CENTENE PHARMACY
SERVICES

CENTENE® Corporation

Emerging Migraine Treatments

Joey Diaz, PharmD 2025 candidate (University of South Florida)

Objectives

- Overview
- Epidemiology
- Updated pathophysiology
- Newest classes of medications
- Summary

Migraine Overview

- Episodic headache disorder characterized by moderate to severe headaches, as well as photophobia, phonophobia, nausea, allodynia, etc.
- Migraines are considered a complex neurobiological disorder that is often unilateral with throbbing pain
- Intracranial and extracranial changes are responsible for the four phases of a migraine which include prodrome, aura, headache, and postdrome
- Increasing evidence has supported migraines being regarded as a neurovascular headache

Epidemiology

- Over 1 billion people globally live with migraines
- 2nd leading cause of years lived with disability, and the most common among patients under 50 years old
- Women are three times more likely to suffer from migraines
- In 2016, migraines were estimated to account for 36 billion dollars in total direct and indirect costs
- Patients living on less than $35,000 of annual income have the highest rate of migraines

Most Recently Studied Pathophysiology

Cortical spreading depression: Migraine aura has been linked to the neuronal and glial depolarization that spreads across the cerebral cortex. This phenomenon causes the activation of trigeminal afferents and as result leads to inflammatory changes.

Trigeminovascular system: Stimulation of the trigeminal ganglion causes the release of nociceptive signals and vasoactive neuropeptides, such as CGRP, which in turn causes vasodilation.

Sensitization: Peripheral nociceptors become increasingly responsive to nociceptive and non-nociceptive stimulation thus leading to central sensitization as well as allodynia.

Calcitonin gene-related particle (CGRP): Neuropeptide that is expressed in trigeminal ganglia nerves and released after their stimulation. Known for its potent vasodilation effect on cerebral and dural vessels.

Conventionally Used Migraine Treatments

- Prophylaxis
  - Topiramate: Inhibits the excitatory activity of glutamate, decreases the frequency of action potentials by blocking sodium channels, and enhances GABA-A activity
  - Beta-blockers: Inhibit norepinephrine release, reduce blood vessel dilation, and are theorized to reduce the spread of brain signals as well as the cortical spreading
- Acute
  - Triptans: Selective agonist for the serotonin receptors (5-HT1B & 5-HT1D) on intracranial blood vessels and trigeminal sensory neurons causing vasoconstriction and inhibition of peripheral nociceptors
  - NSAIDs: Blocks cyclooxygenase and thus decreases the synthesis of prostaglandins

Emerging Classes of Migraine Medications

- CGRP antagonists
  - Monoclonal antibodies (mabs)
  - Small molecule antagonists (gepants)
- 5-HT1F receptor agonist
- OnabotulinumtoxinA (Botox)

Who's Eligible to Use a CGRP Antagonist for Prophylaxis?

TABLE 2 Updated recommendations for migraine prevention.

A Diagnosis of episodic migraine with or without aura (4–14 MMDs) based upon ICHD-3 with at least moderate disability (MIDAS score ≥11 or HIT-6 score >50). Treatments to consider include:

1. Topiramate
2. Divalproex sodium/valproate sodium
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Candesartan
5. Tricyclic antidepressant: amitriptyline, nortriptyline
6. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
7. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
8. Monoclonal antibodies targeting CGRP or its receptor including erenumab, fremenezumab, galcanezumab, or eptinezumab
9. Small-molecules targeting the CGRP receptor ("gepants") including atogepant and rimegepant

B Diagnosis of chronic migraine with or without aura (≥15 MHDs) based upon ICHD-3. Treatments to consider include:

1. Topiramate
2. Divalproex sodium/valproate sodium
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Candesartan
5. Tricyclic antidepressant: amitriptyline, nortriptyline
6. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
7. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
8. OnabotulinumtoxinA
9. Monoclonal antibodies targeting CGRP or its receptor including erenumab, fremenezumab, galcanezumab, or eptinezumab
10. Small-molecules targeting the CGRP receptor ("gepants") including atogepant

Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A; American Headache Society. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. *Headache*. 2024;64(4):333-341. doi:10.1111/head.14692

Who's Eligible to Use a CGRP Antagonist for Acute Treatment?

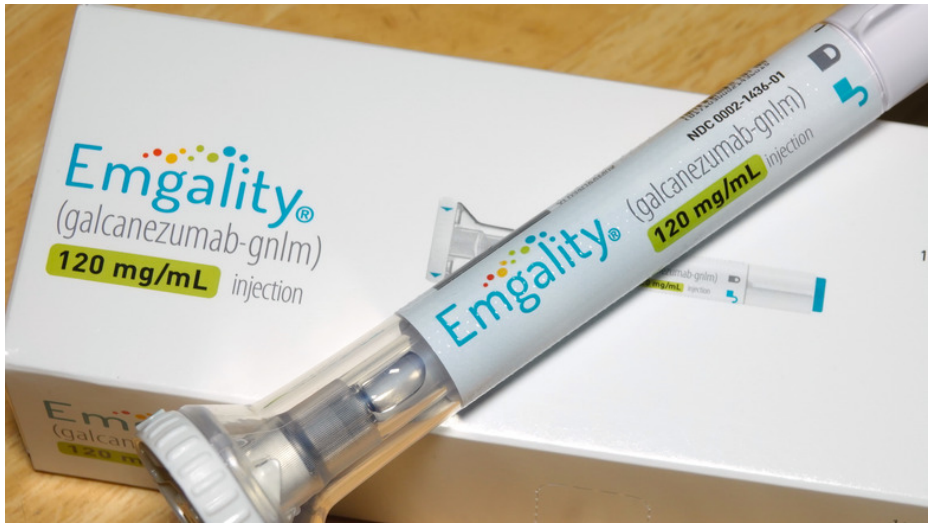
TABLE 3 Criteria for initiating acute treatment with gepants, ditans, or neuromodulatory devices[a]

Use is appropriate when ALL the following are met:
(A) Prescribed/recommended by a licensed clinician
(B) Patient is at least 18 years of age[b]
(C) Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine
(D) Either of the following:
a. Contraindications to or inability to tolerate triptans[c]
b. Inadequate response to two or more oral triptans, as determined by EITHER of the following
(i) Validated acute treatment patient-reported outcome questionnaire (mTOQ, Migraine-ACT, PPMQ-R, FIS, PGIC)
(ii) Clinician attestation

Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61(7):1021-1039. doi:10.1111/head.14153

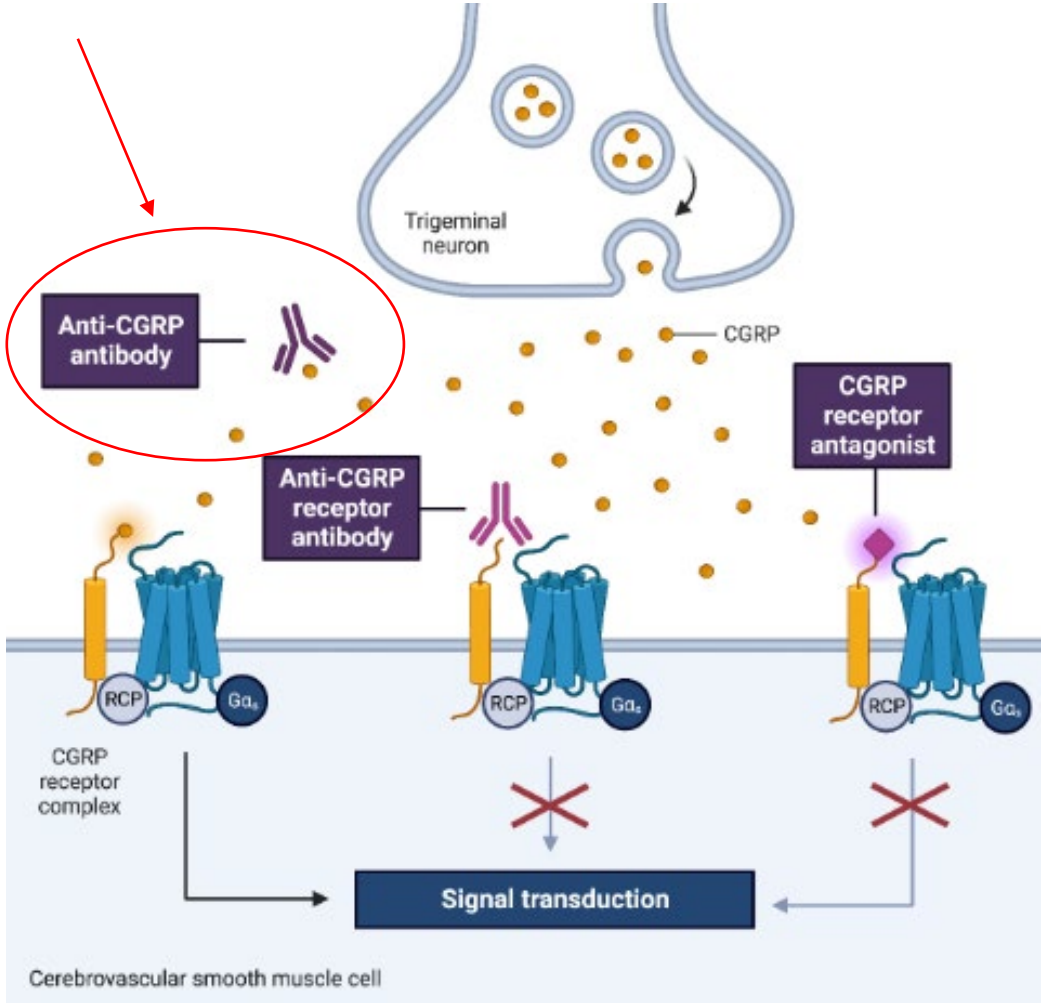
CGRP Antagonist: Monoclonal Antibodies

- Medications:
  - Emgality (Galcanezumab)
  - Vyepti (Eptinezumab)
  - Ajovy (Fremanezumab)
- Indication: Migraine prophylaxis (Episodic & chronic)



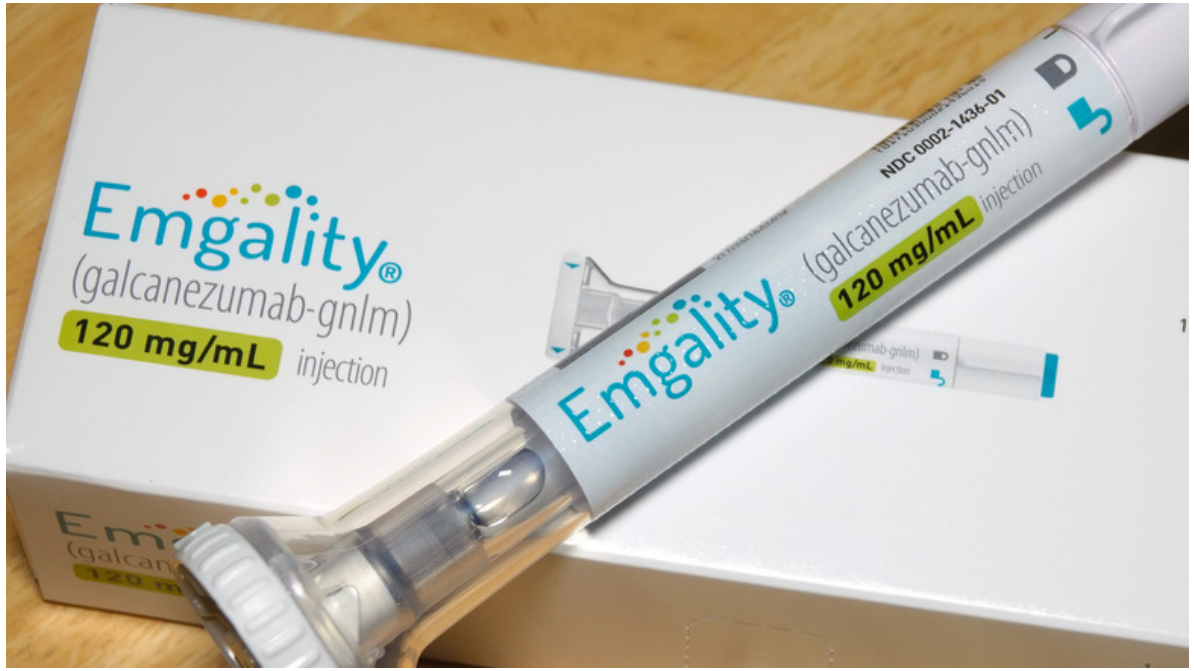
CGRP Antagonist: Monoclonal Antibodies

- Mechanism of action:
  - The humanized monoclonal antibodies target CGRP, bind to it, and deactivate CGRP after it is released by trigeminal sensory nerve fibers



Emgality (Galcanezumab)

- Route of administration: SQ
- Regimen: 240 mg SQ loading dose then 120 mg SQ monthly
- Adverse effects:
  - Injection site reaction
- Price (Wholesale Acquisition Cost):
  - $706-$847 (1 month)



Vyepti (Eptinezumab)

- Route of administration: IV
- Regimen: 100-300 mg IV infusion every three months
- Adverse effects:
  - Nasopharyngitis
- Price (Wholesale Acquisition Cost):
  - $2,121 (3 months)

Ajovy (Fremanezumab)

- Route of administration: SQ
- Regimen: 225 mg SQ monthly or 675 mg SQ every three months
- Adverse effects:
  - Injection site reaction
- Price (Wholesale Acquisition Cost):
  - $586 (1 month)

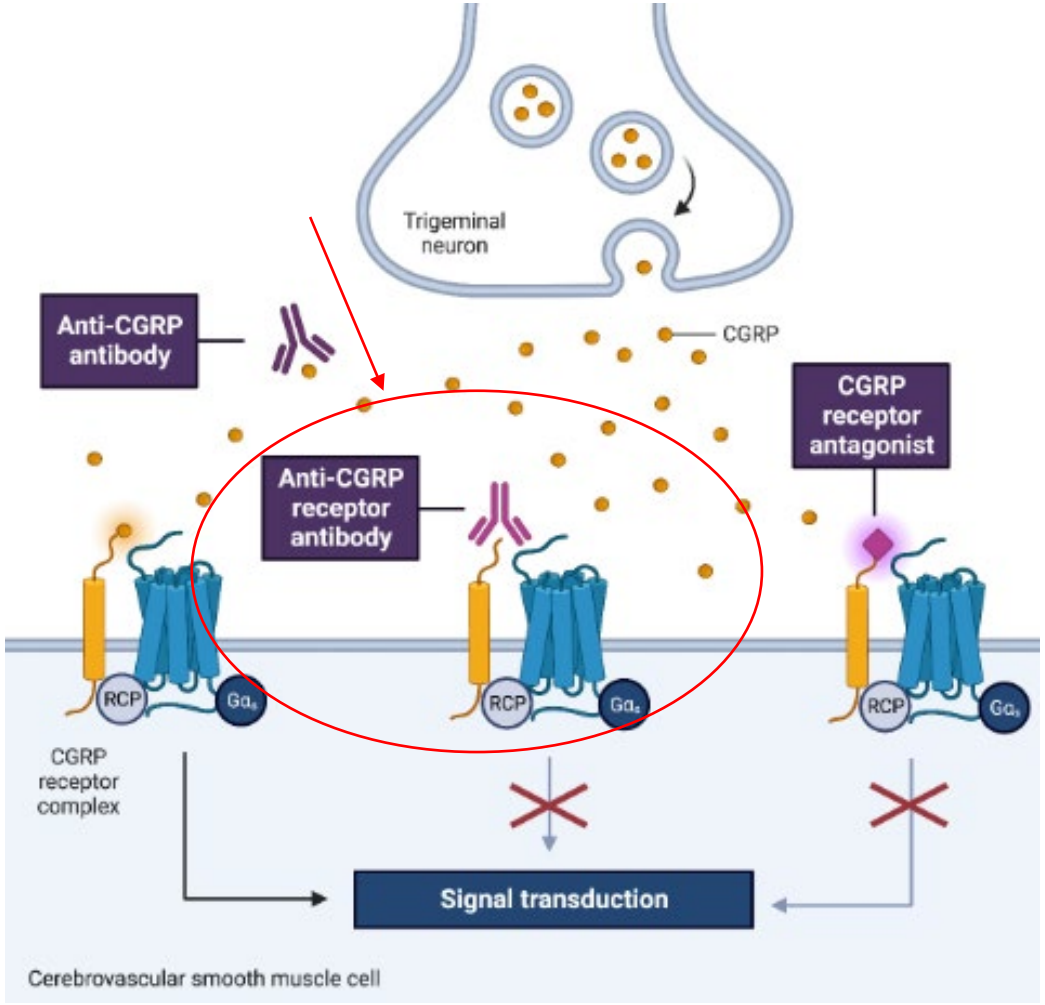
CGRP Antagonist: Monoclonal Antibodies (Receptor Blockers)

- Medications: Aimovig (Erenumab)
- Indication: Migraine prophylaxis (Episodic & chronic)

aimovig® (erenumab-aooe) injection 70 mg/mL • 140 mg/mL

CGRP Antagonist: Monoclonal Antibodies (Receptor Blockers)

- Mechanism of action:
  - Erenumab is a humanized monoclonal antibody that antagonizes the CGRP receptor function



Aimovig (Erenumab)

- Route of administration: SQ
- Regimen: 70-140 mg SQ once monthly
- Adverse effects:
  - Injection site reaction
  - Constipation
  - Hypertension (new-onset and worsening of pre-existing)
- Price (Wholesale Acquisition Cost):
  - $903.14 per month

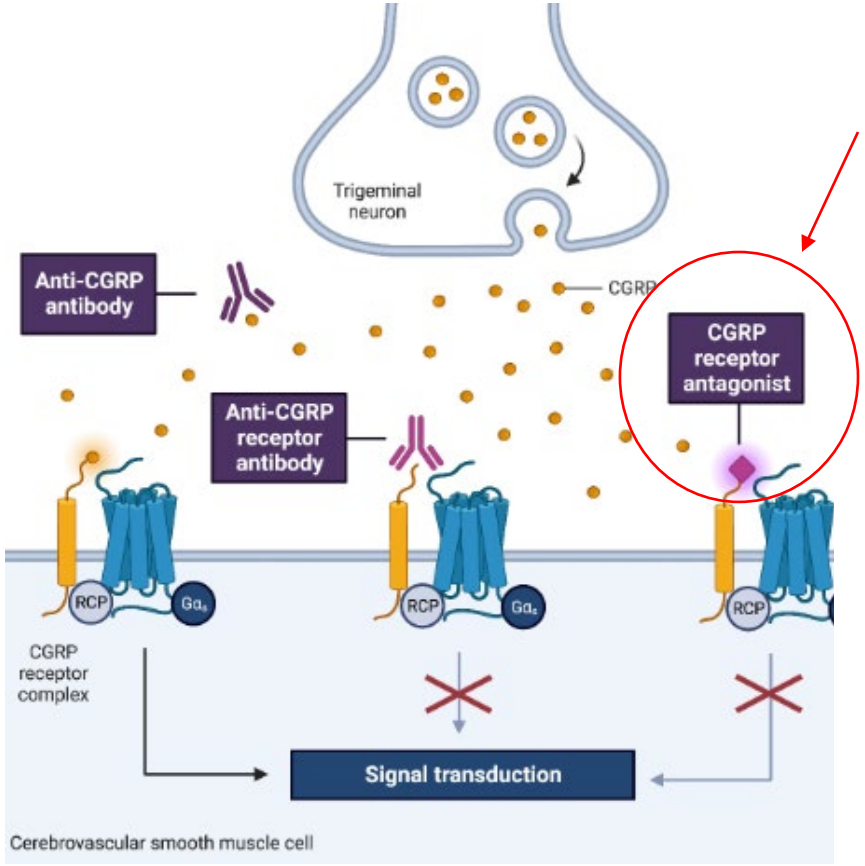
aimovig® (erenumab-aooe) injection 70 mg/mL • 140 mg/mL

CGRP Antagonist: Small Molecule Antagonists

- Medications:
  - Ubrelvy (Ubrogepant)
  - Nurtec (Rimegepant)
  - Qulipta (Atogepant)
  - Zavzpret (Zavegepant)
- Indication:
  - Prophylaxis:
    - Qulipta (Episodic & chronic)
  - Acute:
    - Ubrelvy
    - Zavzpret
  - Acute & Prophylaxis:
    - Nurtec (Episodic)

CGRP Antagonist: Small Molecule Antagonists

- Mechanism of action:
  - Selective and competitive CGRP receptor antagonist



Ubrelvy (Ubrogepant)

- Route of administration: PO
- Regimen:
  - Acute: 50-100 mg PO PRN (Max 200 mg/24h)
  - Maximum of 8 doses per month
- Adverse effects:
  - Nausea
  - Drowsiness
  - Xerostomia
- Price (Wholesale Acquisition Cost):
  - $960 (1 month)

Nurtec (Rimegepant)

- Route of administration: ODT
- Regimen:
  - Acute: 75 mg PO PRN
  - Prophylaxis: 75 mg PO every other day (Max 75 mg/day)
  - Maximum of 18 doses per month
- Adverse effects:
  - Nausea
- Price (Wholesale Acquisition Cost):
  - $2697 (1 month)

Qulipta (Atogepant)

- Route of administration: PO
- Regimen:
  - Prophylaxis: 10, 30, or 60 mg PO once daily
- Adverse effects:
  - Nausea
  - Constipation
  - Fatigue/Somnolence
  - Decreased appetite
- Price (Wholesale Acquisition Cost):
  - $1311 (1 month)

Zavzpret (Zavegepant)

- Route of administration: Intranasal
- Regimen:
  - Acute: 1 spray (10 mg/spray) in one nostril as a single dose PRN
  - Maximum of 1 spray per 24 hours and 8 sprays per month
- Adverse effects:
  - Taste disorders
  - Nausea & Vomiting
  - Nasal discomfort
- Price (Wholesale Acquisition Cost):
  - $1,100 for 6 sprays

Who is Eligible for a 5-HT1F Receptor Agonist?

TABLE 3 Criteria for initiating acute treatment with gepants, ditans, or neuromodulatory devices[a]

Use is appropriate when ALL the following are met:
(A) Prescribed/recommended by a licensed clinician
(B) Patient is at least 18 years of age[b]
(C) Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine
(D) Either of the following:
a. Contraindications to or inability to tolerate triptans[c]
b. Inadequate response to two or more oral triptans, as determined by EITHER of the following
(i) Validated acute treatment patient-reported outcome questionnaire (mTOQ, Migraine-ACT, PPMQ-R, FIS, PGIC)
(ii) Clinician attestation

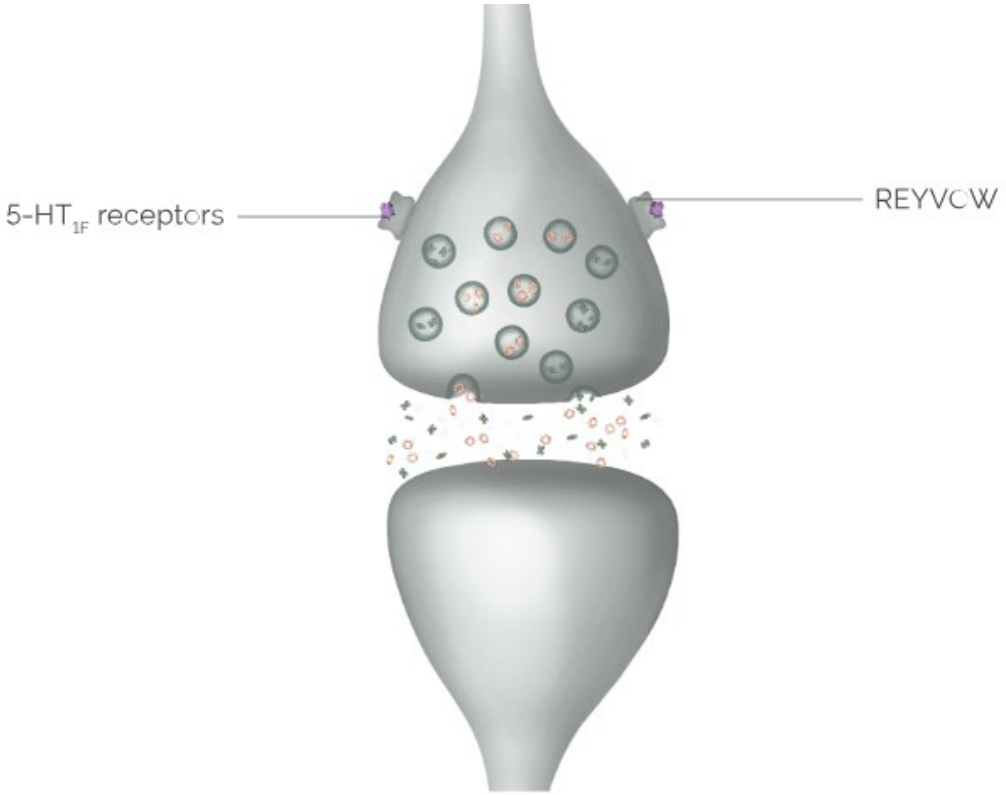
Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61(7):1021-1039. doi:10.1111/head.14153

5-HT1F Receptor Agonist

- Medications: Reyvow (Lasmiditan)
- Indication: Acute migraine

5-HT1F Receptor Agonist

- Mechanism of action:
  - Selective 5-HT1F receptor agonist
    - Decreases stimulation of the trigeminal system



Reyvow (Lasmiditan)

- Route of administration: PO
- Control Schedule V
- Regimen:
  - Acute: 50-100 mg as a single dose PRN. May increase to 100-200 mg as a single dose (Max one dose per 24hr)
  - Maximum of 4 doses per month
- Adverse effects:
  - Dizziness
  - Fatigue
  - Nausea & Vomiting
  - Paresthesia
- Price (Wholesale Acquisition Cost):
  - $444-$800 (1 month)

Who is Eligible to Use Botox?

B Diagnosis of chronic migraine with or without aura (≥15 MHDs) based upon ICHD-3. Treatments to consider include:

1. Topiramate
2. Divalproex sodium/valproate sodium
3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
4. Candesartan
5. Tricyclic antidepressant: amitriptyline, nortriptyline
6. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
7. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence
8. OnabotulinumtoxinA
9. Monoclonal antibodies targeting CGRP or its receptor including erenumab, fremenezumab, galcanezumab, or eptinezumab
10. Small-molecules targeting the CGRP receptor ("gepants") including atogepant

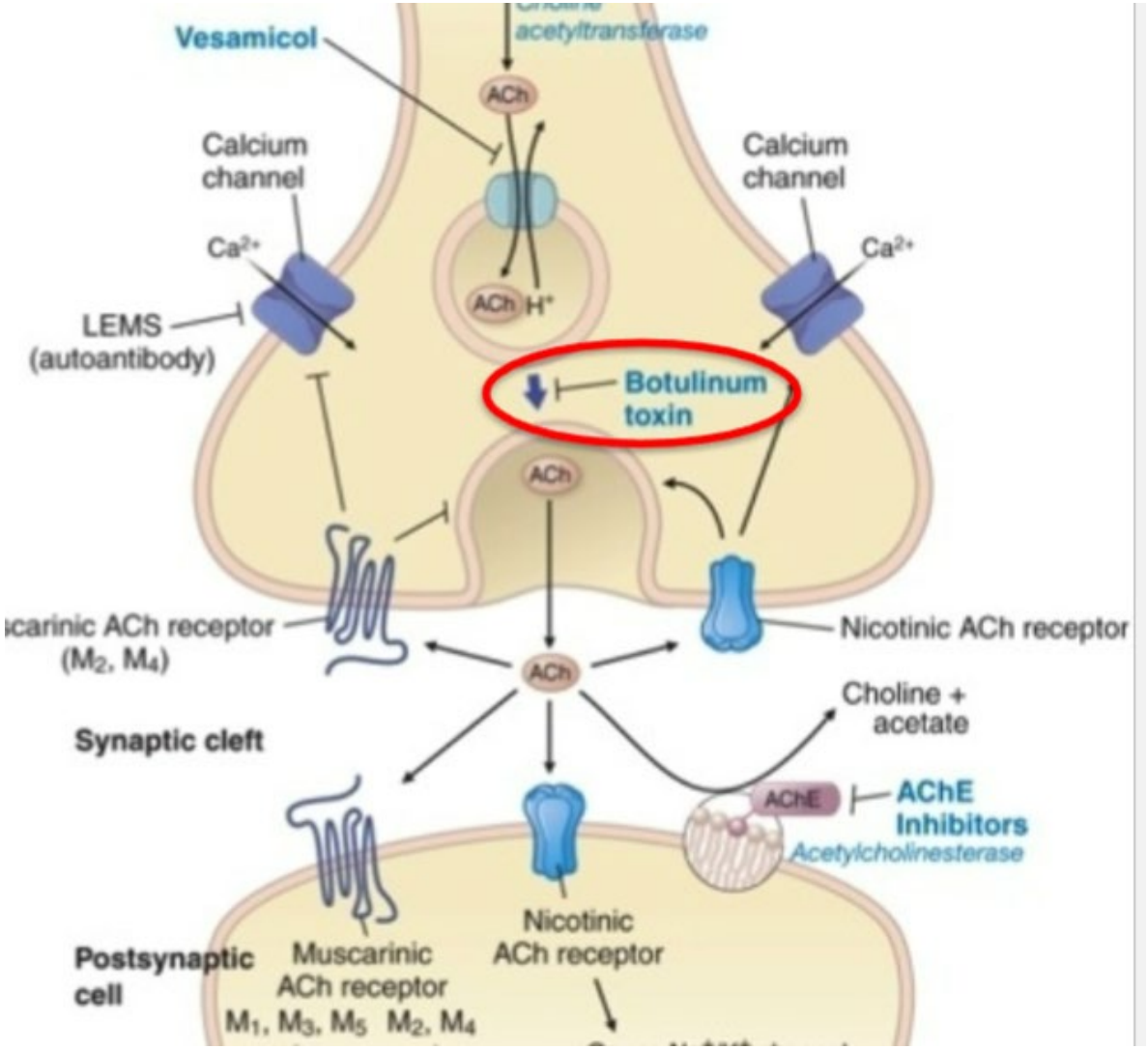
Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A; American Headache Society. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. *Headache*. 2024;64(4):333-341. doi:10.1111/head.14692

Botox (OnabotulinumtoxinA)

- Indication: Migraine prophylaxis (Chronic)

Botox (OnabotulinumtoxinA)

- Mechanism of action:
  - Blocks neuromuscular transmission by inhibiting the release of acetylcholine
  - Botox cleaves SNAP-25, a protein that plays a central role in the fusion and eventual release of acetylcholine from the presynaptic neuron



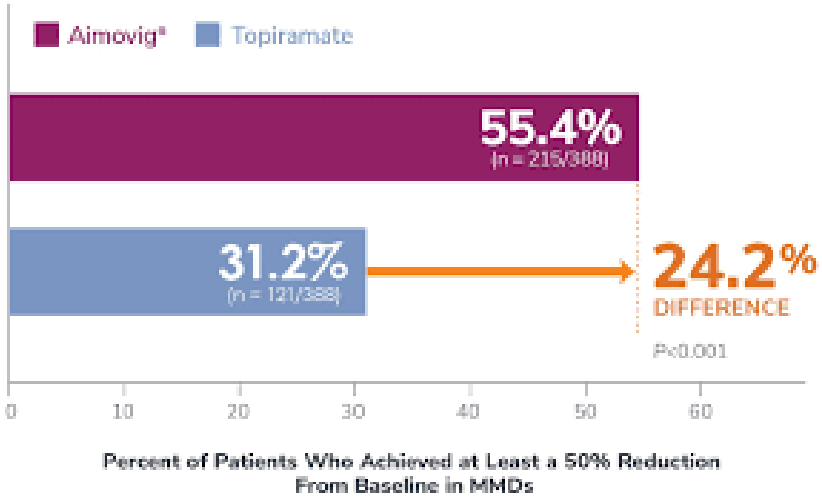
Botox (OnabotulinumtoxinA)

- Route of administration: IM
- Regimen:
  - Prophylaxis: 155 units IM every 12 weeks
    - 5 units per injection site with a total of 31 sites
- Adverse effects:
  - Neck pain
  - Headache
  - Ptosis
- Black box warning:
  - Spread of toxin effect
- Price (Wholesale Acquisition Cost):
  - $1,244 for a 200-unit vial

Summary of Benefits from Emerging Treatments

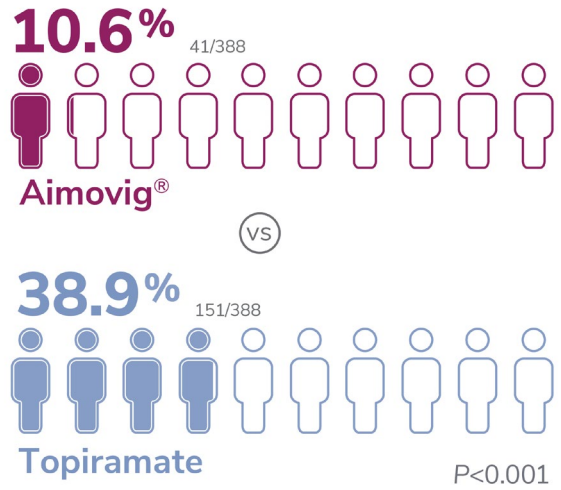
- Improved adherence
- Reduced incidence of medication-overuse headaches
- No serious adverse events reported across the classes
- CGRP-targeting therapies
  - Nearly all of them can be used for prevention of episodic and chronic migraines
  - Can be considered a first-line therapy option per AHS 2024 update

Efficacy →



Percent of Patients Who Achieved at Least a 50% Reduction From Baseline in MMDs

Safety →



Primary Endpoint: Proportion of Patients With Treatment Discontinuation Due to AEs During the 6-Month DBTP[1]

References

1. Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A; American Headache Society. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. *Headache*. 2024;64(4):333-341. doi:10.1111/head.14692
2. Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61(7):1021-1039. doi:10.1111/head.14153
3. Nguyen, J.L., Munshi, K., Peasah, S.K. *et al.* Trends in utilization and costs of migraine medications, 2017–2020. *J Headache Pain* 23, 111 (2022). https://doi.org/10.1186/s10194-022-01476-y
4. Zobdeh F, Ben Kraiem A, Attwood MM, et al. Pharmacological treatment of migraine: Drug classes, mechanisms of action, clinical trials and new treatments. *Br J Pharmacol*. 2021;178(23):4588-4607. doi:10.1111/bph.15657
5. Reuter U, Ehrlich M, Gendolla A, et al. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. *Cephalalgia*. 2022;42(2):108-118. doi:10.1177/03331024211053571
6. Ray JC, Kapoor M, Stark RJ, et al. Calcitonin gene related peptide in migraine: current therapeutics, future implications and potential off-target effects. *J Neurol Neurosurg Psychiatry*. 2021;92(12):1325-1334. doi:10.1136/jnnp-2020-324674