EMERGING FRONTIERS IN MIGRAINE PREVENTION: INNOVATIONS IN CGRP-TARGETED THERAPIES AND NEXT-GENERATION TREATMENT STRATEGIES

Dr. Ann Jency A[1], Dr. Aswini Suresh[1], Dr. Gayathri P[1], Dr. DhivyaPrasath P[1],

Dr. Angelin Grace T[1]

[1]Assistant Professor, Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy.

ABSTRACT

Recurrent episodes of moderate to severe headaches are the hallmark of migraine, a very common and incapacitating neurological condition that is often accompanied by nausea, photophobia, and phonophobia. Since calcitonin gene-related peptide (CGRP) has been identified as a major neuropeptide contributing to migraine, our understanding of migraine pathophysiology has greatly improved. Since CGRP is essential for nociceptive signal transmission, vasodilation, and trigeminovascular activation, it is a prospective target for treatment. A significant advancement in the prevention and acute treatment of migraines is represented by CGRP-targeted treatments. Monoclonal antibodies (mAbs) and small-molecule receptor antagonists, or gepants, are the two main kinds that have been created. Administered subcutaneously or intravenously, CGRP monoclonal antibodies, such as erenumab, galcanezumab, fremanezumab, and eptinezumab, have favourable safety profiles and sustained efficacy in lowering monthly migraine days. Gepants, like rimegepant and atogepant, provide an option for patients who are not responding to triptans and have both acute and preventative uses. Refractory migraine patients respond better to combination regimens using CGRP blockers with gepants or onabotulinumtoxin A. Pituitary adenylate cyclase-activating polypeptide (PACAP), adenosine, δ-opioid receptors, and ion channels are examples of emerging molecular targets that show promise for next-generation treatments. All things considered, CGRP blocking has transformed the treatment of migraines by providing mechanism-based, well-tolerated, and efficient therapeutic choices that enhance patients' functional outcomes and quality of life. It is anticipated that further investigation into CGRP-mediated pathways and new molecular modulators will expand therapy options and improve individualised migraine prevention tactics.

KEY WORDS: Migraine, Calcitonin gene-related antibodies, Gepants, Preventive and acute therapy

INTRODUCTION

Migraine is the most prevalent neurological issue in Primary Care[1]. Patients with migraine, a complex illness, may have preictal symptoms like mood swings and exhaustion in the hours to days leading up to the headache phase [2]. Migraines can affect men and women of all ages. are the second most frequent reason for years spent disabled; in the case of young women, they rank initial. Over 1 billion individuals, or more than 10% of adults globally, suffer from chronic illness, with women making up over 700 million of those affected [3]. The characteristic of migraine, a debilitating neurological disorder that frequently causes sensory abnormalities, nausea, and light and sound sensitivity, is recurrent episodes of pounding headaches [4]. Trigeminovascular system activation and aberrant sensory processing are features of migraine, a neurovascular condition [5]. Cortical spreading depression, a wave of neuronal depolarization that moves across the cerebral cortex and alters blood flow and activates trigeminal sensory fibers in the meninges, is linked to migraine aura [6]. Neuropeptides such substance P, neurokinin A, and calcitonin gene-related peptide (CGRP) are released when the trigeminal nerve terminals are activated. This causes vasodilation and neurogenic inflammation [5,7]. CGRP is now recognized as a key mediator of migraine pain, which is why CGRP receptor antagonists are effective in treatment [8]. Pain modulating centers like the periaqueductal gray and dorsal raphe nucleus show functional alterations, lowering the threshold for pain and increasing susceptibility to triggers [5]. Sustained activation of the trigeminal system causes sensitization, leading to Throbbing headache, Photophobia, Phonophobia, Allodynia Sensitization explains why pain worsens with physical activity [8]. Migraine attacks are associated with decreased **serotonin (5-HT)** levels, contributing to vasodilation and pain transmission. Triptans act as **5-HT1B/1D agonists**, inhibiting CGRP release and relieving headache [6]. Angina, epilepsy, ulcerated stomachs and/or bleeding, anxiety, depression, and insomnia are risk factors [9]. Migraines are often diagnosed using the International Classification of Headache Disorders-3 (ICHD-III) criteria based on the patient's medical history. Adults must have at least five untreated episodes lasting four to seventy-two hours that

include symptoms such unilateral pain, a pulsating nature, moderate to severe intensity, and increasing with routine exercise. About 20% of patients may experience an aura, a sensory or visual disruption, and attacks may also include light and sound sensitivity, nausea, or vomiting. Each of the several stages of migraine progression—premonitory, aura, headache, and postdrome—offers important diagnostic clues [10]. Identifying and avoiding these triggers is a crucial non-pharmacological preventive method because migraine attacks can be caused by a variety of internal and environmental variables. Understanding triggers enables patients to anticipate when they are at risk of an attack and take preventative measures. Additionally, patients should be aware that headaches might begin hours after being exposed to a trigger. For example, chocolate can cause attacks after 22 hours, whereas red wine can cause attacks after 3 hours. Patients feel more in control of their migraine when they are informed about their specific trigger patterns, as triggers differ from person to person and can operate alone or in combination [10]. mainly to two categories of medications designed especially to treat acute migraine, which include 5-HT (serotonin) receptor agonists, and medications that act against CGRP. More generic analgesics, such as COX inhibitors, are included in the second class and are widely utilised to treat many pain-related diseases [11].

2. Role of CGRP in Migraine

The 37-amino acid neuropeptide CGRP, a powerful vasodilator, was discovered in 1983 and belongs to the calcitonin family of peptides [12].Cranial cerebral blood vessels are innervated by immunoreactive fibers that originate in the trigeminal ganglia and contain CGRP [13].

CGRP is a neuropeptide, has long been thought to be crucial to the pathogenesis of migraine [14]. The extracerebral circulation releases large levels of CGRP during an acute migraine attack, according to groundbreaking investigations [15].After trigeminal nerve activation, perivascular nerve fibers produce the neuropeptide CGRP, which plays a crucial part in the pathogenesis of migraine [16]. The cell bodies of both ventral and dorsal root neurons are where CGRP is primarily generated, according to immunohistochemistry [17].Research has shown that levels in the external jugular vein are higher during the migraine's headache phase and lower after the headache has subsided[18]. The importance of CGRP in migraine became widely acknowledged when CGRP-receptor antagonism was demonstrated to be an effective

treatment for migraine attacks and CGRP infusion produced migraine-like episodes in people with migraine without aura [19].

3. CGRP - TARGETED THERAPIES:

Treatments that target the calcitonin gene-related peptide (CGRP) were the first drugs created especially to prevent migraines. These treatments block CGRP, the trigeminovascular system's most prevalent neuropeptide, which is believed to be crucial to the pathogenesis of migraines.20 Although the exact mechanism by which CGRP causes migraines is unknown, impacts on meningeal blood vessel vasodilation and modulation of pain transmission in the central nervous system have been suggested.21 CGRP-targeted therapies fall into two categories: small-molecule CGRP receptor antagonists (the "gepants," rimegepant, and atogepant) and monoclonal antibodies that target either the CGRP ligand (galcanezumab, fremanezumab, and eptinezumab) or receptor (erenumab). Acute migraines are also treated with gepants.22

a. Monoclonal antibodies

Compared to gepants, the monoclonal antibodies have a longer half-life and a higher binding specificity, and they are licensed as migraine preventive drugs. The four monoclonal antibodies now available in the US are eptinezumab, fremanezumab, galcanezumab, and erenumab. The first three have been administered subcutaneously in the US since 2018.23 Pivotal clinical studies of CGRP-targeting preventative therapies have shown statistically significant improvement in migraine (or headache) days for both episodic and chronic migraine in nearly all agents, as mentioned in our prior consensus statements. The US Food and Drug Administration (FDA) suggested all medications to prevent both episodic and chronic migraines as a result of this research. CGRP monoclonal antibodies (galcanezumab, fremanezumab, erenumab) are administered intravenously every three months (eptinezumab)

or subcutaneously once a month.24 The CGRP monoclonal antibody drugs and their half-life and dosage form are described in the table.1

Table.1 CGRP MONOCLONAL ANTIBODIES [24]

Drug	Half-life [NB1]	Dosage and administration [NB1]	50% responder rate in chronic migraine [NB2]	PBS listed [NB3]
Galcanezumab	27 days	240 mg loading dose followed by 120 mg every 4 weeks, subcutaneous	27.6 to 32% (versus 8.9 to 15.4% in placebo group)	Yes, for chronic migraine
Eptinezumab	31 days	225 mg every 4 weeks or 675 mg every 12 weeks, subcutaneous [NB4]	41 to 53% (versus 18 to 28% in placebo group)	Yes, for chronic migraine and high-frequency episodic migraine (listed as 'treatment-resistant migraine' on the PBS)
Fremanezumab	27 days	100 mg every 12 weeks, intravenous [NB5]	55 to 57.6% (versus 39.3 to 40.5% in placebo group)	Yes, for chronic migraine
Erenumab	28 days	70 to 140 mg every 4 weeks, subcutaneous [NB6]	40 to 41% (versus 23% in placebo group)	No

Effectiveness and Adverse effects of CGRP monoclonal antibodies:

Randomized placebo-controlled studies and meta-analyses have shown that CGRP monoclonal antibodies are effective migraine preventers for many people with episodic and chronic migraines.25,26 Real-world data, open-label extension studies, and clinical trials all demonstrate that CGRP monoclonal antibodies are typically well tolerated.25,27 Because they are large molecules that are broken down by the reticuloendothelial system, there are no known drug interactions or limitations on their use in renal or hepatic diseases. The most common side effects of the subcutaneous formulations are mild, nonspecific injection-site reactions, which can be controlled by moving the injection sites around the thighs and belly, using ice both before and after, and taking an antihistamine if necessary. The initial trials also revealed a low incidence of nasopharyngitis; additional side effects were rare. Constipation, hypertension, and the Raynaud phenomenon have been identified in postmarketing research.28

Precautions using monoclonal antibody treatment for CGRP

The only clear contraindication of CGRP monoclonal antibodies is past hypersensitivity. While more study is being done on potential vascular risk, CGRP monoclonal antibodies should not be used in patients with recent or chronic cardiovascular or cerebrovascular illness. However, because of their lack of vasoconstrictive action, they are a reasonable alternative in patients with stable disease.29 Alopecia and exacerbations of autoimmune diseases are uncommon reports of possible immune-related occurrences.30,31

b. Gepants:

The neuropeptide CGRP has a critical role in migraine, according to a large corpus of basic, preclinical, and clinical research. According to groundbreaking research that first identified CGRP as a potential migraine mediator in pre-clinical models, blood levels of CGRP are elevated during both migraine and cluster headache attacks, and these elevated blood levels return to baseline levels after the attacks are successfully treated.32 Small-molecule CGRP receptor antagonists, or "gepants," were developed as a result of these discoveries and have been demonstrated to be effective in treating acute migraines.33,34 The term "gepants" refers to small-molecule CGRP receptor antagonists that are administered orally. They can be used either proactively or urgently to treat migraines. The Therapeutic Goods Administration has

approved atogepant and rimegepant.24 Rimegepant is used every two days to prevent migraines. It has a 50% response rate of 49%, which is comparable to the CGRP monoclonal antibodies. The 35 Gepants are recommended if a migraine episode cannot be controlled by triptan monotherapy or combo treatment.22 In actuality, gepants can be used for acute treatment in combination with a CGRP monoclonal antibody to prevent migraines, as well as in conjunction with triptans if necessary. 36, A maximum of 75 mg should be used in a 24-hour period when rimegepant is used for acute therapy. 5 Regular usage of Gepants does not seem to raise the risk of prescription overuse headaches.37

c. COMBINATION THERAPY:

An emerging strategy to improve outcomes for patients with chronic or challenging-to-treat migraine is combination therapy using CGRP-targeted medicines for migraine prevention.38 CGRP monoclonal antibodies (mAbs), which function peripherally to prevent migraine, are usually used in conjunction with other treatments such as onabotulinumtoxin A or gepants (small molecule CGRP receptor antagonists), which may offer further blocking or acute therapeutic benefits.39

RATIONALE AND EFFICACY:

As preventive measures, CGRP mAbs have shown significant effectiveness in lowering migraine frequency and intensity. With comparable mechanisms, onabotulinumtoxin A is another authorised preventive therapy for chronic migraine (CM).40 The combination of CGRP mAbs with onabotulinumtoxinA is well-tolerated and therapeutically effective, resulting in considerable decreases in monthly migraine days and disability, according to real-world data and certain controlled studies. For instance, a research with 194 patients indicated that such combination medication significantly improved their migraine symptoms, suggesting its usage in individuals who were not responding to monotherapy.41

d. NOVEL THERAPEUTIC TARGETS FOR MIGRAINE:

Pituitary adenylate cyclase-activating polypeptide (PACAP), adenosine-opioid receptors (DOR), potassium channels, transient receptor potentialion channels (TRP), and acid-sensing ion channels (ASIC) are some of these novel targets.40

1. PituitaryAdenylate Cyclase-Activating Polypeptide

From sensory nuclei to ganglia, PACAP is highly concentrated in many of the CNS's migraine and nociception-related structures.41 It binds to the G-protein coupled receptors VPAC1, VPAC2, and PAC1. Mammals are more likely to express the two bioactive forms of PACAP, PACAP38 and PACAP27.42 The internalization capability and cAMP accumulation of PACAP receptors vary, leading to a biased agonism.43 PACAP may contribute to migraine through pathways unrelated to potassium, nitric oxide, and CGRP. Peripherally given PACAP decreased allodynia, hyperalgesia, and nocifensive behavior.44

2. Adenosine Receptor

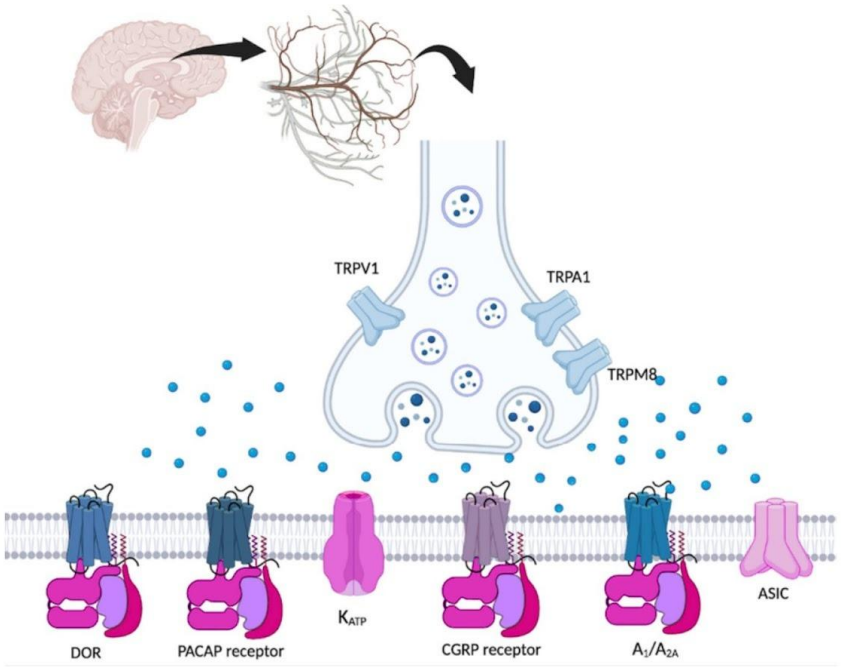
Four G protein-coupled receptors (A1, A2A, A2B, and A3) for the purinergic vasoactive amine neurotransmitter adenosine are expressed all over the body. Numerous ailments, including as headaches, agitation, mood disorders, sleep control, and epilepsy, are influenced by it.45 Adenosine may potentially have a role in the pathophysiology of migraines as a component of the breakdown product of adenosine triphosphate (ATP) and its interaction with ATP-gated P2X3 receptors.46 Adenosine is a desirable target for migraines because of its association with energy metabolism and the sleep-wake cycle. Human research has shown that blood levels of adenosine are higher ictally than interictally.47

3. δ-Opioid Receptor

For the mediation of various types of pain, the four classical types of opioid receptors (μ, κ, δ, and nociception/orphanin FQ) are essential. However, most of the μ-opioid receptor (MOR) drugs on the market are not suitable for treating migraine. They are widely recognized for causing tolerance, dependence, misuse, and medication overuse headaches (MOH), as well as decreasing the efficacy of concurrent migraine treatments like triptans.48

4. Potassium Channels

Neurons are shielded from ischemia and oxidative damage by KATP channels.49 Another potassium channel connected to migraines is the large (big)-conductance calcium-activated K+ channels (BKCa), which are found in TG and TNC.50,51 The KATP and BKCa channels are thought to be phosphorylated and activated by PACAP38.52



Safety and tolerability considerations

Galcanezumab is well tolerated across a wide dose range, both as a single subcutaneous dose and with repeated dosing [53]. Erenumab has a favorable short- and long-term safety profile, with constipation and local skin reactions being the most frequent adverse events [54,55]. Fremanezumab is generally safe and well tolerated, with mostly mild injection-site reactions and few discontinuations or serious events [56,57]. Eptinezumab also demonstrates good safety and tolerability when administered intravenously every 12 weeks for migraine prevention [58]

Conclusion

The intricate pathophysiology of migraine, a persistent and crippling neurological disorder, involves the trigeminovascular system and neuropeptides such as calcitonin gene-related peptide (CGRP).The field of migraine prophylaxis has changed with the advent of CGRP-targeted treatments, which offer safe and efficient alternatives to conventional medication. Together with small-molecule antagonists like rimegepant and atogepant, monoclonal antibodies like erenumab, galcanezumab, fremanezumab, and eptinezumab provide favourable safety profiles and considerable decreases in migraine frequency and disability. Combination regimens show promise for treating chronic or treatment-resistant cases, especially when CGRP therapies are combined with gepants or onabotulinumtoxin A. A paradigm shift towards

mechanism-based, individualised migraine therapy is further highlighted by the investigation of new targets like PACAP, adenosine, δ-opioid receptors, potassium, and TRP channels. CGRP regulation and new molecular targets have the potential to revolutionise preventive migraine treatment and enhance the quality of life for those who suffer from migraines as future research elucidates the long-term safety and relative efficacy of various therapies.

6. Reference:

1.Aguilar-Shea AL, Membrilla JA, Diaz-de-Teran J. Migraine review for general practice. Atencion primaria. 2022 Feb 1;54(2):102208.

2. Fernandes C, Dapkute A, Watson E, Kazaishvili I, Chądzyński P, Varanda S, Di Antonio S, Munday V, MaassenVanDenBrink A, Lampl C, European Headache Federation School of Advanced Studies (EHF-SAS). Migraine and cognitive dysfunction: a narrative review. The Journal of Headache and Pain. 2024 Dec 19;25(1):221.

3. Singh S, Kopruszinski CM, Watanabe M, Dodick DW, Navratilova E, Porreca F. Female-selective mechanisms promoting migraine. The journal of headache and pain. 2024 Apr 24;25(1):63.

4. Tanaka M, Tuka B, Vécsei L. Navigating the Neurobiology of Migraine: From pathways to potential therapies. Cells. 2024 Jun 25;13(13):1098.

5. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiol Rev*. 2017;97(2):553-622.

6. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol*. 2018;17(2):174-182.

7. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation during migraine. *Ann Neurol*. 1990;28(2):183-187.

8. Ashina M. Migraine. *Lancet*. 2020;397(10283):2280-2291.

9. Amiri P, Kazeminasab S, Nejadghaderi SA, Mohammadinasab R, Pourfathi H, Araj-Khodaei M, Sullman MJ, Kolahi AA, Safiri S. Migraine: a review on its history, global epidemiology, risk factors, and comorbidities. Frontiers in neurology. 2022 Feb 23;12:800605.

10. Haghdoost F, Togha M. Migraine management: Non-pharmacological points for patients and health care professionals. Open Medicine. 2022 Nov 23;17(1):1869-82.

11. Zobdeh F, Ben Kraiem A, Attwood MM, Chubarev VN, Tarasov VV, Schiöth HB, Mwinyi J. Pharmacological treatment of migraine: Drug classes, mechanisms of action, clinical trials and new treatments. British journal of pharmacology. 2021 Dec;178(23):4588-607.

12.Wrobel Goldberg S, Silberstein SD. Targeting CGRP: a new era for migraine treatment. CNS drugs. 2015 Jun;29(6):443-52.

13.Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen JC. CGRP may play a causative role in migraine. Cephalalgia. 2002 Feb;22(1):54-61.

14.Durham PL. Calcitonin gene-related peptide (CGRP) and migraine. Headache: The Journal of Head and Face Pain. 2006 Jun;46:S3-8.

15.Labastida-Ramírez A, Rubio-Beltrán E, Villalón CM, MaassenVanDenBrink A. Gender aspects of CGRP in migraine. Cephalalgia. 2019 Mar;39(3):435-44.

16.Favoni V, Giani L, Al-Hassany L, Asioli GM, Butera C, De Boer I, Guglielmetti M, Koniari C, Mavridis T, Vaikjärv M, Verhagen I. CGRP and migraine from a cardiovascular point of view: what do we expect from blocking CGRP?. The journal of headache and pain. 2019 Dec;20(1):27.

17.Bigal ME, Walter S, Rapoport AM. Calcitonin gene-related peptide (CGRP) and migraine current understanding and state of development. Headache: The Journal of Head and Face Pain. 2013 Sep;53(8):1230-44.

18.Cauchi M, Robertson NP. CGRP and migraine. Journal of Neurology. 2016 Jan;263(1):192-4.

19.Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia. 2010 Oct;30(10):1179-86.

20.Levin M, Silberstein SD, Gilbert R, Lucas S, Munsie L, Garrelts A, Kennedy K, Everman N, Pearlman E. Basic considerations for the use of monoclonal antibodies in migraine. Headache: The Journal of Head and Face Pain. 2018 Nov;58(10):1689-96.

21.Bell IM. Calcitonin gene-related peptide receptor antagonists: new therapeutic agents for migraine. Journal of medicinal chemistry. 2014 Oct 9;57(19):7838-58.

22.Puledda F, Sacco S, Diener HC, Ashina M, Al-Khazali HM, Ashina S, Burstein R, Liebler E, Cipriani A, Chu MK, Cocores A. International Headache Society global practice recommendations for the acute pharmacological treatment of migraine. Cephalalgia. 2024 Aug;44(8):03331024241252666.

23.Chiang CC, Schwedt TJ. Calcitonin gene-related peptide (CGRP)-targeted therapies as preventive and acute treatments for migraine—the monoclonal antibodies and gepants. Progress in brain research. 2020 Jan 1;255:143-70.

24.Barnes S, Aldous L, Jenkins B. Calcitonin gene-related peptide-targeted therapies for migraine. *Aust Prescr*. 2025;48(2):40-46. doi:10.18773/austprescr.2025.

25.Aleksovska K, Hershey AD, Deen M, de Icco R, Lee MJ, Diener HC. Efficacy and safety of monoclonal antibodies targeting CGRP in migraine prevention. GRADE tables elaborated by the ad hoc working group of the International Headache Society. Cephalalgia. 2023 Oct;43(10):03331024231206162.

26.Sun W, Cheng H, Xia B, Liu X, Li Y, Wang X, Liu C. Comparative efficacy and safety of five anti-calcitonin gene-related peptide agents for migraine prevention: a network meta-analysis. The Clinical Journal of Pain. 2023 Oct 1;39(10):560-9.

27.Ashina M, Mitsikostas DD, Amin FM, Kokturk P, Schankin CJ, Sahin G, Pozo-Rosich P, Dorman PJ, Nežádal T, Poole AC, Martins IP. Real-world effectiveness of fremanezumab for the preventive treatment of migraine: Interim analysis of the pan-European, prospective, observational, phase 4 PEARL study. Cephalalgia. 2023 Nov;43(11):03331024231214987.

28.Evans RW. Raynaud's phenomenon associated with calcitonin gene-related peptide monoclonal antibody antagonists. Headache: The Journal of Head and Face Pain. 2019 Sep;59(8):1360-4.

29.Kudrow D, Dafer R, Dodick DW, Starling A, Ailani J, Dougherty C, Kalidas K, Zhang F, Jeswani R, Patel N, Khodavirdi AC. Evaluation of vascular risk in patients with migraine with and without aura treated with erenumab: Post hoc analysis of pooled long-term clinical trial data. Headache: The Journal of Head and Face Pain. 2023 Mar;63(3):418-28.

30.Ruiz M, Cocores A, Tosti A, Goadsby PJ, Monteith TS. Alopecia as an emerging adverse event to CGRP monoclonal antibodies: cases series, evaluation of FAERS, and literature review. Cephalalgia. 2023 Feb;43(2):03331024221143538.

31.Ray JC, Allen P, Bacsi A, Bosco JJ, Chen L, Eller M, Kua H, Lim LL, Matharu MS, Monif M, Ruttledge M. Inflammatory complications of CGRP monoclonal antibodies: a case series. The journal of headache and pain. 2021 Dec;22(1):121.

32.Edvinsson L, Goadsby PJ. Neuropeptides in migraine and cluster headache. Cephalalgia. 1994 Oct;14(5):320-7.

33.Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. Nature Reviews Neurology. 2010 Oct;6(10):573-82.

34.Charles A, Pozo-Rosich P. Targeting calcitonin gene-related peptide: a new era in migraine therapy. The Lancet. 2019 Nov 9;394(10210):1765-74.

35.Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, Stock EG, Coric V, Goadsby PJ. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. The Lancet. 2021 Jan 2;397(10268):51-60.

36.Alsaadi T, Suliman R, Santos V, Al Qaisi I, Carmina P, Aldaher B, Haddad S, Bader Y. Safety and tolerability of combining CGRP monoclonal antibodies with gepants in patients with migraine: a retrospective study. Neurology and Therapy. 2024 Apr;13(2):465-73.

37.Croop R, Berman G, Kudrow D, Mullin K, Thiry A, Lovegren M, L'Italien G, Lipton RB. A multicenter, open-label long-term safety study of rimegepant for the acute treatment of migraine. Cephalalgia. 2024 Apr;44(4):03331024241232944.

38.Ailani J, et al. Combination Therapy Should Be Considered for People with Chronic Migraine Who Have Continued Disability After Single Preventive Agent Use. Headache. 2021 Dec;61(10):1444-1455.

39.Hennessy M, et al. Combining CGRP Monoclonal Antibodies and OnabotulinumtoxinA for Chronic Migraine: Real-World Data. Practical Neurology. 2025 Nov;

40.Nisar A, Ahmed Z, Yuan H. Novel Therapeutic Targets for Migraine. *Biomedicines*. 2023; 11(2):569.

41.Denes V, Geck P, Mester A, Gabriel R. Pituitary adenylate cyclase-activating polypeptide: 30 years in research spotlight and 600 million years in service. Journal of clinical medicine. 2019 Sep 18;8(9):1488.

42.Miyata A, Arimura A, Dahl RR, Minamino N, Uehara A, Jiang L, Culler MD, Coy DH. Isolation of a novel 38 residue-hypothalamic polypeptide which stimulates adenylate cyclase in pituitary cells. Biochemical and biophysical research communications. 1989 Oct 16;164(1):567-74.

43.Alexander TI, Tasma Z, Siow A, Rees TA, Brimble MA, Harris PW, Hay DL, Walker CS. Novel fluorescently labeled PACAP and VIP highlight differences between peptide internalization and receptor pharmacology. ACS pharmacology & translational science. 2022 Dec 8;6(1):52-64.

44.Sándor K, McDougall JJ, Schuelert N, Reglődi D, Elekes K, Pethő G, Pintér E, Szolcsányi J, Helyes Z. Divergent peripheral effects of pituitary adenylate cyclase-activating polypeptide-38 on nociception in rats and mice. PAIN®. 2009 Jan 1;141(1-2):143-50.

45.Tabrizchi R, Bedi S. Pharmacology of adenosine receptors in the vasculature. Pharmacology & therapeutics. 2001 Aug 1;91(2):133-47.

46.Giniatullin R, Nistri A. Role of ATP in migraine mechanisms: focus on P2X3 receptors. The Journal of Headache and Pain. 2023 Jan 3;24(1):1.

47.Thuraiaiyah J, Kokoti L, Al-Karagholi MA, Ashina M. Involvement of adenosine signaling pathway in migraine pathophysiology: a systematic review of clinical studies. Cephalalgia. 2022 Jul;42(8):781-92.

48.Ho, T.W.; Rodgers, A.; Bigal, M.E. Impact of recent prior opioid use on rizatriptan efficacy. A post hoc pooled analysis. *Headache* **2009**, *49*, 395–403.

49.Toulorge, D.; Guerreiro, S.; Hirsch, E.C.; Michel, P.P. KATP channel blockade protects midbrain dopamine neurons by repressing a glia-to-neuron signaling cascade that ultimately disrupts mitochondrial calcium homeostasis. *J. Neurochem.* **2010**, *114*, 553–564.

50.Koide, M.; Syed, A.U.; Braas, K.M.; May, V.; Wellman, G.C. Pituitary adenylate cyclase activating polypeptide (PACAP) dilates cerebellar arteries through activation of large-conductance Ca(2+)-activated (BK) and ATP-sensitive (K ATP) K (+) channels. *J. Mol. Neurosci.* **2014**, *54*, 443–450.

51.Wulf-Johansson, H.; Amrutkar, D.V.; Hay-Schmidt, A.; Poulsen, A.N.; Klaerke, D.A.; Olesen, J.; Jansen-Olesen, I. Localization of large conductance calcium-activated potassium channels and their effect on calcitonin gene-related peptide release in the rat trigemino-neuronal pathway. *Neuroscience* **2010**, *167*, 1091–1102.

52.Wu, S.; Ren, X.; Zhu, C.; Wang, W.; Zhang, K.; Li, Z.; Liu, X.; Wang, Y. A c-Fos activation map in nitroglycerin/levcromakalim-induced models of migraine. *J. Headache Pain* **2022**, *23*, 128.

53.Monteith D, Collins EC, Vandermeulen C, Van Hecken A, Raddad E, Scherer JC, Grayzel D, Schuetz TJ, de Hoon J. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the CGRP binding monoclonal antibody LY2951742 (Galcanezumab) in healthy volunteers. Frontiers in Pharmacology. 2017 Oct 17;8:740.

54.Ashina M, Kudrow D, Reuter U, Dolezil D, Silberstein S, Tepper SJ, Xue F, Picard H, Zhang F, Wang A, Zhou Y. Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: a pooled analysis of four placebo-controlled trials with long-term extensions. Cephalalgia. 2019 Dec;39(14):1798-808.

55.Deligianni CI, Mitsikostas DD, Ashina M. Safety and tolerability evaluation of erenumab for the preventive treatment of migraine. Expert opinion on drug safety. 2021 Aug 3;20(8):867-76.

56.Goadsby PJ, Silberstein SD, Yeung PP, Cohen JM, Ning X, Yang R, Dodick DW. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: a randomized study. Neurology. 2020 Nov 3;95(18):e2487-99.

57.Silberstein SD, McAllister P, Ning X, Faulhaber N, Lang N, Yeung P, Schiemann J, Aycardi E, Cohen JM, Janka L, Yang R. Safety and tolerability of fremanezumab for the prevention of migraine: a pooled analysis of phases 2b and 3 clinical trials. Headache: The journal of Head and Face Pain. 2019 Jun;59(6):880-90.

58.Smith TR, Spierings EL, Cady R, Hirman J, Schaeffler B, Shen V, Sperling B, Brevig T, Josiassen MK, Brunner E, Honeywell L. Safety and tolerability of eptinezumab in patients with migraine: a pooled analysis of 5 clinical trials. The journal of headache and pain. 2021 Dec;22(1):16.