able to…
Describe the role of CGRP in the pathophysiology of migraine headache.
Describe the role of targeted CGRP therapy and approved CGRP antagonists in the acute and preventive treatment of migraine headache.
Describe patient preferences and how they impact drug compliance and treatment outcomes.

Outline



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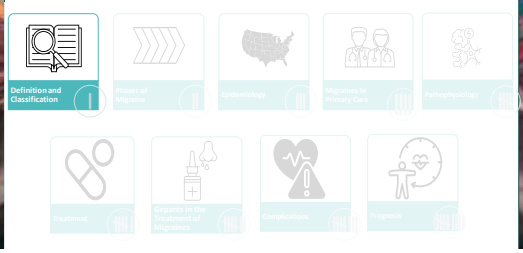


Migraine is the second most common cause of primary headache after tension headache. . . .**Migraine is the most common type of primary headache seen in primary care!**

	Tension headache	Migraine
Age of onset	20 – 50 years	10 – 40 years
Location	Bilateral and symmetrical	Usually unilateral
Severity	Mild to moderate	Moderate to severe
Duration	30 minutes – 7 days	4 – 72 hours
Character	"Pressure" "Tightening"	"Throbbing"
Associated symptoms	None present	Prodromal symptoms and an aura

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. doi:10.1177/0333102417738202.

A migraine is a complex neurological disorder that is usually characterised by a unilateral headache.

Throbbing headache lasting 4 – 72 hours

Sensitivity to light and sound

Nausea in 80%

Vomiting in 50%

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. doi:10.1177/0333102417738202.

Diagnosis of Migraine without Aura

At least 5 attacks lasting 4-72 hours with at least 2 of the following:

1. Unilateral location
2. Pulsating quality
3. Moderate to severe pain
4. Aggravation or avoidance of physical activity

During the headache at least one of the following:

1. Nausea and/or vomiting
2. Photophobia and phonophobia
3. Not better accounted for by another ICHD-3 diagnosis

The International Classification of Headache Disorders. 3rd ed. *Cephalalgia*. 2013;33(9).

Diagnosis of Migraine with Aura

At least 2 attacks with 1 or more of the following fully reversible aura symptoms:

1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal

At least 3 of the following:

1. At least 1 aura symptom spreads gradually over >5 minutes
2. 2 or more occur in succession
3. Each aura symptom lasts 5-60 minutes
4. At least one aura symptom is unilateral
5. At least one aura symptom is positive
6. Aura accompanied or followed by headache within 60 minutes

The International Classification of Headache Disorders. 3rd ed. *Cephalalgia*. 2013;33(9).

Quick Diagnosis for the busy PCP: ID Migraine™ - validated screener

During the last 3 months, did you have the following with your headaches?		
You felt nauseated or sick to your stomach?	❑ YES	❑ NO
Light bothered you (a lot more than when you don't have headaches)?	❑ YES	❑ NO
Your headaches limited your ability to work, study, or do what you needed to do?	❑ YES	❑ NO

- 2/3 for migraine
- Sensitivity: 0.81
- Specificity: 0.75

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

Migraines can be classified based on frequency. (Classifications affect treatment choices)

Episodic

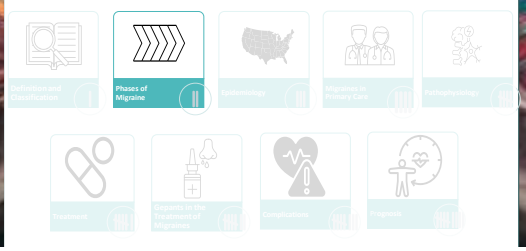
Headache frequency of 14 days or less per month

Chronic

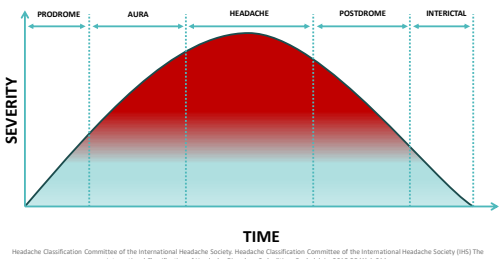
Headache frequency of 15 or more days per month (8 of which meet criteria for migraine) for more than 3 months

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. doi:10.1177/0333102417738202.

Outline



Migraine occurs in 5 phases.

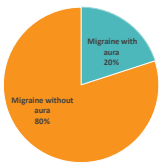


Headache Classification Committee of the International Headache Society. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018.38 (1):1-211.

The prodrome phase occurs in 60% of patients with migraine.

- **Occurs hours to days before headache**
- **Heightened sensitivity to light and sound**
- **Lethargy**
- **Uncontrollable yawning**
- **Mood changes**
- **Changes in bowel movements**
- **Excessive thirst and polyuria**

In 20% of patients, the headache phase is preceded by an aura.



What is an aura?

An aura is a set of complex neurological symptoms that precede or accompany migraines or occur in isolation; usually visual, sensory, motor or a combination.

Visual auras are the most common.

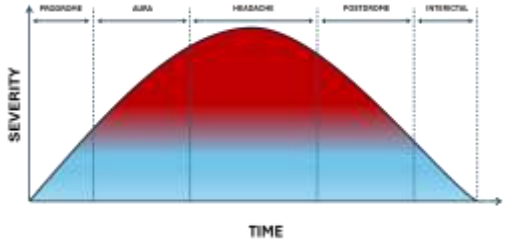
The aura phase or cortical phenomenon is a result of cellular depolarisation of neurons and glial cells in the cerebral cortex.

Photopsia

Fortification spectrum

Scintillating scotoma

Maximal pain occurs during the headache phase which lasts 4 – 72 hours.



The postdrome phase is the winding down phase with mild symptoms.

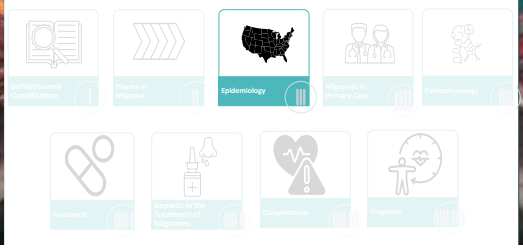
- **Fatigue**
- **Euphoria**
- **Myalgia**
- **Anorexia**
- **Food cravings**

The interictal phase is the period between migraine attacks.

Mild symptoms may persist, though rarely.
Usually, patients experience trepidation when making plans due to unpredictability of attacks.

Vincent M, Viktrup L, Nicholson RA, Ossipov MH, Vargas BB. The not so hidden impact of interictal burden in migraine: A narrative review. Front Neurol. 2022;13:1032103.

Outline



How Common is Migraine?

- 1 billion people worldwide
- 13% prevalence in US (approx. 39 million Americans)
  - Other diseases with similar prevalence
    - Type 2 DM
    - Asthma
- 18% women; 6-7% men
- Most common neurologic disease seen in primary care
- Most common type of primary headache seen in primary care

GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2017;390(10100):1211-1259.

The United States has the highest prevalence of migraines in the world.

More than 30 million American experience one or more migraines per year

According to the WHO, the worldwide lifetime prevalence of migraines is 14%

Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. Neurology. 2002;58(6):885-94.

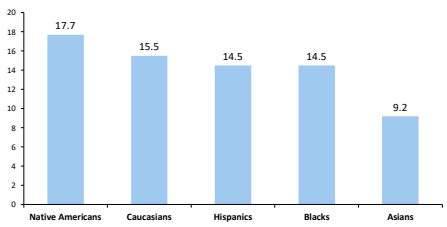
Women are more likely to experience migraines than men.

75% of all persons who experience migraine are women

1 in 6 American women experience migraines

Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. Neurology. 2002;58(6):885-94. doi:10.1212/wnl.58.6.885.
Sun-Edelstein C, Mauskop A. Role of magnesium in the pathogenesis and treatment of migraine. Expert Rev Neurother. 2009;9(3):369-79. doi:10.1586/14737175.9.3.369.

Prevalence in US in Underrepresented Groups



- Loder S. *Headache*. 2015;55(2):14-28.

Disability of Migraine

- One of leading causes of disability world-wide
  - 2nd cause of YLDs (years lived with disability)
  - #1 in women <50
- Peaks in ages 22-55 for men and women
- Affects 1 in every 4 households in US
- High socio-economic burden
  - Annual total cost (US) estimated $36 Billion
  - Annual direct + indirect costs is $9K more in patients diagnosed w/ migraine than "similar" patients w/o migraine

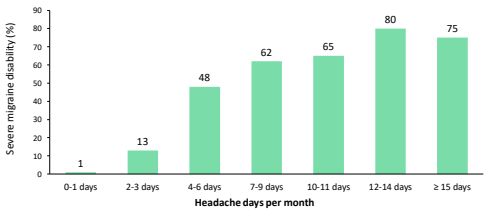
GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2017;390(10100):1211-1259. Steiner TJ, et al. Migraine is the *first* cause of disability in under 50's: will health politicians now take notice? *J Headache Pain*. 2018;19(1):17. Steiner, T.J., Stovner, L.J., Jensen, R. *et al.* Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J Headache Pain* 21, 137 (2020). https://doi.org/10.1186/s10194-020-01208-0
Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and indirect healthcare resource utilization and costs among migraine patients in the United States [published online February 15, 2018]. *Headache*. doi: 10.1111/head.13275. Bonafede M et al. *Headache*. 2018;58(5):700-714.

Migraines also have a negative impact on the economy.

- **40% of adults with chronic migraines are unemployed**
- **Migraines are responsible for 4 million ER visits annually**
- **Migraines are responsible for $13 billion loss of productive time in the workforce annually**

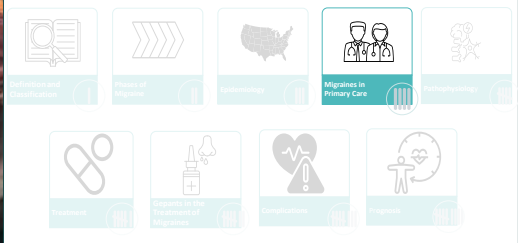
Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: Updated age, sex, and socioeconomic-specific estimates from government health surveys. Headache. 2021;61(1):60-68. doi:10.1111/head.14024. Epub

Severe Headache-Related Disability Increases at ≥ 4 Headache Days/Month



- **Blumenfeld AM. *Cephalalgia*. 2010;31(3):301-315.**

Outline

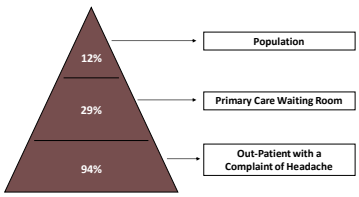


Migraine in Primary Care

- >37% of women of reproductive age in a primary care provider's waiting room have migraine
- People with episodic tension headache rarely seek medical advice
- Other primary headache disorders infrequently appear in a primary care office
- According to the United Council for Neurologic Subspecialties, there are only 636 (down from 706) certified headache specialists in the United States[1]

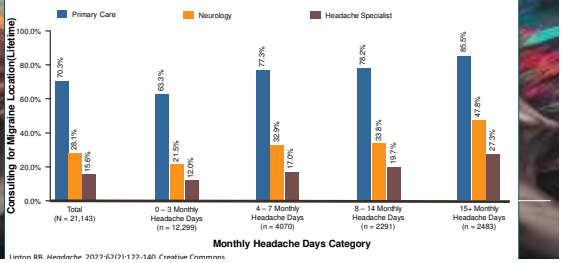
Couch JC, et al. *Headache*. 2003;43(5):570-571.
[1]https://www.ucns.org/Online/Diplomate_Directory/Online/Diplomate_Directory

The Prevalence of Migraine in Primary Care



Lipton RB, et al. *Neurology*. 2007;68: 343-349. Couch J, et al. *Headache*. 2003;43:570-571. Tepper SJ, et al. *Headache*. 2004;44:856-864.

Lifetime Consultation by Specialty



Lipton RB. *Headache*. 2022;62(2):122-140. Creative Commons

Current Challenges in Migraine Management

- Access to Healthcare Provider
- Accurate Diagnosis
- Appropriate Treatment Plan

This occurs in only 26.3% for those with episodic migraine and less than 5% for those with chronic migraine!

"Research Shows Treatment Disparities Affect Patients with Headache Disorders." AJMC, AJMC, 17 June 2021. Accessed June 20, 2023. https://www.ajmc.com/view/research-shows-treatment-disparities-affect-patients-with-headache-disorders.)

Disparities

- African American and Hispanic patients are 25% and 50% less likely to receive a migraine diagnosis than White patients, respectively
- Low socioeconomic background at high risk of underdiagnosis/poor treatment and therefore worse outcomes since household income is associated with migraine prevalence.
- Low income is associated with being uninsured or underinsured – harder to get acute treatment – leading to higher incidence of chronic migraine and therefore worse disability.
- Many patients of color (33% African Americans, 20% AIAN) report experiencing racial discrimination within the healthcare system. Resulting in 22% and 15% of them avoiding seeking healthcare altogether.

"Research Shows Treatment Disparities Affect Patients with Headache Disorders." AJMC, AJMC, 17 June 2021. Accessed June 20, 2023. https://www.ajmc.com/view/research-shows-treatment-disparities-affect-patients-with-headache-disorders.)

Less than 30% of patients take their medicine correctly.

Poor patient education leads to poor drug adherence

Invalidation of patient experience leads to dissatisfaction and poor drug adherence

Guerrero AL, Negro A, Pyrilin P, Skorobogatykh K, Sanchez-De La Rosa R, Israel-Willner H, Sundal C, MacGregor EA. Need of guidance in disabling and chronic migraine identification in the primary care setting, results from the european MyLife anamnesis survey. BMC Fam

To improve patient satisfaction and drug adherence, care givers need to know what patients' value:

- ☑ **Drug efficacy**
- ☑ **Mode of administration with oral being overwhelming preferred**
- ☑ **No or minimal side effects**

Hubig LT, Smith T, Chua GN, Lloyd AJ, Powell L, Johnston K, Harris L, L'Italien G, Coric V, Lo SH. A stated preference survey to explore patient preferences for novel preventive migraine treatments. Headache. 2022;62(9):1187-1197. doi:10.1111/head.14386.

Outline

Migraines have a strong genetic component.

70% of migraine patients have a first degree relative with a history of migraines

Hamed SA. The vascular risk associations with migraine: relation to migraine susceptibility and progression. Atherosclerosis. 2009;205(1):15-22.

Environmental and behavioral factors trigger migraine attacks in predisposed patients.

- Hormonal changes
- Stress
- Excessive or insufficient sleep
- Drugs e.g. vasodilators
- Smoking
- Strong odors
- Exposure to bright light
- Weather changes
- Lack of exercise

Allais G, Gabellari IC, De Lorenzo C, Mana O, Benedetto C. Oral contraceptives in migraine. Expert Rev Neurother. 2009;9(3):381-93.
Wöber C, Brannath W, Schmidt K, Kapitan M, Rudel E, Wessely P, et al. Prospective analysis of factors related to migraine attacks: the PAMINA study. Cephalalgia. 2007;27(4):304-14.

Chocolate was previously thought to be a trigger, but this has been disproven.

Hypothalamic activation at the start of a migraine

↓

Chocolate craving

(effect not cause)

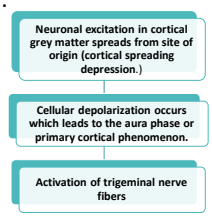
Wöber C, Brannath W, Schmidt K, Kapitan M, Rudel E, Wessely P, et al. Prospective analysis of factors related to migraine attacks: the PAMINA study. Cephalalgia. 2007;27(4):304-14.

Primary neurogenic and secondary vascular events initiate migraines.

At baseline, patients with migraine have a state of hyperexcitability in their cerebral cortex due to genetic predisposition, and environmental and behaviour factors.

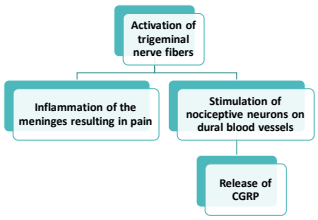
Kaube H, Katsarava Z, Przywara S, Drepper J, Ellrich J, Diener HC. Acute migraine headache: possible sensitization of neurons in the spinal trigeminal nucleus? Neurology. 2002;58(8):1234-8. doi:10.1212/wnl.58.8.1234.

This neuronal excitation spreads (cortical spreading depression) resulting in cellular depolarization.



Takano T, Nedergaard M. Deciphering migraine. J Clin Invest. 2009;119(1):16-9. doi:10.1172/JCI38051.

Activation of trigeminal nerve fibers leads to the headache phase.

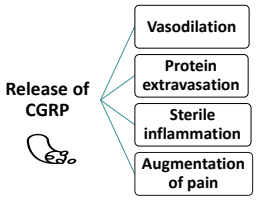


Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med. 2002;8(2):136-42. doi:10.1038/nm0202-136.

CGRP – The "New Kid" on the Block

- Calcitonin gene-related peptide (CGRP) – a 37 amino acid polypeptide in neurons and glial cells (universally present)
- Receptors to CGRP are located throughout the trigeminal system and multiple brain regions (as well as other locations throughout the body)
- CGRP is a vasodilator and causes neurogenic inflammation
- CGRP modulates pain signaling

CGRP is a potent vasodilator that interacts with the vessel walls.



Benarroch EE. CGRP: sensory neuropeptide with multiple neurologic implications. Neurology. 2011;77(3):281-7. doi:10.1212/WNL.0b013e3182255b2.

Outline

The management of migraines involves acute and preventive treatment.

Goals of Acute Treatment	Goals of Preventive Treatment
Eliminates headache (i.e. pain freedom, freedom from most bothersome symptom)	Reduce frequency and severity of migraine attacks
Prevent the progression of headaches	Make acute attacks more responsive to acute treatment

Burch RC, Ailani J, Robbins MS. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2022;62(1):111-112. doi:10.1111/head.14245.

Goals for Acute Treatment

- Rapid relief of headache pain
- Relief of "most bothersome symptoms" (MBS) including nausea, photophobia and phonophobia
- Sustained pain freedom
- No need to rescue or take a 2nd dose
- Return to full function
- Little to no side effects from acute medication

Acute Treatment Options

- Triptans (5 HT-1B and 1D receptor agonists)
- Ergots/Dihydroergotamine
- NSAIDS
- Non-specific options (Analgesics, Butalbital, Narcotics) NO!!
- Non-invasive devices
- Oral CGRP receptor antagonists
- Ditan (Lasmiditan - selective 5 HT-1F receptor agonist)

Safety Concerns: Acute Migraine Treatment Options

- Triptans and Ergots/Dihydroergotamine are all contraindicated in patients with coronary artery disease, peripheral vascular disease, uncontrolled high blood pressure and those at high risk of cardiac disease
- Triptans and Ergots/Dihydroergotamine should not be taken in the same 24-hour period due to risk of vasoconstriction
- Risk of medication overuse with triptans
- Narcotics and Butalbital are non-specific in treatment of acute migraine, can lead to medication overuse, overdose, sedation, abuse, and can cause preventives to be less effective
- NSAIDs contraindicated in many patients due to GI issues or those at risk for GI bleeding and those with certain kidney conditions
- Driving precaution with the Ditan - Lasmiditan (8 hours)

Medication overuse can lead to progression of episodic migraines to chronic migraines.

Opiates
If taken for more than eight days per month
Barbiturates
If taken for more than five days per month
Triptans
Associated with frequency of migraines and medication use for 10 - 14 days per month

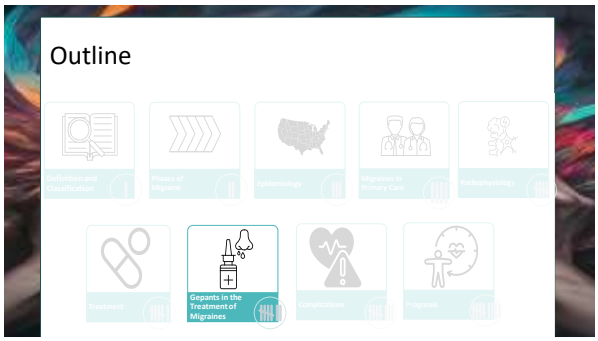
Goadsby PJ, Blumenfeld AM, Lipton RB, Dodick DW, Kalidas K, M Adams A, Jakate A, Liu C, Szegedi A, Trugman JM. Time course of efficacy of ubrogepant for the acute treatment of migraine: Clinical implications. Cephalalgia. 2021;41(5):546-560.

Acute Medications

Medication Class	Dosing/Formulations	Prescribing Considerations
Triptans (7 available): Sumatriptan, Rizatriptan, Zolmitriptan, Almotriptan, Eletriptan, Naratriptan, Frovatriptan	Multiple dosing options Oral, nasal, injectable, breath powered formulations	Contraindicated in patients with CV disease, uncontrolled HTN, PVD Risk of medication overuse and MOH Cannot take within 24 hrs of DHE
DHE - Dihydroergotamine mesylate	0.725mg delivered via a "POD" (precision olfactory delivery)	Contraindicated in CVD, HTN, PVD Cannot take within 24 hrs of triptan
Gepants Rimegepant Ubrogepant	75mg oral dissolvable tablet 50mg, 100mg tablet	
Ditan (Lasmiditan)	50mg, 100mg (up to 200mg)	Driving restriction 8 hours
NSAIDS (Diclofenac, Naproxen, Celecoxib)		GI, CV

DHE (Trudhesa) Data on File 2019: Impel NeuroPharma, Inc
Rimegepant (Nurtec ODT) Data on file. 2018. Biohaven Pharmaceutical
Ubrogepant (Ubrelvy) Data on file. 2018. Allergan.
Lasmiditan (Reyvow) Indianapolis, IN: Lilly USA, LLC. 1/2021; Data on File

Outline

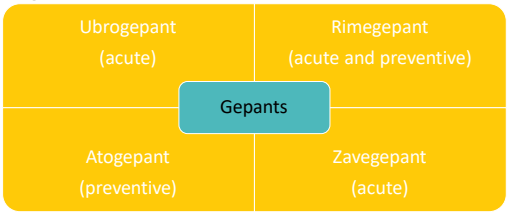


CGRP and Migraine: Where is the Evidence?

- CGRP levels are elevated during a migraine attack (measured external jugular vein)[1]
- Infusion of CGRP in migraine patients can cause migraine[2]
- Infusion of CGRP blocking medication can resolve a migraine attack in a migraine individual[3]
- New targeted CGRP blocking molecules highly effective in the acute treatment of migraine as well as prevention
  - Acute: "Gepants" small molecules
  - Preventive: large monoclonal antibodies, as well as small molecules (gepants)

1. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol*. 1990;28:183-187.
2. G Lassen LH, Haderslev PA, Jacobsen VB, et al. CGRP may play a causative role in migraine. *Cephalalgia*. 2002;22:54-61.
3. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol*. 1993;33:38-56.

The FDA has approved 4 small molecule CGRP receptor antagonists (AKA: gepants) for the treatment of migraine



Ubrogepant

- Ubrogepant is an oral CGRP receptor antagonist
- It is metabolized in the liver
- It is used to treat acute migraines studies showed statistically significant percentage of pain freedom within two hours lasting twelve hours compared to placebo
- It is better tolerated than triptans and has the least drug – drug interactions

34. Voss T, Lipton RB, Dodick DW, Dupre N, Ge JY, Bachman R, Assaid C, Aurora SK, Michelson D. A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. Cephalalgia. 2016;36(9):887-98.

Rimegepant

- Rimegepant is an oral CGRP receptor antagonist
- It is used for both acute and preventive treatment of migraine (pain freedom range 2 to 48 hours)
- Rimegepant has minor side effects such as nausea and vomiting

Scott LJ. Rimegepant: First Approval. Drugs. 2020;80(7):741-746. doi:10.1007/s40265-020-01301-3.

Atogepant

- Oral CGRP receptor antagonist
- Preventive treatment: once daily atogepnt reduces migraine days per month for more than 50% when compared to placebo
- Adverse effects occur at higher doses and include nausea, constipation and upper respiratory tract infections

Chowdhury S, Dave T. Novel Oral CGRP Receptor Antagonist Atogepant in the Prevention of Migraine. Discoveries (Craiova). 2023;11(2):e167. doi:10.15190/d.2023.6.

Zavegepant

- First third generation gepant approved by the FDA
- Intranasal spray (poor oral bioavailability)
- Rapid onset of action with relief from pain within fifteen minutes, lasting two hours
- Altered sense of taste is the most common side effect

Ahmed U, Saleem MM, Osman MA, Shamat SF. Novel FDA-approved zavegepant drug for treating migraine. Ann Med Surg (Lond). 2023;86(2):923-925. doi:10.1097/MS9.0000000000001620.

Triptans vs New Acute Meds?

- A systematic review indirectly compared the performance of triptans vs lasmiditan, rimegepant, and ubrogepant.
- The review included 64 randomized clinical trials with 46442 participants.
- Primary outcome was the odds ratio (OR) for pain freedom 2 hours after dose
- Secondary outcomes were ORs for pain relief at 2 hours after the dose and any adverse events
- Results: Pain freedom/pain relief OR of new agents higher than placebo but lower than triptans
- Adverse events higher for Lasmiditan and triptans than gepants

There are NO clinical trials that directly compare triptans with gepants (and Lasmiditan). This review recommended such a study be carried out for a better picture on how these classes of drugs compare.

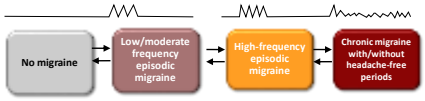
Yang CP, Liang CS, Chang CM, Yang CC, Shih PH, Yau YC. Comparison of New Pharmacologic Agents With Triptans for Treatment of Migraine: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021;4(10):e2128544. doi: 10.1001/jamanetworkopen.2021.28544.

Summary of benefits of gepants

- ☑ **Better tolerated/ fewer milder adverse effects**
- ☑ **Not associated with progression to chronic migraines due to medication overuse**
- ☑ **Can be used with other medications as dual therapy**

When Do We Offer Prevention for Migraine?

- Migraine Frequency
  - 4 or more migraine headache DAYS (with impact) offer prevention (Disability increases!)
- Migraine Classification
  - Episodic (EM) less than 15 days per month of headache
  - Chronic (CM) 15 or more headache days per month of which 8 or more meet criteria for migraine for at least 3 months



Lipton RB. *Neurology.* 2009;72(5 suppl):S3-S7.

Conversion from EM to CM at the rate of 2.5% per year

FDA Approved Oral Medications for Prevention of Episodic Migraine

- Divalproex sodium
- Topiramate
- Timolol
- Propranolol

Note: Others commonly used but not FDA approved include Amitriptyline, Venlafaxine, Metoprolol, Naldolol, Atenolol, Nortriptyline, Duloxetine, Verapamil, Gabapentin, Candesartan, Fluoxetine, Escitalopram, Cyproheptadine

Short-term prevention menstrual migraine: Frovatriptan, Naratriptan, Sumatriptan, Zolmitriptan, Rizatriptan. All have shown efficacy in clinical trials but not FDA approved for prevention.

Onabotulinum Toxin A

- FDA approved for chronic migraine only (not EM)
- Approved protocol is 155 units injected in 31 individual sites every 12 weeks
- Sites include procerus, corrugators, frontalis, temporalis, occipitalis, upper paracervicals, and upper trapezius
- FDA approved for chronic migraine in 2010
- MOA includes inhibition of release of neuropeptides including CGRP from peripheral nervous system

Onabotulinum Toxin A (Botox)

Gepants – For Prevention

- Atogepant
  - Oral CGRP **Receptor** Antagonist for the prevention of episodic and chronic migraine
  - Dosing: 10mg, 30mg, 60mg options
- Rimegepant
  - Oral CGRP **Receptor** Antagonist for the prevention of episodic migraine
  - Dosing 75mg QOD

Atogepant (Qulipta) Data on file. 2021. Allergan Pharmaceutical
Rimegepant (Nurtec ODT) Data on file – Biohaven US-RIMODT-210025105/10/2021

Anti-CGRP Monoclonal Antibodies for Migraine Prevention

- Target specific
  - Block CGRP receptor or bind the CGRP ligand
- Net effect
  - Block CGRP activity
  - Lessen the migraine cascade of inflammatory activity
  - Prevent transmission of pain signals to travel to higher order neurons
- Anti-CGRP mABs are large monoclonal antibodies and cannot cross the blood-brain barrior to any significant degree
- Anti-CGRP mABs work on the peripheral nervous system (PNS)

Anti-CGRP Monoclonal Antibodies

- Work on peripheral nervous system
- No central nervous system (CNS) side-effects
- No effect on liver or kidney
- No drug-drug interactions
- Degraded by enzymatic proteolysis
- Favorable side-effect profile in clinical trials
- Approved for migraine prevention in adults **(EPISODIC AND CHRONIC)**
- No data in pregnancy and breast-feeding
- Not available in oral tablet
- Expensive to make (grown in cell cultures)
- CGRP is a vasodilator – CV considerations?
  - Stable CV in trials – no "red flags"
- Immunogenicity is possible – impact unclear
- More similar than different

CGRP – mAB's

mAB	Dosing/Frequency	Safety Considerations
erenumab CGRP receptor blocker	70mg or 140mg SC monthly	Constipation, HTN (post-marketing), Rash, alopecia, angioedema, anaphylaxis
fremanezumab CGRP ligand blocker	225mg SC monthly or 3x225mg SC quarterly (=675mg)	Hypersensitivity reactions (rash, pruritis, urticaria)
galacnezumab* CGRP ligand blocker	120mg SC monthly (requires 240mg loading dose)	Hypersensitivity reactions (rash, urticaria, dyspnea, angioedema, anaphylaxis)
eptinezumab CGRP ligand blocker	100mg or 300mg IV infusion monthly	Hypersensitivity reactions (angioedema, urticaria, facial flushing, rash)

*Additional indication for treatment of episodic cluster headache: Dosing is 300mg (3x100mg syringes) SC
At onset of cluster attach and continue monthly until cluster attack breaks.

erenumab (Aimovig) Aimovig (erenumab-aooe) prescribing information. 2018. Amgen Inc. fremanezumab (Ajovy) Fremanezumab-vfrm prescribing information. 2018. Teva Pharmaceuticals USA.
galacnezumab (Emgality) Stauffer VL, et al. Presented at: *IHC 2017*. Abstract PO-01-184. Data on file, Eli Lilly and Company
eptinezumab (Vyepti) Vyepti (Eptinezumab) prescribing information. 2020. Lundbeck Seattle BioPharmaceuticals, Inc.

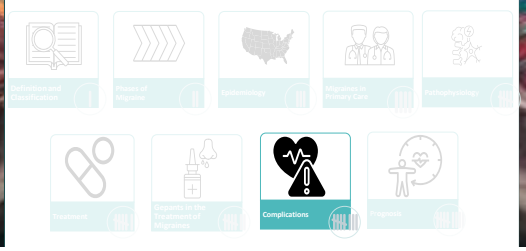
The American Headache Society recommends CGRP targeted treatments in the following migraine patients:

Guidelines

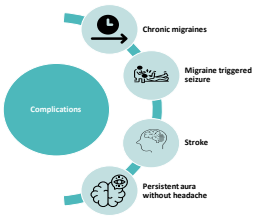
- Acute treatment in moderate to severe attacks in patients who do not respond, or have a contraindication, to triptans
- Gepants/mAbs for preventive treatment in patients who respond well to acute gepants.
- As part of dual therapy in patients with severe attacks

Burch RC, Ailani J, Robbins MS. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2022;62(1):111-112. doi:10.1111/head.14245.

Outline



Migraines are associated with the following complications:



Woodward M. Migraine and the risk of coronary heart disease and ischemic stroke in women. Women's Health (Lond Engl). 2009;5(1):69-77.

Patients with migraine are more likely to suffer from cerebrovascular and cardiovascular events if:

- Women
- Smokers
- Migraine with aura
- Oestrogen use

Anderson, P. Migraine Tied to Hypertension Risk in Women. Medscape Medical News. Available at https://www.medscape.com/viewarticle/879249. April 28, 2017; Accessed: July 9, 2024.

Migraine as Risk Factor for Stroke

- Migraine is an independent risk factor for stroke in women <45 years old
- 2-fold increase in ischemic stroke compared to women without migraine
- This increase primarily driven by the subgroup of women who have migraine with aura
- Approximately 1.5 increased risk hemorrhagic stroke in women with migraine
- Other risk factors such as smoking amplify this risk

Risk of Stroke with Use of Estrogen Containing Contraception in Women with Migraine

- Risk for both ischemic and hemorrhagic stroke higher in high dose (>50 mcg) ethinyl estradiol dose than lower dose (<50 mcg)
- OR ischemic stroke 50 mcg EE 2.9-4.8, OR 1.6-2.7 30-40 mcg EE, OR 1.7 20 mcg EE, OR .9-1 progestin only pills (data from 3 studies)
- Ischemic stroke risk higher in women **with aura** (OR 6.1) using combined oral contraception vs women without aura (OR 1.8) who used CHC's within 90 days prior to the first diagnosis of stroke

Sheikh, H., Pavlovic J., Loder, E., Burch R. Risk of Stroke Associated With Use of Estrogen Containing Contraception in Women with Migraine: A Systematic Review. *Headache*. 2018;58:5-21.

Outline

Migraines have a favourable prognosis.

Prolonged periods of remission are common

Severity and frequency diminish with age

After 15 years, complete remission occurs in:

- 30 % of men
- 40% of women

Bille B. Migraine in childhood and its prognosis. Cephalalgia. 1981 Jun. 1(2):71-5.

QR Code for Resource Toolkit

URL:
https://www.pceconsortium.org/toolkit/migraine

Resource Toolkit

Remember this question?
When should you offer a preventive treatment for your patients with migraine?

A. When they have "chronic migraine" (i.e. more than 15 headache days per month)
B. When they have 4 or more migraine attacks per month.
C. When they have 4 or more migraine headache days per month.
D. All patients with migraine should be offered a preventive treatment regardless of their migraine or headache frequency.

Remember this question?
Which of the following medications is approved for both the acute and preventive treatment of migraine?

A. Sumatriptan 100mg oral tablet
B. Rimegepant 75mg oral dissolvable tablet
C. Lasmiditan 50mg oral tablet
D. Galcanezumab 120mg SC injection