PainWeek

Migraine Headache: New and Emerging Therapies

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Disclosures

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Learning Objectives

- Identify migraine prevalence and disease burden
- Describe the challenges and unmet needs in migraine
- Examine the new insights in migraine pathophysiology and the impact on new treatments

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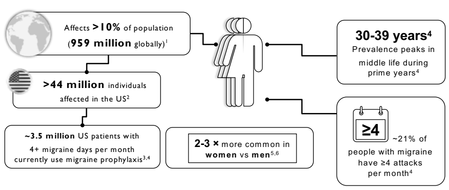
- Migraine is more than a headache, it is a distinct neurological disease that changes brain biology and function[1]
- Migraine is characterized by moderate to severe headache, often accompanied by nausea, vomiting, phonophobia, and photophobia[2]
- Migraine is a long-term disabling disease that can profoundly impair patients' abilities to carry out everyday activities such as managing a family and going to work, and can also be a burden on family members[3-5]

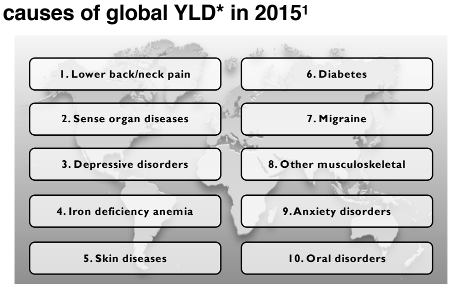
- 1. Russo AF. Annu Rev Pharmacol Toxicol. 2015;55:533–552. 2. Headache Classification Committee of the International Headache Society. Cephalalgia. 2013;33:629–808. 3. Buse D, et al. Neurology. 2015;84(14 Suppl):P5.039. 4. Lipton RB, et al. Cephalalgia. 2003;23:429–440. 5. Lipton RB, et al. Neurology. 2007;63:343–349.

Migraine is a Global Problem



1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2016;388:1545–602. 2. GBD Results Tool. GBD 2015 Data Resources. Available from: http://ghdx.healthdata.org/gbd-results-tool?params=querytool-permalink/7c3dc4972502afe131c6794349a8c39b [accessed 28 March 2017]. 3. Marketscan data on file; 24 March 2017. 4. Lipton RB, et al. *Neurology*. 2007;68:343–349. 5. Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533–552. 6. Gasparini CF, et al. *Curr Genomics*. 2013;14:300–315.

Global Burden of Disease Study: Top causes of global YLD* in 2015[1]



*YLD represents number of years of healthy life lost as a result of disability caused by the non-fatal experience of disease or injury in a population.[2]

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2016;388:1545–1602.
2. Kirch W, ed. Encyclopedia of Public Health. Available from https://rd.springer.com/referenceworkentry/10.1007/978-1-4020-5614-7_3817 [accessed 22 March 2017].

Using data from the AMPP study of patients with <15 headache days/month (n=11,249) or ≥15 headache days/month (n=655),[1] the prevalence of comorbidity was found to be:

Condition	<15 headache days/month, %	≥15 headache days/month, %
Arthritis	22.2	33.6
Chronic pain	15.1	31.5
Anxiety	18.8	30.2
Depression	17.2	30.2
Obesity	21.0	25.5
Heart disease	6.3	9.6
Hypertension	27.8	33.7
Asthma	17.2	24.4
Chronic bronchitis	4.5	9.2
COPD	2.6	4.9

Some comorbid conditions, including chronic pain, anxiety, and depression, were significantly more prevalent in patients with ≥15 headache days/month than in those with <15 headache days/month, after adjusting for patient demographics (age, gender, income)[1]

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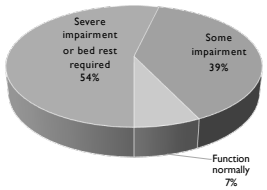
1. Buse D.C. et al. *J Neurol Neurosurg Psychiatry.* 2010;81:428–432.

Migraine-related impairment was common in the AMPP study of >18,000 individuals with migraine[1]



Respondents were asked how they are "usually affected by severe headaches" with the following response options: able to work/function normally; working ability or activity impaired to some degree; working ability or activity severely impaired; and bed rest required.2

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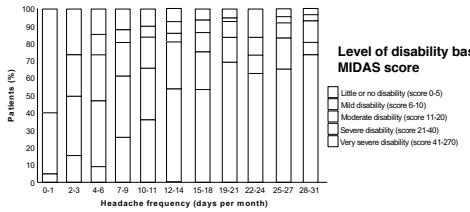
1. Lipton RB, et al. Neurology. 2007;63:343–349. 2. Buse DC, et al. Headache. 2013;53:1278–1299.

Disability Increases Progressively with Increasing Number of International Burden of Migraine Study (N=8,281) Headache Days



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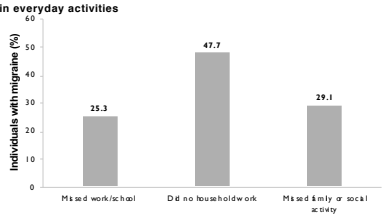
Blumenfeld AM, et al. Cephalalgia. 2011;31:301–315.

Migraine: AMPP Study of Social Activities

Migraine is a disabling disease with substantial impact on work/school, household, and reduced participation in everyday activities



School/work/social impact on ≥1 day in previous 3 months

Lipton RB, et al. Neurology. 2007;63:343–349.

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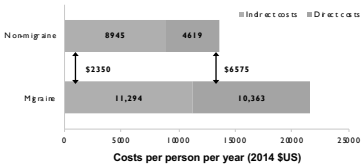
US insurance claims database analysis: 84,245 migraine patients vs matched controls[1]



Healthcare resource utilization and costs increase in proportion with an increase in the frequency and severity of migraine attacks per month[2]

1. Bonafede MM, et al. Value Health. 2016;19:A430.
2.Desai P, et al. J Manag Care Spec Pharm. 2016;22(Suppl.):S73.

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Challenges and Unmet Needs in Migraine

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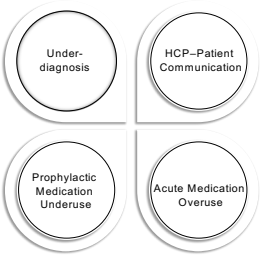
Challenges and Unmet Needs with Current Migraine Management



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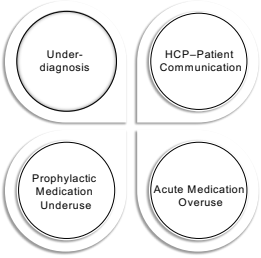
Challenges and Unmet Needs with Current Migraine Management



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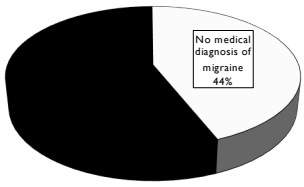
AMPP Study (N=18,968) Underdiagnosed



A substantial proportion of people who meet ICHD criteria for migraine report never having received a medical diagnosis

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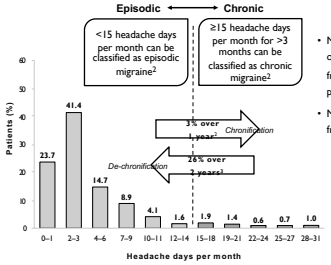
ICHD, International Classification of Headache Disorders.
Diamond S, et al. Headache. 2007;47:355–363.

Frequency of Headache Days in Migraine (N=8,281)[1]



- Migraine frequency can increase over time, and may transition from episodic to chronic: a process termed 'chronification'[2]
- Migraine can also transition from chronic to episodic[2]

1. Blumenfeld AM, et al. *Cephalalgia*. 2011;31:301–315. 2. Headache Classification Committee of the International Headache Society. *Cephalalgia*. 2013;33:629–808.

Pharmacological Treatment Options for Migraine Include Both Acute and Prophylactic Therapies

Acute Therapy — Used to **abort** a migraine attack[1,2]

Prophylactic Therapy — Used to **reduce the frequency, duration, or severity** of attacks[1,3]

- **Pre-emptive:** Used when a known trigger exists (eg, exercise)[3]
- **Short term:** Used when patients are undergoing a time-limited exposure to a provoking factor (eg, menstruation)[3]
- **Maintenance:** Used when patients need ongoing treatment (eg, those with risk of chronic migraine [CM])[3]

Treatment guidelines typically recommend using prophylactic migraine therapies for patients who have ≥4 migraine attacks per month, are overusing acute medication, or experience significant disability from migraine[3]

1. Silberstein SD. *Neurology*. 2000;55:754–762.
2. Marmura MJ, et al. *Headache*. 2015;55:3–20.
3. Silberstein SD. *Continuum*. 2015;21:973–989.

The AAN and the AHS provide the following goals for acute and prophylactic therapy:

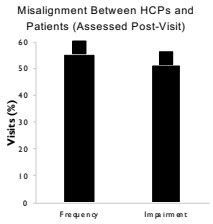
Acute[1,2]	Prophylactic[1,3]
1. Treat attacks rapidly and consistently without recurrence	1. Reduce frequency, duration, or severity of attacks
2. Restore the patient's ability to function	2. Enhance responsiveness to acute therapy
3. Minimize the use of backup and rescue medications	3. Improve the patient's ability to function
4. Optimize self-care and reduce subsequent use of resources	4. Reduce disability
5. Be cost-effective for overall management	5. Reduce healthcare costs
6. Have minimal or no adverse events	

Despite the availability of effective acute and prophylactic therapies, patients may still have unmet needs due to several barriers; including lack of consultation, incomplete awareness of diagnosis, adequate treatment, and treatment optimization & follow-up.[4]

AAN, American Academy of Neurology; AHS, American Headache Society.
1. Silberstein SD. Neurology. 2000;55:754–762. 2. Marmura MJ, et al. Headache. 2015;55:3–20. 3. Silberstein SD. Continuum. 2015;21:973–989. 4. Bigal M, et al. Headache. 2009;49:1028–1041.

American Migraine Communication Study

- Analyzed 60 patient–HCP interactions
- Patients and HCPs were not aligned regarding frequency and impairment following >50% of visits



HCPs should evaluate parameters beyond headache frequency to fully assess the impact migraines have on patients' lives

- HCP, healthcare provider
- Lipton RB, et al. *J Gen Intern Med*. 2008;23:1145–1151.

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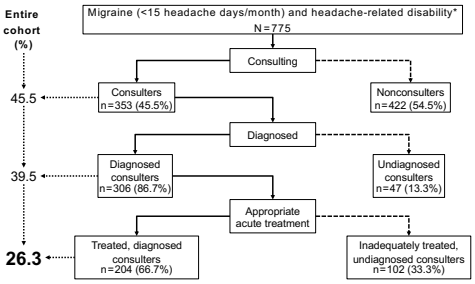

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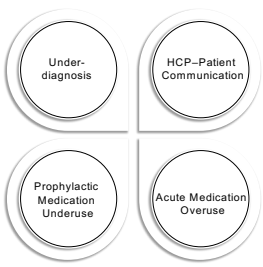
*MIDAS grade ≥II. Lipton RB, et al. *Headache*. 2013;53:81–92.



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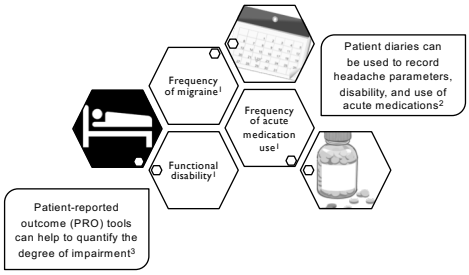

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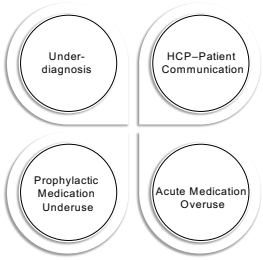
1. Silberstein SD. *Neurology*. 2000;55:754–762. 2. Diener HC, et al. *Clin Med*. 2015;15:334–350. 3. Buse DC, et al. *Mayo Clin Proc*. 2008;84(5):422–435.

Challenges and Unmet Needs with Current Migraine Management



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- Based on available evidence, some acute medications established as effective[1]
- Guidelines recommend limiting the use of acute medication, as overuse can lead to medication overuse headache[2]
- Despite recommendations to avoid opioid treatment of migraine,[3,4] they are prescribed in >50% of migraine emergency department visits[5]
  - Use of opioids in migraine is associated with more severe headache-related disability, symptomology, and greater healthcare resource utilization[6]
- Opioids are only a temporary solution for migraine and risk of dependence is high[7]
  - Opioid abuse is associated with significant economic burden to society (estimated at $55B annually in the US)[8]
- Up to 13% of patients with migraine receiving acute and/or prophylactic therapy still have at least 1 emergency department visit/year, suggesting that available treatments are not optimally addressing patient symptoms and needs[9]

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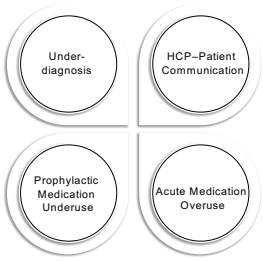
Challenges and Unmet Needs with Current Migraine Management



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AMPP Study of 18,968: Migraine Prophylaxis is Underused

- ~39% were candidates for or should be considered for prophylactic treatment[1]
- ~26% had received prophylactic medication for migraine in the past but discontinued treatment[2]
- ~12% were current users of prophylactic medication for the treatment of migraine[1]

Data from the AMPP study suggest that approximately 2/3s of individuals with migraine who qualify for prophylaxis do not receive it[2]

1. Lipton RB, et al. Neurology. 2007;63:343–349.
2. Diamond S, et al. Headache. 2007;47:355–363.

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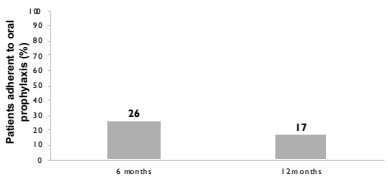
Retrospective claims database analysis: insured patients with migraine and ≥15 headache days/month (N=8,688)*



*Oral prophylactic medications analyzed in this retrospective study were limited to specific antidepressants, β-blockers, and anticonvulsants.
Adherence rates were reported as the proportion of patients with a proportion of days covered ≥80%.
Hepp Z, et al. Cephalalgia. 2015;35:478–488.

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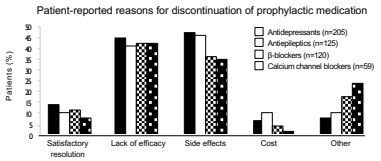
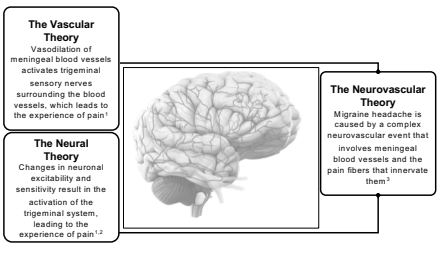
International Burden of Migraine Study-II assessed prophylactic therapy patterns in patients with migraine



Lack of efficacy and/or medication side effects are the most common reasons for discontinuation of prophylactic medications

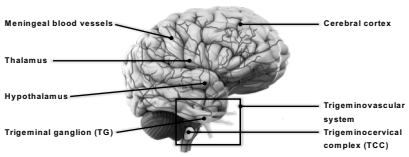
Blumenfeld AM, et al. Headache. 2013;53:644–655.

- The burden of migraine is substantial, complex, variable, and multifaceted
  - Migraine imposes a personal, family, and economic burden
- Unmet needs arise from challenges with current migraine management:
  - Many migraine patients have not received a medical diagnosis
  - Effective migraine management requires that physicians and patients consider the scope of migraine induced disability in addition to migraine symptoms
  - Excessive use of acute medications commonly occurs in patients with migraine
  - Preventive treatment is underutilized
- Healthcare providers should consider opportunities to enhance migraine management



1. Gasparini CF, et al. *Curr Genomics.* 2013;14:300–315. 2. Reddy DS. *Expert Rev Clin Pharmacol.* 2013;6:271–288.
3. Bernstein C, Burstein R. *J Clin Neurol.* 2012;8:89–99.

Central and Peripheral Brain Structures Are Involved in Migraine Pathophysiology



1. Burstein R, et al. *J Neurosci*. 2015;35:6619–6629. 2. Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533–552. 3. Charles A. *Headache*. 2013;53:413–419. 4. Gasparini CF, et al. *Curr Genomics*. 2013;14:300–315.

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Peripheral components:[1–4]

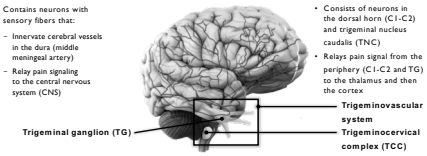
Trigeminal ganglion:

- Contains neurons with sensory fibers that:
  - Innervate cerebral vessels in the dura (middle meningeal artery)
  - Relay pain signaling to the central nervous system (CNS)

Central components:[1,3,5]

Trigeminocervical complex:

- Consists of neurons in the dorsal horn (C1-C2) and trigeminal nucleus caudalis (TNC)
- Relays pain signal from the periphery (C1-C2 and TG) to the thalamus and then the cortex



Feedback from a sensitized brain may further exacerbate pain signaling in the trigeminal system[1,3,6]

The trigeminal system has components on both sides of the blood–brain barrier[3,4]

1. Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533–552. 2. Eftekhari S, Edvinsson L. *Ther Adv Neurol Disord*. 2010;3:369–378. 3. Raddant AC, Russo AF. *Expert Rev Mol Med*. 2011;13:e36. 4. Edvinsson L. *Brit J Clin Pharmacol*. 2015;80:193–199. 5. Karsan N, Goadsby PJ. *Curr Neurol Neurosci Rep*. 2015;15:25. 6. Bigal ME, et al. *Headache*. 2013;53:1230–1244. 7. Gasparini CF, et al. *Curr Genomics*. 2013;14:300–315. 8. Burstein R, et al. *J Neurosci*. 2015;35:6619–6629.

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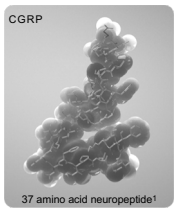

- CGRP is a neuropeptide thought to play a role in migraine pathophysiology[1-3]
  - There are 2 isoforms of CGRP[1,4,5]
    - CGRPα is the principal form found in the peripheral and central nervous systems[4]
    - CGRPβ is mainly found in the enteric nervous system[5]

1. Russo AF. *Annu Rev Pharmacol Toxicol*. 2015;55:533–552. 2. Edvinsson L. *Headache*. 2015;55:1249–1255. 3. Raddant AC, Russo AF. *Expert Rev Mol Med*. 2011;13:e36. 4. Russell FA, et al. *Physiol Rev*. 2014;94:1099–1142. 5. Bigal ME, et al. *Headache*. 2013;53:1230–1244.

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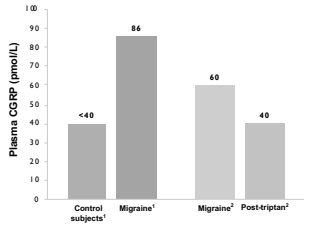

Plasma CGRP levels (measured from external jugular blood) increase significantly during migraine attacks and return to normal following relief of migraine pain with triptan therapy[1,2]

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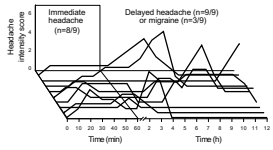
1. Goadsby PJ, et al. *Ann Neurol.* 1990;28:183–187. 2. Goadsby PJ, Edvinsson L. *Ann Neurol.* 1993;33:48–56. 3. Russo AF. *Annu Rev Pharmacol Toxicol.* 2015;55:533-552.



- CGRP caused moderate to severe headaches in all subjects

Infusion of CGRP can induce migraine attacks in patients who have migraine

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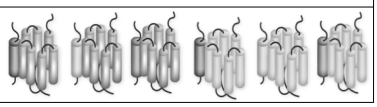
- Lines represent individual headache scores following CGRP infusion.
- Adapted from Lassen LH, et al. *Cephalalgia.* 2002;22:54–61.

Ligand	CGRP	Adrenomedullin		Amylin		
Receptor composition[1,2]	CLR+ RAMP1	CLR+ RAMP2	CLR+ RAMP3	CTR+ RAMP1	CTR+ RAMP2	CTR+ RAMP3
Receptor [name][1]	CGRP	ADM1	ADM2	AMY1	AMY2	AMY3
Structure[1]						

- The CGRP receptor is a complex that requires both RAMP1 and CLR[1]
- RAMP1 and CLR are also components of other calcitonin receptors[1,2]
- Ligands cross-interact with other receptors in the family[1,2]
- Only the CGRP receptor has been implicated in migraine pathophysiology[2]

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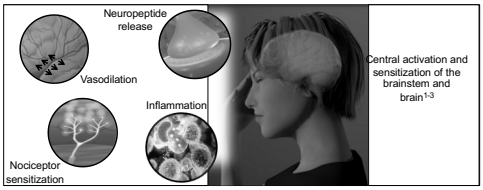
- ADM, adrenomedullin; AMY, amylin; CLR, calcitonin receptor-like receptor; CTR, calcitonin receptor; RAMP, receptor activity-modifying protein.

1. Walker CS, Hay DL. *Br J Pharmacol.* 2013;170:1293–1307. 2. Russo AF. *Annu Rev Pharmacol Toxicol.* 2015;55:533–552.

The role of CGRP in migraine pathophysiology may involve multiple central and peripheral processes, including:[1,2]



Research has yet to determine which of these processes play a causal role, or if they occur as a result of, or in parallel with, migraine[1,2]

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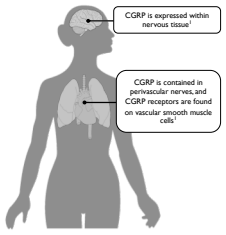
1. Russo AF. Annu Rev Pharmacol Toxicol. 2015;55:533–552.
2. Raddant AC, Russo AF. Expert Rev Mol Med. 2011;13:e36.
3. Edvinsson L. Brit J Clin Pharmacol. 2015;80:193–199.



- CGRP is widely distributed in the central and peripheral nervous systems[1]
- CGRP-containing nerve fibers innervate organ systems[2]
- The clinical relevance of CGRP beyond migraine and the nervous system[3,4] has not been clearly demonstrated[1]

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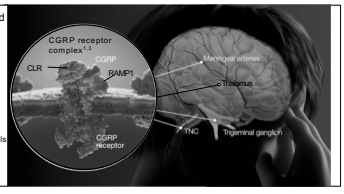
Adapted from Russell FA, et al. *Physiol Rev.* 2014;94:1099–1142.
1. Russell FA, et al. *Physiol Rev.* 2014;94:1099–1142. 2. Russo AF. *Annu Rev Pharmacol Toxicol.* 2015;55:533–552.
3. Silberstein S, et al. *Headache.* 2015;55:1171–1182. 4. Lassen LH, et al. *Cephalalgia.* 2002;22:54–61.

CGRP receptors are located on both sides of the blood–brain barrier*[1,2]

CGRP receptors are found in multiple areas:[2,3]
- Trigeminal ganglion
- Dura vasculature
- Brainstem, eg, TNC
- Brain, eg, thalamus

CGRP receptors are expressed on numerous cell types:[2,3]
- Vascular smooth muscle cells
- Neurons
- Glial cells
- Mast cells



CGRP receptors are localized at several sites within the trigeminal pathway and brain[2]

*CGRP receptor localization data are based on evidence of co-localization of the receptor components (RAMP1, CLR) and binding of CGRP receptor antagonists.2 CGRP may be expressed in additional brain regions in which CGRP receptor localization has not been established.4

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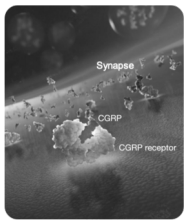
1. Russo AF. Annu Rev Pharmacol Toxicol. 2015;55:533–552. 2. Eftekhari S, Edvinsson L. Ther Adv Neurol Disord. 2010;3:369–378.
3. Raddant AC, Russo AF. Expert Rev Mol Med. 2011;13:e36.



Peripherally:
- Release of CGRP from trigeminal nerve endings is thought to trigger multiple responses induced by CGRP receptor binding, which eventually lead to the sensitization of nociceptor trigeminal neurons[1,2]
- The stimulation of nociceptive trigeminal neurons is hypothesized to relay the migraine pain signal through the brainstem into the brain, ultimately leading to the experience of migraine pain[3]

Centrally:
- CGRP binding to its receptor at sites within the CNS might have numerous effects, including central sensitization and activation[1]
- Other central processes (eg, feedback from a sensitized brain) may also contribute to the experience of migraine pain[1]

The interaction of CGRP with the CGRP receptor plays an important role in migraine[1-5]

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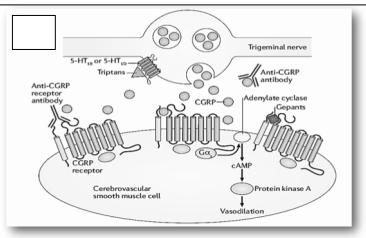
1. Russo AF. *Annu Rev Pharmacol Toxicol.* 2015;55:533–552. 2. Rabbitt AC, Russo AF. *Expert Rev Mol Med.* 2011;13:e36. 3. Silberstein S, et al. *Headache.* 2015;55:1171–1182. 4. Russell FA, et al. *Physiol Rev.* 2014;94:1099–1142. 5. Ellahham S, Edvinsson L. *Ther Adv Neurol Disord.* 2010;3:369–378.

Migraine Treatment Targets



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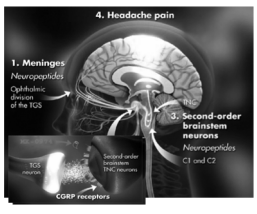
Edvinsson L et al. *Nat Rev Neurol.* 2018;14(6):338-350.

CGRP Receptor Antagonists in Migraine

- Potent vasodilator
- Widely expressed in CNS and PNS
- Trigeminal system activated and CGRP released during migraine and cluster headaches
- CGRP receptor antagonists:
  - Block CGRP at multiple sites in CNS and inhibit pain transmission
  - Not direct vasoconstrictors



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4 Injectable MABs to CGRP or Its Receptor: 3 Now FDA Approved and Available

n = neurologic; umab = fully human; zumab = humanized; Human = 100%; humanized = 90%-95%

	Erenumab-aooe AIMOVIG (fully human)	Fremanezumab-vfrm AJOVY (fully humanized)	Galcanezumab-gnlm EMGALITY (humanized)	Eptinezumab (humanized)
Studied for	EM, CM	EM, CM, eCH	EM, CM, eCH	EM, CM
Route and Dosing	Monthly subcu 70, 140 mg	Monthly or quarterly subcu; 225 mg monthly, or 675 mg quarterly	Monthly subcu; 240 mg loading dose, then 120 mg SC monthly thereafter	Q3 month IV
Target	CGRP receptor	CGRP peptide or ligand	CGRP peptide or ligand	CGRP peptide or ligand
$T_{1/2}$ (days)	31	21	40-48	28
Regulatory status	**FDA approved 5/17/18 for migraine prevention**	**FDA approved 9/14/18 for migraine prevention**	**FDA approved 9/26/18 for migraine prevention**	In development; Presented (+) phase 3 EM & CM RCTs

Tepper SJ. *Headache*. 2018;58 (Suppl 3):238–275. Tepper SJ. *Headache*. 2018;58 (Suppl 3):276–290. Edvinsson L. *Headache*. 2018;58(suppl 1):33–47; Alder Biopharmaceuticals Press Release. Bothwell, WA: 2018; U.S. Food & Drug Administration. FDA approves novel preventive treatment for migraine. May 17, 2018. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm608120.htm. Accessed October 26, 2018; Teva Pharmaceutical Industries Press Release. Jerusalem: 2017; Eli Lilly and Company Press Release.

EM= Episodic Migraine; CM= Chronic Migraine; eCH= Episodic Cluster Headache

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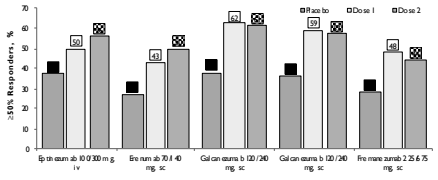
Phase 3 Studies of CGRP mAbs in EM 50% Responder Rates



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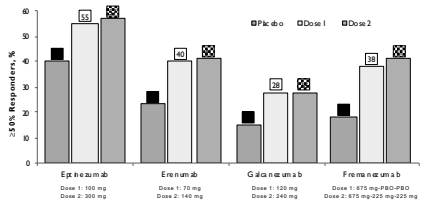
Saper J et al. Paper presented at: American Academy of Neurology 2018 Annual Meeting; April 21-27, 2018; Los Angeles, CA. Abstract S20; Goadsby PJ, et al. *Headache*. 2017;57(suppl 3):128; Stauffer VL et al. *JAMA Neurol*. 2018;75(9):1080-1088; Skljarevski V et al. *Cephalalgia*. 2018;38(8):1442-1454; Dodick DW et al. *JAMA Neurol*. 2018;319(19):1999-2008.

Studies of CGRP mAbs in CM *50% Responder Rates*



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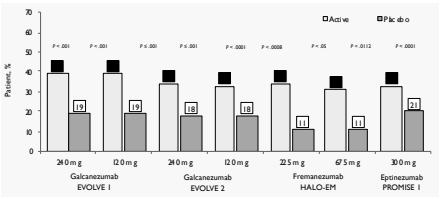
Smith J, et al. *Headache*. 2017;57(suppl 3):130; Tepper S et al. *Lancet Neurol*. 2017;16(6):425-434; Detke HC, et al. *Cephalalgia*. 2017;37:338; Silberstein SD et al. *N Engl J Med*. 2017;377(22):2113-2122.

Studies of CGRP mAbs in EM
75% Responder Rates



Stauffer VL, et al. *JAMA Neurol.* 2018;75(9):1080-1088; Skljarevski V et al. *Cephalalgia.* 2018;38(8):1442-1454; Bigal ME et al. *Lancet Neurol.* 2015;14(11):1081-1090; Smith J et al. *Headache.* 2017;57(suppl 1):130.

Small Molecules vs mAbs

	Small Molecules	mAbs
Target Specificity	Low	High
Clearance	Liver, kidney	RES
Size, kD	< 1 kD	~150 kD
Route of Administration	Oral, nasal	Parenteral
Cross the BBB	Yes/no	No
$T_{1/2}$	Minutes to hours	1-4 weeks
Immunogenicity	No	Yes
Binding Site	Multiple	CGRP receptor or peptide

Edvinsson L. *Headache.* 2018;58(suppl 1):33-47.

Preventive Trials (EM)
Dropout Rates Due to AEs

	Propranolol	Valproate	Topiramate 100 mg	Amitriptyline
Dropout for AE, active	20%	8%	32%	12%

	Galcanezumab 120 mg, 240 mg	Erenumab 70 mg, 140 mg	Eptinezumab 100 mg, 300 mg	Fremanezumab 225 mg/mo, 675 mg
Dropout for AE, active	4.2%, 2.3%	2.2% in each group	2% in each group	1.7% in each group

- mAbs
  - No serious treatment related AEs in phase 2 or phase 3 trials
  - Generally, tolerability comparable to placebo

Diener HC, et al; MIGR-003 Study Group. *J Neurol.* 2004;251(8):943-950; Freitag FG et al. *Neurology.* 2002;58(11):1652-1659; Brandes JL et al; MIGR-002 Study Group. *JAMA.* 2004;291(8):965-973; Couch JR; Amitriptyline Versus Placebo Study Group. *Headache* 2011;51(1):33-51; Stauffer VL et al. *JAMA Neurol.* 2018;75(9):1080-1088; Goadsby PJ et al. *N Engl J Med.* 2017;377(22):2123-2132; Silberstein S et al. Paper presented at: American Academy of Neurology 2018 Annual Meeting; April 21-27, 2018; Los Angeles, CA. Abstract P4.091; Dodick DW et al. *JAMA.* 2018;319(19):1999-2008.

CGRP mAbs and Current Oral Preventive Medications

	mAbs for EM and CM	Currently Available Oral Medications EM
Specificity	+	-
Formulation	scIV Solution	Oral/Tablet
Dose titration	No	Yes
Frequency of intake	Monthly/Quarterly	Daily
Onset of action	Fast (hours-days)	Slow (weeks-months)
Effect in "refractory" patients	+	-
Side effects*		
Effect on weight	-	+
Mood change	-	+
Drowsiness / fatigue	-	+
Cognitive impairment	-	+
Dizziness	-	+
Teratogenicity	?	+
Adherence/long-term patient outcomes	+	-

*Side effects listed pertain to only certain medications; not all oral preventive drugs cause all side effects listed.

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Reuter U. *Headache*. 2018;58(suppl 1):49-59.

Summary

- CGRP is abundantly expressed in the trigeminal system
- CGRP binds to multiple receptors, but only the CGRP receptor has been implicated in migraine pathophysiology
- CGRP receptors are found both centrally and peripherally, including several sites in the trigeminal pathway
- CGRP signaling is critically positioned at the intersection of peripheral migraine events and central pain modulation
  - CGRP signaling in the periphery regulates key events that underlie migraine pathophysiology, including nociceptor sensitization, neuropeptide release, vasodilation, and neurogenic inflammation
- Research continues to reveal a complex pathophysiology underlying migraine that may involve CGRP and its functional interactions between the CNS and the periphery
- New treatments have emerged and are in development as a result of these new insights

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