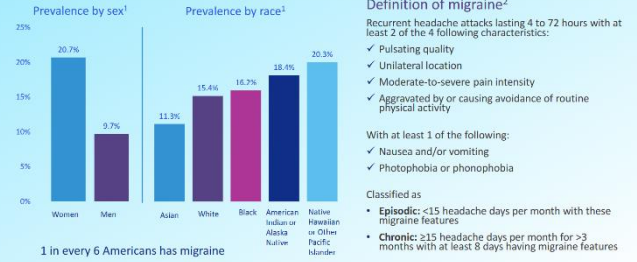


Please choose what you believe to be the correct answer - both questions require a response to proceed.

Which of the following statements most accurately describes migraine's impact on a person's quality of life? *

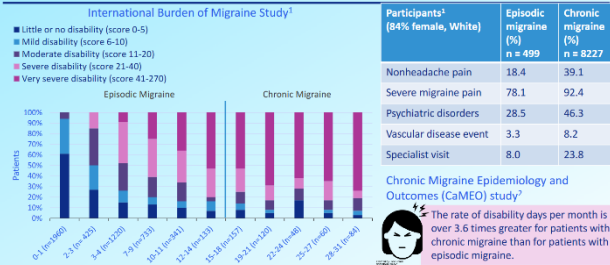
- Women responding to the Eurolight project survey lost nearly twice as much work time as men as a result of disability from migraine attacks
- Workplace stigma is widespread, with three-quarters of participants in the Observational survey of the Epidemiology, Treatment and Care of Migraine (OVERCOME) (US) study reporting that they experience it often or very often
- According to the Chronic Migraine Epidemiology and Outcomes (CaMEO) study, people living with chronic migraine experience over 3 times more headache-related disability days than those with episodic migraine
- More than 50% of people surveyed in the CaMEO study believe they would be better parents and partners if they did not have migraine attacks

Prevalence and Definition of Migraine Headache



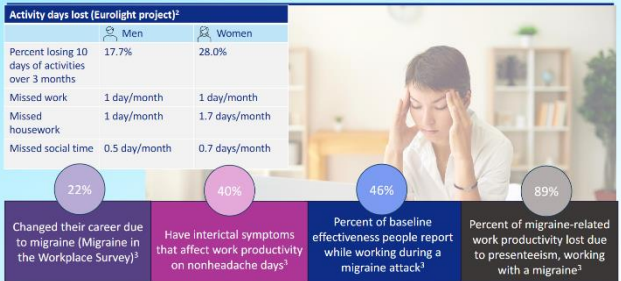
1. Branch R, et al. *Headache*. 2018;58(4):496-505; 2. *Headache Classification Committee of the International Headache Society (IHS). Cephalalgia*. 2018;38(1):1-211.

Disability Increases With Increasing Number of Headache Days



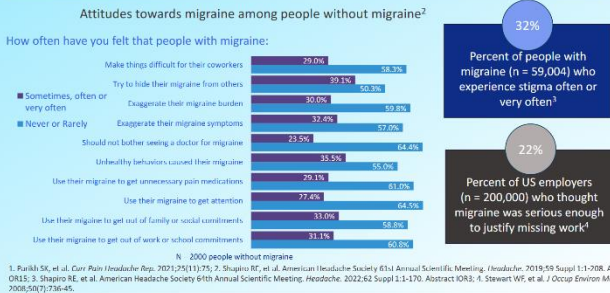
1. Blumenfeld AM, et al. *Cephalalgia*. 2011;31(3):301-15; 2. Adams AM, et al. *Cephalalgia*. 2015;35(7):563-78.

The Lives of People Living With Migraine Are Impacted in Many Domains, Including Work¹



1. Fitzam PM, et al. *Headache*. 2017;57(7):1004-70; 2. Sletten TL. *Headache Pain*. 2014;15(1):31; 3. Beggs et al. *Neurologist*. 2017;27:1004R.

Experiencing Migraine Stigma Is Common, Especially Among People Living With Chronic Migraine¹



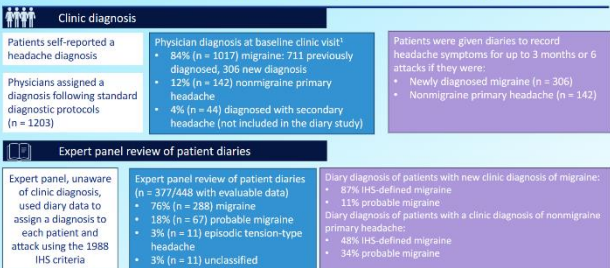
1. Rankl SK, et al. *Curr Pain Headache Rep*. 2021;25(1):75; 2. Shapiro RF, et al. American Headache Society 61st Annual Scientific Meeting. *Headache*. 2019;59 Suppl 1:1-208. Abstract ON5; 3. Shapiro RF, et al. American Headache Society 61st Annual Scientific Meeting. *Headache*. 2022;62 Suppl 1:1-170. Abstract JOR3; 4. Stewart WF, et al. *J Occup Environ Med*. 2006;50(7):336-45.

Please choose what you believe to be the correct answer - both questions require a response to proceed.

Based on data from the Chronic Migraine Epidemiology and Outcomes (CaMEO), Observational survey of the Epidemiology, Treatment and Care of Migraine (OVERCOME), and LANDMARK studies, which of the following statements regarding migraine diagnosis and treatment is most accurate? *

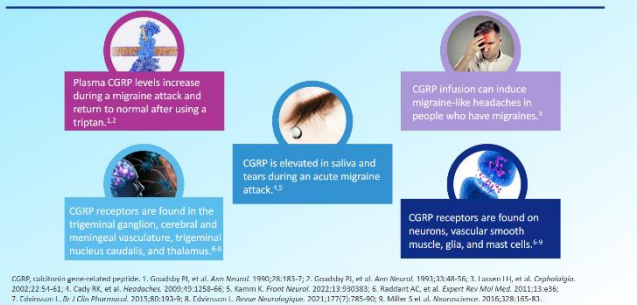
- An expert panel in the LANDMARK study found that fewer than half of people living with migraine could be diagnosed using diary entries alone
- Fewer than half of participants eligible for migraine preventative treatment in the OVERCOME study were taking it
- Among CaMEO participants who had received an inaccurate diagnosis, the most common misdiagnosis was tension-type headache
- Opioids and triptans were the most frequently used and overused medications to treat migraine attacks in the CaMEO study

An Episodic, Disabling Headache With an Otherwise Normal Physical Exam and No Contradictory Evidence Is Migraine



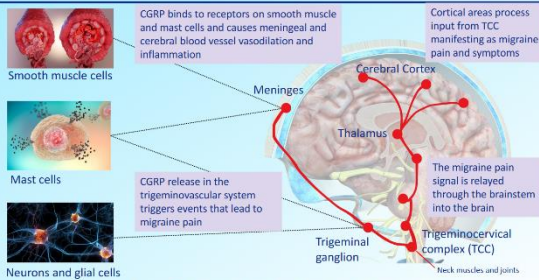
LANDMARK study: 178 patients (93% primary care), 15 countries, 1203 patients, 84% female, 80% White
 IHS: International Headache Society. *Headache*. 1988;28(2):160-72. *Headache*. 2002;42 Suppl 1:1-170. Abstract JOR3; 4. Stewart WF, et al. *J Occup Environ Med*. 2006;50(7):336-45.

Clinical and Physiologic Evidence Supports the Role of CGRP in Migraine Pathophysiology



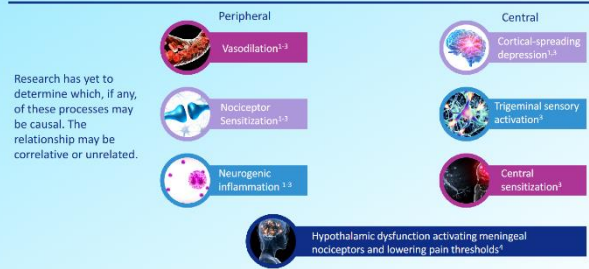
CGRP (calcitonin gene-related peptide): 1. Goadsby PJ, et al. *Ann Neurol*. 1993;38:183-7; 2. Goadsby PJ, et al. *Ann Neurol*. 1993;33:48-56; 3. Leone IH, et al. *Cephalalgia*. 2002;22:54-61; 4. Cady RK, et al. *Headaches*. 2009;49:1258-66; 5. Kamm K. *Front Neurol*. 2022;13:930383; 6. Radtarski AC, et al. *Expert Rev Mol Med*. 2011;13:436; 7. Edvinsson L. *Br J Clin Pharmacol*. 2015;80:193-9; 8. Edvinsson L. *Rev Neurol (Paris)*. 2011;177(7):785-90; 9. Miller S, et al. *Neuroscience*. 2016;338:165-81.

CGRP Receptors Are Localized on Cells and in Areas Associated With Migraine Pathophysiology



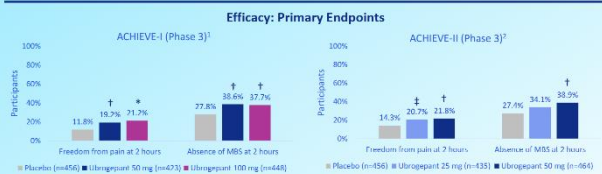
Dodd DW. *Headache*. 2018;58:1-16. Illustration adapted from The Role of CGRP in Migraine. (n.d.). Science of migraine.com. Accessed December 16, 2023. <https://www.scienceofmigraine.com/journal/physiology/cgrp>

CGRP-CGRP-R Signaling in Migraine Pathophysiology May Involve Multiple Central and Peripheral Nervous System Processes



1. Riedman AC, et al. *Papert Rev Med Med*. 2011;13:36; 2. Fehérsson L. *Br J Clin Pharmacol*. 2015;80:151-9; 3. Russo AF, et al. *Annu Rev Pharmacol Toxicol*. 2015;55:33-43; 4. Burstein R, et al. *J Neurosci*. 2015;35:6819-29.

Ubrogepant: Efficacy and Safety Data For Acute Migraine Attack Treatment



Safety: Adverse Events

Study group	Adverse events reported in ≥2%
Treatment	Nausea, ^{1,2} somnolence, ³ dry mouth, ¹ upper respiratory tract infection, ^{1,2} dizziness, ² nasopharyngitis ⁴
Placebo	Nausea ^{1,2}

*P < 0.001; †P < 0.01; ‡P < 0.05 vs placebo. MBS, most bothersome symptom.

1. Dodd DW, et al. *W Engl J Med*. 2019;381(23):2230-41; 2. Lipkin RB, et al. *JAMA*. 2019;322(19):1887-98.

Please choose what you believe to be the correct answer - both questions require a response to proceed.

Laura, age 42, has episodic migraine with aura (average 3 headache days per month) accompanied by severe vomiting at migraine onset. She has had dizziness and fatigue when taking rizatriptan and experiences chest tightness with sumatriptan. Her medical history is notable for constipation. Would a CGRP receptor antagonist (gepant) be an appropriate option for acute migraine treatment? *

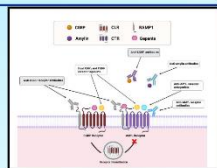
- Yes, rimegepant or zavegepant, given her triptan intolerance and severe vomiting
- Yes, atogepant or ubrogepant, given her history of constipation
- Yes, but only atogepant, given her history of constipation
- No, because recommended criteria for gepant use have not been met

Constipation Is Not a Consistent Adverse Effect Across Gepants

- Constipation has an incidence of 3.41 per 100 person years in the migraine population vs 1.48 per 100 person years in the general population. About 1 in every 5 of these cases was rated as serious¹
- CGRP antagonism may reduce gastrointestinal motility and increase constipation risk²
- Atogepant (phase 3, double-blind, 12-week trial)³

Dose	Constipation (%)
Atogepant 10 mg (n = 221)	7.7%
Atogepant 30 mg (n = 228)	7.0%
Atogepant 60 mg (n = 211)	6.9%
Placebo (n = 222)	0.5%

- Constipation was not noted in other gepant trials,⁴ but was reported by 4.7% of 106 participants in a ubrogepant post-marketing cohort study⁵



- ✓ CGRP is widely expressed in the enteric nervous system
- ✓ CGRP receptors are found throughout the gastrointestinal system
- ✓ Blocking the CGRP receptor may reduce gastrointestinal motility
- ✓ Increased free CGRP binds to the myosin I receptor, which can contribute to constipation⁶

1. Alizani J, et al. *Neurology*. 2022;99(19):841-53; 2. Lattanzi C, et al. *Neural Ther*. 2022;11(3):135-52; 3. Alzari L, et al. *N Engl J Med*. 2021;385(8):695-706; 4. Hober P, et al. *Front Physiol*. 2022;13:82006; 5. Chang CC, et al. *Headache*. 2021;61(5):820-7; Image: Labatola-Bainfoc, et al. *J Neurosci Res*. 2023;24(1):125. (CC BY 4.0)

Please choose what you believe to be the correct answer - both questions require a response to proceed.

Toni, a 36-year-old lawyer and mother, experiences 7 to 8 disabling migraine days per month. Her headaches frequently reach moderate-to-severe intensity. Toni takes zolmitriptan, but delays treatment due to concerns about medication overuse headaches. She desires pregnancy within 6 months. Would preventative treatment with a CGRP antagonist (gepant or anti-CGRP monoclonal antibody) be appropriate, and if so, which type? *

- Yes, select a gepant due to their shorter half-lives
- Yes, select an anti-CGRP monoclonal antibody, considering their favorable safety profile during pregnancy
- No, because all CGRP inhibitors require a 6-month wash-out period prior to pregnancy
- No, preventative therapy would not be indicated, but a gepant could be used for acute treatment

Anti-CGRP Monoclonal Antibodies Have Longer Half-Lives Than Gepants

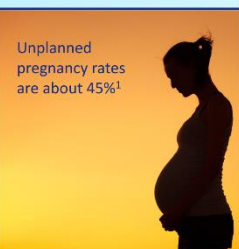
	Acute/Preventative treatment	Administration form	Half-life
Gepants			
Atogepant ¹	Prevention	Tablet	11 hours
Rimegepant ²	Acute/Prevention	Oral disintegrating tablet	11 hours
Ubrogepant ¹	Acute	Tablet	5-7 hours
Zavegepant ⁴	Acute	Nasal spray	6.55 hours
Monoclonal Antibody			
Erenumab ⁵	Prevention	SC injection	28 days
Eptinezumab ⁶	Prevention	IV infusion	27 days
Galcanezumab ⁷	Prevention	SC injection	27 days
Fremanezumab ⁸	Prevention	SC injection	31 days

A drug is considered eliminated from the body after 5 times its half-life.⁹

SC, subcutaneous; IV, intravenous; 1. Qybio. Package insert. AbbVie; 2023; 2. Nurtec. ODT. Package insert. Pfizer Inc.; 2023; 3. Ubrovelo. Package insert. AbbVie Inc.; 2023; 4. Zenpep. Package insert. Pfizer Inc.; 2023; 5. Amnogen. Package insert. Amgen Inc.; 2023; 6. Vyepti. Package insert. Lundbeck Seattle BioPharmaceuticals, Inc.; 2022; 7. Enfalyx. Package insert. Eli Lilly and Company; 2023; 8. Ajovy. Package insert. Teva Pharmaceuticals; 2023; 9. Al-Hassany I, et al. *Lancet Neurol*. 2022;21(3):284-24.

CGRP Antagonists Are Not Recommended For Use in Pregnancy or Breastfeeding

- CGRP is an important mediator in pregnancy, increasing uteroplacental blood flow and decreasing vascular resistance¹
- Animal testing at high gepant doses found fetal toxicity and fetal loss³



	Gepants	Anti-CGRP monoclonal antibodies
Half-life	5-11 hours	28 days (must be stopped 6 months before pregnancy)
ACOG recommendations for use during pregnancy ²	Do not use	Do not use
Fetal risks ³	Unknown	Unknown

Clinical trials are underway to assess the risk of pregnancy and infant outcome after gepant exposure.

ACOG, American College of Obstetricians and Gynecologists.

1. Babbler J. Management of headache in pregnant women - practical neurology. (May/June 2021). Accessed December 21, 2023. <https://practicalneurology.com/articles/2022-05/management-of-headache-in-pregnant-women/>; 2. Headaches in Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 3. *Obstet Gynecol*. 2023;136(5):844-73; 3. Tepper D. *Headache*. 2020;60(5):1079-86.