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Rimegepant in airplane headache treatment: a case report

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Abstract

Background Airplane headache is a rare condition first identified in 2004 and subsequently included in the International Classification of Headache Disorders (Headache Classification Committee of the International Headache Society in Cephalalgia 33:629–808, 2013. https://doi.org/10.1177/0333102413485658). Airplane headache typically presents as intense, stabbing, unilateral pain in the frontal or orbital regions, with a severity of 8–10 on the numeric rating scale. Despite its relatively low prevalence and generally nondisabling nature, the intense pain associated with airplane headache often leads to significant anxiety and fear of flying, underscoring the need for effective treatment strategies. Currently, there are no established guidelines for the treatment of airplane headache. Various anecdotal treatments have been reported, including nasal decongestants, nonsteroidal antiinflammatory drugs, and triptans.

Case presentation We describe the case of a 28-years old Caucasian female patient with recurrent airplane headache successfully treated with rimegepant, a calcitonin gene-related peptide receptor antagonist, taken half an hour before plane departure. A 10-month follow-up confirmed the treatment efficacy.

Conclusion This novel use of rimegepant, typically employed in migraine management, demonstrates a promising therapeutic option for airplane headache.

Keywords Headache, Rimegepant, Airplane headache

Introduction

The first case of airplane headache (AH) was described in 2004 [1]. Since then, numerous other case reports and series have been documented in literature [2–9], leading to the recognition of this condition in the International Classification of Headache Disorders, third edition (beta version) under headaches attributed to disturbances of homeostasis [10]. Diagnosis is primarily clinical and based on patient history, typically made in individuals with normal neurological examinations and unremarkable brain magnetic resonance imaging (MRI) findings [11]. The headache is characterized by an intense, stabbing, unilateral pain located in the frontal or orbital region, with a severity of 8–10 according to numeric rating scale (NRS). Accompanying symptoms are reported in up to 30% of cases. The most common symptoms are restlessness and unilateral tearing, while other localized parasympathetic symptoms, as well as nausea or photo/phonophobia, have been reported in fewer than 5% of cases. The pain lasts approximately 30 min [12] and occurs in about 85% of cases during the descent phase of flight [10]. Airplane headache is distinct from other primary headache disorders, such as migraine or tension-type headache, owing to its specific clinical presentation, which occurs exclusively during flight. It is important to note that while some individuals with airplane headaches may also experience tension-type headache or migraine in daily life, the majority are able to clearly differentiate between these conditions [9]. In some cases, similar headache episodes are triggered during activities involving pressure changes, such as mountain descents or

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diving. Although sinus barotrauma has been implicated as a contributing factor in the pathophysiology of airplane headache, it is unlikely to be the sole mechanism [3, 13].

While airplane headache is not typically disabling in everyday life, it is strongly associated with a significant fear of flying. In some instances, affected individuals may entirely forgo air travel, imposing substantial restrictions on their quality of life. Although brief in duration, the pain often reaches an intensity that many find unbearable. This condition's psychological and physiological impact is underscored by elevated cortisol levels observed in affected patients [14], highlighting the stress response linked to this headache disorder.

Aside from triptans, none of the proposed treatment strategies in literature have demonstrated significant efficacy in the cohort of patients studied. However, triptans also come with certain disadvantages, including the need for precise timing of administration and specific contraindications for their use. This highlights the need for an appropriate pharmacological strategy to manage this condition.

Here, we report on a patient who experienced recurrent AH during landing and achieved successful treatment with rimegepant when the medication was taken half an hour before landing. As far as we are aware, this represents the first documented case of airplane headache successfully managed with rimegepant.

Case presentation

A 28-year-old Caucasian female patient reported experiencing headache attacks exclusively during plane landings. Her first attack occurred 2 years ago during her initial flight. She took another five flights and noted that each subsequent flight were similarly accompanied by these headache attacks. During the descent phase, she experienced severe, stabbing headaches localized to the right orbitofrontal region. She did not report any nausea, vomiting, or other autonomic symptoms. The attacks lasted approximately 30 min after landing. The patient's medical history did not reveal any significant surgeries or noteworthy underlying conditions. She had no family history of migraine or other headaches. No abnormal findings were found on brain MRI (Fig. 1).

The patient exhibited a normal gait with a negative Romberg test. Cranial nerve function was intact, and deep tendon reflexes were brisk in all four limbs. No motor or sensory deficits were identified. There were no signs of frontal release, and palpation revealed no tenderness in the pericranial muscles or paranasal sinuses. The patient reported no signs of autonomic-trigeminal involvement and no history of tension-type headaches. She did not report prior episodes of sinusitis. The possibility of a secondary headache was ruled out, supported by the SNOOP10 criteria [15]. The presentation, symptoms, and triggering factors were consistent with a suspected diagnosis of airplane headache (AH). The patient underwent an otolaryngological evaluation, which excluded any anatomical abnormalities that could account for the headache and any sinus involvement. On the basis of the diagnostic criteria outlined in the International Classification of Headache Disorders, third edition (ICHD-3) [10], a definitive diagnosis of AH was made.

During flights, she attempted to use rizatriptan 10 mg and sumatriptan 20 mg nasal spray at the first signs of headache, but these provided only limited clinical benefit. On one occasion, she experienced side effects such as chest tightness and dizziness with the use of rizatriptan (Table 1). The patient was required to undertake frequent air travel for work, approximately twice a month. However, due to the disabling nature of her headache episodes, she was often compelled to travel by train instead. This alternative mode of transportation not only caused significant stress but also proved impractical for the effective performance of her professional duties.

With the patient's consent, an acute treatment with rimegepant 75 mg (oral administration) was initiated. The patient was instructed to take the medication approximately 30 min before the onset of the aircraft's landing phase. This timing was chosen on the basis of the pharmacokinetics of rimegepant, which reaches peak plasma concentration approximately 90 min after ingestion, and considering that the patient experienced headaches that persisted for 30 min following the plane landing stage. At the 6-month follow-up visit, the patient reported having undertaken approximately six flights while adhering to the prescribed medication regimen. Notably, she did not experience any of the previously reported headache symptoms during any of these flights. The use of rimegepant was well-tolerated, with no significant adverse effects observed. At a subsequent 10-month follow-up, the patient continued to report substantial clinical benefit from rimegepant administration. The effectiveness of the prescribed therapy resulted not only in a reduction of the patient's overall stress levels but also in an improvement in work productivity, facilitated by more favorable travel conditions.

Discussion

The pathophysiology of AH is not fully understood. The most widely accepted hypothesis involves a combination of factors. Rapid shifts in cabin pressure, particularly during ascent or descent, create a mismatch between external atmospheric pressure and the pressure within the paranasal sinuses. This imbalance, especially in the

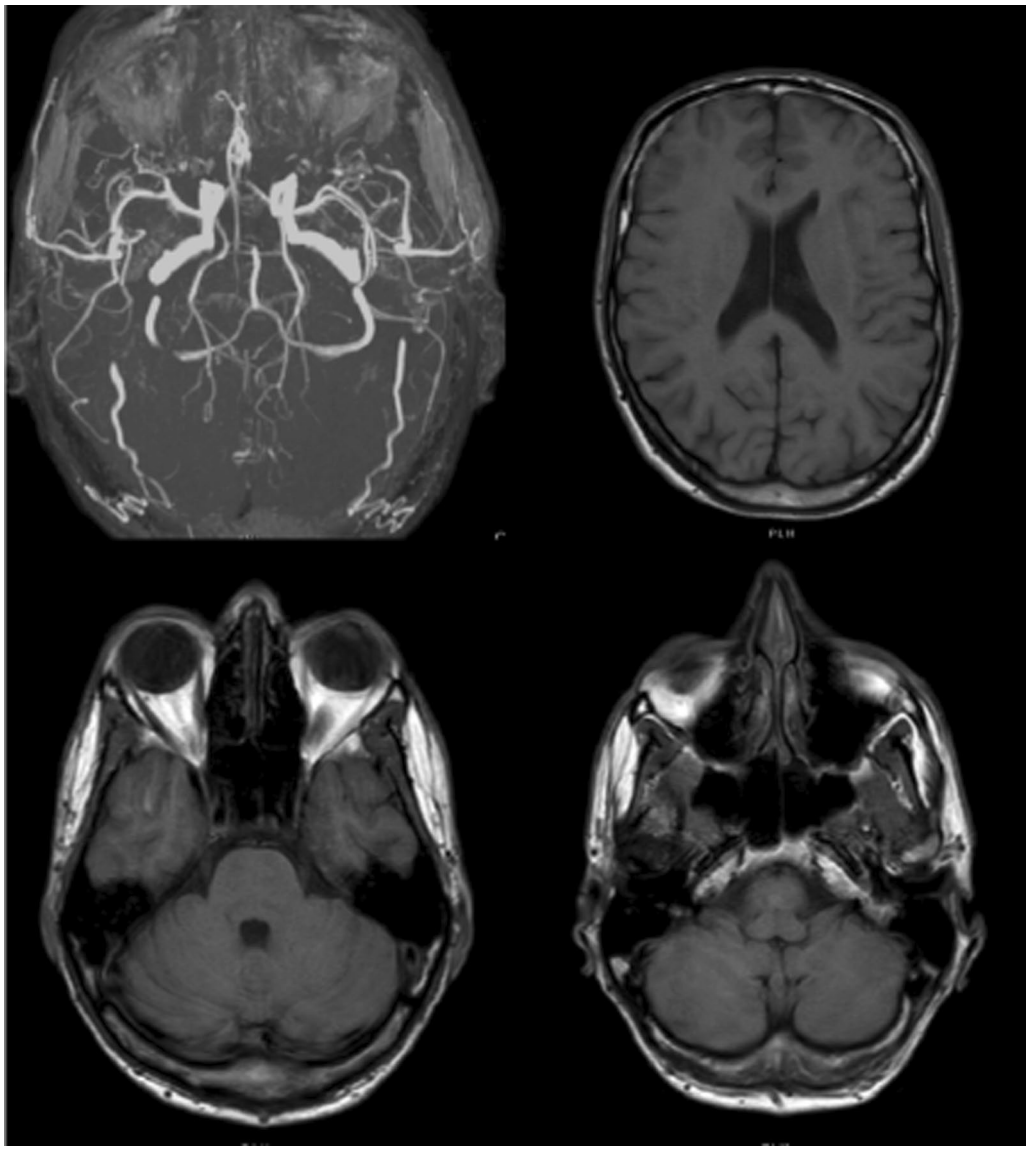

Fig. 1 Patient's magnetic resonance imaging. Angio and T1-weighted sequences

Table 1 Headache episodes and relative treatment

Treatment	Time of assumption	Duration of headache	Clinical benefits	Side effect
Nonsteroidal antiinflammatory drugs (NSAIDs)	At the first symptoms of headache	35 min	None	None
Rizatriptan	At the first symptoms of headache	20 min (mild intensity)	Partial	Chest compression, dizziness
Sumatriptan	30 min prior to landing	20 min (mild intensity)	Partial	None
Rimegepant	30 min prior to landing	–	Complete	None

ethmoid sinuses, often fails to be adequately compensated, leading to mechanical stimulation of sensory nerve endings in the sinus mucosa. This phenomenon is thought to activate the trigeminal nerve, which mediates the acute onset of pain, predominantly localized in the frontoorbital region [3, 4, 16]. This last mechanism aligns with broader models of headache pathogenesis [3, 13]. The role of inflammation in AH is supported by evidence indicating elevated levels of prostaglandin E2 (PGE2) during simulated flight scenarios. PGE2, a potent inflammatory mediator, is hypothesized to contribute to AH by promoting local inflammation and vasodilation, further activating the trigeminovascular system [3, 12]. In addition, pressure fluctuations during flight may lead to cerebral vasodilation, exacerbating nociceptive signaling and amplifying headache intensity. [13, 17]. Moreover, stress and anxiety associated with air travel may exacerbate AH episodes in predisposed individuals. Elevated cortisol levels, observed in affected individuals during simulated flight conditions, highlight the potential contribution of stress-induced physiological changes in amplifying pain perception [17]. Radiological and clinical examinations have not revealed significant structural abnormalities in most cases. This supports the hypothesis that AH is primarily a functional disorder arising from dynamic physiological changes during flight rather than underlying anatomical pathology [3, 4, 16]. In addition, it is known that during a migraine attack, the activation of the sensory fibers of the trigeminal system leads, among other things, to the release of calcitonin gene-related peptide (CGRP) [18]. CGRP is associated with pain in migraines, causing vasodilation and neurogenic inflammation, which perpetuates its release and modulates pain transmission to the brain [19, 20] (Fig. 2). However, to the best of our knowledge, there is a lack of evidence about the role that CGRP could play in AH.

The lack of effective treatment is primarily attributed to the limited understanding of the pathogenic mechanisms underlying this condition and the challenges associated with conducting controlled studies. These challenges stem from the condition's low incidence and the specific environmental factors under which it occurs.

Currently, there are no established guidelines for the treatment of airplane headache (AH) [12]. Our

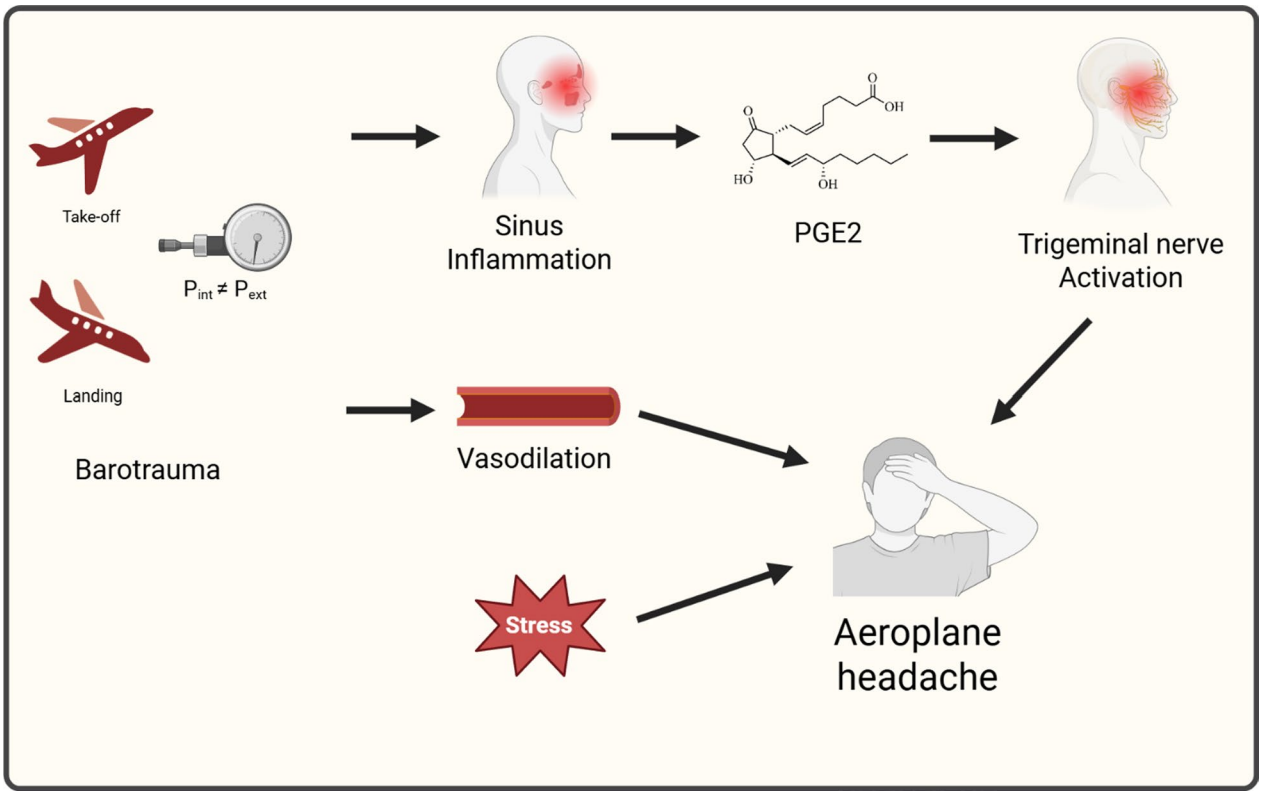

Fig. 2 Rapid pressure fluctuations during the takeoff and landing phases of air travel may lead to insufficient compensation in certain predisposed individuals, resulting in barotrauma. This barotrauma triggers inflammation within the paranasal sinuses, associated with the release of prostaglandin E2. The inflammatory response subsequently activates the trigeminal system, contributing to the characteristic headache pain. Additionally, pressure changes can induce vasodilation, which further amplifies nociceptive signaling and exacerbates pain. Finally, stress associated with the condition serves as a contributing factor, intensifying the overall symptom burden

Table 2 Comparison between different therapeutic strategies for AH

Drugs	Advantages	Limitations
NSAIDs	Available over the counter, cost-effective, and generally well-tolerated with minimal adverse effects	Limited efficacy in high-intensity headaches. No impact on the potential vascular component of AH. Increased risk of gastrointestinal injury
Triptans	Effective in higher-intensity headaches. Rapid onset of action in sublingual or intranasal formulations. Target the potential vascular component of AH	Higher cost and require a medical prescription for use. Contraindicated in patients with cardiovascular and cerebrovascular diseases. Mild headache in long-lasting flights
Nasal decongestant	Easy to administer. Improve pressure balance between the middle ear and the external environment. Vasoconstrictive action begins within minutes and can last for several hours	Rebound congestion, increased blood pressure, tachycardia, insomnia, anxiety, and agitation. Ineffective against the vascular component of AH
Rimegepant	Targets the vasodilatory component. Effective in severe headache cases, including patients with cardiovascular or cerebrovascular conditions. Provides long-lasting effects with a convenient mode of administration	High cost and requires a medical prescription. Delayed peak plasma concentration 4o

understanding is largely based on anecdotal evidence reported in literature. Mainardi *et al.* [11] suggest the use of nasal decongestants approximately 30 min before take-off and/or landing phases. Other strategies include the use of analgesics or nonsteroidal antiinflammatory drugs (NSAIDs), which have shown limited efficacy; only a portion of patients experience relief, and complete relief is achieved in only half of these cases [9]. Recently, some case reports have proposed the use of triptans as a potential treatment strategy [21, 22]. Among the triptans, rizatriptan and eletriptan are considered suitable owing to their pharmacokinetics; rizatriptan should be taken 30 min before take-off, and eletriptan 1.5 h before landing (Table 2).

If CGRP plays a role in AH, then drugs that inhibit its release or activation may provide pain relief for these patients.

Gepants, small-molecule antagonists of the CGRP receptor, are gaining credibility for the acute and chronic treatment of migraines [23, 24]. Specifically, rimegepant, a second-generation oral gepant, antagonizes CGRP-mediated signaling via the AMY1 receptor in addition to the CGRP receptor [25]. Rimegepant prevents CGRP from binding to its receptor, thereby reducing vasodilatation, alleviating neuroinflammation, and dampening down pain transmission along the trigeminal pathway [19]. It has been approved for the treatment of acute migraine attacks.

Compared with triptans, one advantage of rimegepant is the lack of cerebrovascular or coronary vasoconstriction, which contraindicates the use of triptans in patients with cardiovascular disease [19]. Rimegepant could serve as a viable alternative not only for this patient group but also for those who experience side effects from triptans or who have not achieved clinical benefit from their use. Additionally, rimegepant appears to be effective in preventing the mild headaches that some patients with arterial hypertension (AH) experience during long-duration flights [21].

This case report highlights the role of rimegepant as a promising therapeutic option in treating airplane headache (AH). However, several limitations must be acknowledged.

First, the study is based on a single patient's experience, which limits the generalizability of the findings. Placebo effect must to be take into account, and the follow up is too short to make a definitive statement about rimegepant's efficacy in this patient case. Additionally, the lack of a controlled environment and the reliance on self-reported outcomes may introduce bias and affect the reliability of the results. The variability in individual responses to treatments and the rarity of AH further complicate the establishment of definitive conclusions. The absence of a standardized diagnostic protocol for AH and the use of anecdotal evidence in literature also pose challenges in assessing the true efficacy of rimegepant and comparing it with other treatments. Larger controlled studies are needed to further evaluate the actual efficacy of the drug.

Conclusion

Trials with larger cohorts are essential to validate the efficacy and safety of rimegepant in treating AH. These studies should aim to establish optimal dosing regimens, assess long-term outcomes, and identify any potential adverse effects. Comparative studies between rimegepant and other treatments, such as triptans or NSAIDs, could provide further insights into the relative effectiveness and patient satisfaction with different therapeutic options. Additionally, investigating the pathophysiological mechanisms underlying AH and the role of CGRP in this condition may help refine treatment strategies and identify new therapeutic targets. Finally, developing standardized diagnostic criteria and treatment guidelines for AH would be beneficial for clinicians managing this rare but impactful headache disorder.

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Author contributions
MA was responsible for writing, original draft preparation, review, and editing; MDL was responsible for writing, original draft preparation, review, and editing. LF was responsible for data curation and CR was responsible for supervision.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of thisjournal.

Competing interests
The authors declare that they have no competing interests.

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References

1. Atkinson V, Lee L. An unusual case of an airplane headache. Headache. 2004;44:438–9. https://doi.org/10.1111/j.1526-4610.2004.04080.x.

2. Mainardi F, Lisotto C, Maggioni F, Zanchin G. Headache attributed to airplane travel ('airplane headache'): clinical profile based on a large case series. Cephalalgia. 2012;32:592–9. https://doi.org/10.1177/0333102412441720.
3. Bui SBD, Gazerani P. Headache attributed to airplane travel: diagnosis, pathophysiology, and treatment—A systematic review. J Headache Pain. 2017;18:84. https://doi.org/10.1186/s10194-017-0788-0.
4. Berilgen MS, Müngen B. A new type of headache, headache associated with airplane travel: preliminary diagnostic criteria and possible mechanisms of aetiopathogenesis. Cephalalgia. 2011;31:1266–73. https://doi.org/10.1177/0333102411413159.
5. Berilgen M, Müngen B. Headache associated with airplane travel: report of six cases. Cephalalgia. 2006;26:707–11. https://doi.org/10.1111/j.1468-2982.2006.01096.x.
6. Kararizou E, Anagnostou E, Paraskevas GP, Vassilopoulou SD, Naoumis D, Kararizos G, Spengos K. Headache during airplane travel ("airplane headache"): first case in Greece. J Headache Pain. 2011;12:489–91. https://doi.org/10.1007/s10194-011-0337-1.
7. Kim H-J, Cho Y-J, Cho J-Y, Hong K-S. Severe jabbing headache associated with airplane travel. Can J Neurol Sci. 2008;35:267–8. https://doi.org/10.1017/S0317167100008787.
8. Nagatani K. Two reports of flight-related headache. Aviat Space Environ Med. 2013;84:730–3. https://doi.org/10.3357/ASEM.3253.2013.
9. Mainardi F, Maggioni F, Volta GD, Trucco M, Sances G, Savi L, Zanchin G. Prevalence of headache attributed to aeroplane travel in headache outpatient populations: an Italian multicentric survey. Cephalalgia. 2019;39:1219–25. https://doi.org/10.1177/0333102419843676.
10. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629–808. https://doi.org/10.1177/0333102413485658.
11. Mainardi F, Maggioni F, Lisotto C, Zanchin G. Diagnosis and management of headache attributed to airplane travel. Curr Neurol Neurosci Rep. 2013;13:335. https://doi.org/10.1007/s11910-012-0335-y.
12. Nierenburg H, Jackfert K. Headache attributed to airplane travel: a review of literature. Curr Pain Headache Rep. 2018;22:48. https://doi.org/10.1007/s11916-018-0701-9.
13. Maini K, Schuster NM. Headache and barometric pressure: a narrative review. Curr Pain Headache Rep. 2019;23:87. https://doi.org/10.1007/s11916-019-0826-5.
14. Bui SBD, Petersen T, Poulsen JN, Gazerani P. Headaches attributed to airplane travel: a Danish survey. J Headache Pain. 2016;17:33. https://doi.org/10.1186/s10194-016-0628-7.
15. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 List—PubMed. https://pubmed.ncbi.nlm.nih.gov/30587518/. Accessed 14 Dec 2024.
16. Mainardi F, Maggioni F, Zanchin G. Aeroplane headache, mountain descent headache, diving ascent headache. Three subtypes of headache attributed to imbalance between intrasinusal and external air pressure? Cephalalgia. 2018;38:1119–27. https://doi.org/10.1177/0333102417724154.
17. Bui SBD, Petersen T, Poulsen JN, Gazerani P. Simulated airplane headache: a proxy towards identification of underlying mechanisms. J Headache Pain. 2017;18:9. https://doi.org/10.1186/s10194-017-0724-3.
18. Durham PL. Calcitonin gene-related peptide (CGRP) and migraine. Headache J Head Face Pain. 2006;46:S3–8. https://doi.org/10.1111/j.1526-4610.2006.00483.x.
19. Blair HA. Rimegepant: a review in the acute treatment and preventive treatment of migraine. CNS Drugs. 2023;37:255–65. https://doi.org/10.1007/s40263-023-00988-8.
20. Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M, Dubowchik GM, Conway CM, Coric V, Goadsby PJ. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. N Engl J Med. 2019;381:142–9. https://doi.org/10.1056/NEJMoa1811090.
21. Ipekdal HI, Karadaş Ö, Öz O, Ulaş ÜH. Can triptans safely be used for airplane headache? Neurol Sci. 2011;32:1165–9. https://doi.org/10.1007/s10072-011-0603-7.
22. Successful treatment of airplane headache with rizatriptan: case report—PubMed. https://pubmed.ncbi.nlm.nih.gov/34248572/. Accessed 6 Aug 2024.
23. Negro A, Martelletti P. Gepants for the treatment of migraine. Expert Opin Investig Drugs. 2019;28:555–67. https://doi.org/10.1080/13543784.2019.1618830.
24. Silvestro M, Orologio I, Siciliano M, Trojsi F, Tessitore A, Tedeschi G, Russo A. Emerging drugs for the preventive treatment of migraine: a review of CGRP monoclonal antibodies and gepants trials. Expert Opin Emerg Drugs. 2023;28:79–96. https://doi.org/10.1080/14728214.2023.2207819.
25. Pan KS, Siow A, Hay DL, Walker CS. Antagonism of CGRP signaling by rimegepant at two receptors. Front Pharmacol. 2020. https://doi.org/10.3389/fphar.2020.01240.

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