SŁYCHAN, Katarzyna, FRAŃCZUK, Agata, MAKŁOWICZ, Aleksandra, SZPULAK, Angelika, KOPCZYŃSKA, Ewelina, GŁOSKOWSKA, Julia, GRZELKA, Michalina, KULETA, Katarzyna, ŁĘSKA, Aleksandra Elżbieta and KEJNA, Paulina. Advances in migraine treatment - a review. Quality in Sport. 2024;21:54055. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.21.54055
https://apcz.umk.pl/QS/article/view/54055

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 04.08.2024. Revised: 19.08.2024. Accepted: 23.08.2024. Published: 29.08.2024.

Advances in migraine treatment - a review

Postępy w leczeniu migreny - przegląd literatury

1. **Katarzyna Słychan, MD**
   4th Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland,
   https://orcid.org/0000-0003-3772-737X; ksshopn@gmail.com
2. **Agata Frańczuk, MD**
   4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland,
   https://orcid.org/0009-0008-7840-5282; franczuk.agata@gmail.com
3. **Aleksandra Makłowicz, MD**
   4. Military Clinical Hospital SP ZOZ, Rudolfa Weigla 5, 53-114 Wrocław, Poland,
   https://orcid.org/0009-0007-7667-836X; ola.maklowicz@gmail.com
4. **Angelika Szpulak, MD**
   Brzeg Medical Centrum, ul. Mossora 1, 49-300 Brzeg
   https://orcid.org/0009-0000-2660-7538; angelika@brzeg.net
5. **Ewelina Kopczyńska, MD**
   Gromkowski Regional Specialist Hospital, ul. Koszarowa 5, 51-149 Wrocław
   https://orcid.org/0009-0006-5665-6043; ewekop13@gmail.com
6. **Julia Głoskowska, MD**
   4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland
   https://orcid.org/0009-0004-2634-006X; juliagloskowska@icloud.com

7. **Michalina Grzelka, MD**
4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland,
https://orcid.org/0009-0000-1515-5564; michalinagrzelka1@gmail.com

8. **Katarzyna Kuleta, MD**
10. Military Clinical Hospital Powstańców Warszawy 5, 85-681 Bydgoszcz
https://orcid.org/0009-0007-3491-7721; kuletka8@gmail.com

9. **Aleksandra Elżbieta Łęska, MD**
Distriict Hospital in Radomsko, Jagiellońska 36, 97-500 Radomsko, Poland
https://orcid.org/0009-0008-1391-8749; aleksandra.leska1911@o2.pl

10. **Paulina Kejna, MD**
4. Military Clinical Hospital SP ZOZ, Weigla 5, 53-114 Wrocław, Poland,
https://orcid.org/0009-0002-3685-0181; paulina.kejna@wp.pl

Corresponding author: Katarzyna Słychan, kateslychan@gamil.com

Abstract

Introduction

Migraine is a heavily debilitating disease that ranks second place in Global Burden Disease. It is estimated that around 1 billion of people suffer from it. It also has a significant negative impact on health-related quality of life (HRQoL) of patients and can affect their social, occupational, academic and familial life. Thus, it is crucial that all of the patients receive an effective treatment.

Objectives

This article aims to review the most recent advances in treatment of migraine.

Methods

A Literature review of articles published in Pubmed between 2000 and 2024 using the following words ‘migraine’, ‘treatment advances’, ‘CGRP receptor antagonists’, ‘serotonin receptor agonists’, ‘lasmiditan’, ‘zavegepant’, ‘rimegepant’.

Results
Literature search provides several concepts of advances in migraine treatment. Apart from behavioral treatment, new drugs targeting calcitonin gene related receptors (CGRP) and serotonin receptors agonists are emerging.
Conclusion
Migraine is a debilitating disease which significantly reduces health related quality of life in patients. New drugs targeting calcitonin gene related receptors (CGRP) and serotonin receptors agonists give a chance for more effective and tailored treatment.

Keywords: migraine, treatment advances, CGRP receptor antagonists, serotonin receptor agonists, lasmiditan, zavegepant, rimegepant

Introduction

Migraine is a type of primary headache that involves recurrent attacks of moderate to severe throbbing and pulsating pain on one side of the head. According to the last Global Burden Disease, it is a second reason for disability and first among young women (Steiner et al. 2020). It is estimated that around 1 billion of people suffer from migraine with around 18% of women and 6% of men being affected (Ashina et al. 2021; Aguilar-Shea, Membrilla Md, and Diaz-de-Teran 2022). Children, adolescents and elderly have relatively low prevalence of migraines, while the highest prevalence is noted among people aged 35-39 (GBD 2016 Headache Collaborators 2018; R. B. Lipton et al. 2007). While chronic migraine, which is described as having headache on at least 15 days per month, with eight of these having migraine symptoms for at least three months, occurs in 1-2% of global population, 2,5% of people suffering from episodic migraine are said to develop chronic migraine (Burch, Buse, and Lipton 2019). Migraine impacts patients' lives during the symptomatic phase and between attacks. The symptoms include head pain, exacerbation by movement or activity, nausea, vomiting, and sensitivity to environmental stimuli (Peres et al. 2017). That is why, it can affect patients' functioning on multiple levels such as occupational, academic, social, familial, and personal settings (Leonardi et al. 2005). A recent review reports that migraine has a significant negative impact on health-related quality of life (Abu Bakar et al. 2016).

Psychological, behavioral interventions as well as treatment can lead to improvement of health-related quality of life in patients with migraine. Thus, it is crucial that all of the patients receive a proper treatment. This paper aims to review the general concept, pathomechanism and the most recent pharmacological treatment options for migraine.

Definition of migraine

Migraine is a type of headache characterized by recurrent attacks of moderate to severe throbbing and pulsating pain on one side of the head with additional neurological and systemic symptoms. The most common symptoms include photophobia, phonophobia, cutaneous allodynia and gastrointestinal symptoms such as nausea and emesis ('Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition' 2018a; Dodick 2018).

Moreover, patients can experience other neurological symptoms such as vertigo, dizziness, tinnitus and cognitive impairment. The attacks usually last 4-72 and can be divided into 4 overlapping stages (Dodick 2018). The first stage is Prodrome, a stage which can occur one or two days before the attack. It is characterized by yawning, mood changes, difficulty concentrating, neck stiffness, fatigue, thirst and elevated frequency of micturition (Maniyar et al. 2015). The next phase is Aura, which is present in approximately one third of the patients. Visual aura is the most common type (90%) followed by sensory (30-54%) and language aura (31%) (Kissoon and Cutrer 2017). The next stage is the headache. Usually, it increases progressively, reaching its maximum in few hours and then decreases steadily. It is aggravated by head movement and disrupts daily activities. Nausea, vomiting, aversion to touch (allodynia), light (photophobia), sound(phonophobia), and smell (osmophobia) are common accompanying symptoms (Dodick 2018). The last stage is a Postdrome defined as tiredness, drowsiness, difficulty in concentrating and hypersensitivity to noise. This symptoms tend to be more intense and prolonged if the actual headache gets greater (Bose, Karsan, and Goadsby 2018).

Pathomechanism of migraine

The theory behind migraine mechanism is the neurovascular hypothesis (Bigal et al. 2009; Noseda and Burstein 2013). It states that migraine pain comes from from the

trigeminovascular system, which transmits pain signals from the meningeal blood vessels to higher centers of the central nervous system (Golden L. Peters 2019). This system innervates structures such as: the eye, dura mater, large cerebral and pial blood vessels, and the dural venous sinuses (Burstein, Noseda, and Borsook 2015). These structures are innervated by a plexus of largely unmyelinated fibers, these fibers come from the ophthalmic division of the trigeminal nerve and the upper cervical spinal roots. These peripheral nerves than converge and synapse on second-order neurons in the trigeminal cervical complex (Bartsch and Goadsby 2003). This central convergence is a good explanation on the typical regions involved in migraine namely: the eye, periorbital region, the frontal and temporal head regions. The signal from the second-order neuron than goes to the higher portions of central nervous system such as brainstem, thalamus, basal ganglia and cortex, where it is processes as pain signal (Burstein, Noseda, and Borsook 2015). The signal transmission from trigeminal system to second-order neurons is mediated by several neurotransmitters, including calcitonin gene-related peptide (CGRP), glutamate, nitric oxide and substance P. These vasoactive neuropeptides cause vasodilation and dural plasma extravasation, leading to neurogenic inflammation. Moreover, CGRP leads to mast-cell degranulation, which can than activate vascular and meningeal nociceptors cause pain (Dodick 2018; Goadsby et al. 2017). All these pain impulses are than transmitted through brainstem, basal ganglia to higher cortical regions and are detected as pain signals (Dodick 2018; Golden L. Peters 2019).

Symptoms including aversion to touch, light, sound and smell can also be explained by physiology of trigeminal system. Auditory, visual, and olfactory cortical areas receive sensory input from this system thus the characteristic symptoms (Noseda et al. 2011).

The pathophysiology of chronic migraines relies on similar mechanism, but in a slightly different way. Activated meningeal nociceptors can become sensitized, meaning the response threshold is lower and magnitude of response increases itself. That causes a pain response to a stimuli that in physiological settings would not cause pain (Dodick 2018). Patients suffering from chronic migraines have this central sensitisation present between full-blown attacks, which could explain low-grade headache, allodynia and other symptoms characteristic for the chronic type. Moreover, patients with chronic migraines in the interictal periods have an increased CGRP serum concentration, which goes along with CGRP-related mechanisms (Cernuda-Morollón et al. 2013).

Treatment of migraines

Pharmacological treatment of migraines focuses on addressing acute headache and prophylaxis (Zobdeh et al. 2021). What is more, non-drugs therapies have shown to have a good impact on patients' well-being. These therapies include: avoiding trigger factors, behavioural treatments, relaxation techniques and cognitive behavioural therapy. Thus, such treatment options can prove viable for patients who experience medication-overuse headache, those who express a preference for non-drug treatments, identify life stress as a trigger factor or pregnant and lactating women (Seng and Holroyd 2014; Nicholson et al. 2011; Penzien et al. 2005). Also, research suggest that aerobic exercise might reduce attack frequency to a comparable degree as medication (Varkey et al. 2011).

Prophylaxis- preventative treatment is used in cases such as reducing frequency, severity and duration of the attacks, patients with more than 6 attacks per month, recurring migraines producing disability, serious adverse reactions and ineffective or contraindications for acute therapies (S. D. Silberstein et al. 2012; Loder and Rizzoli 2018; Rizzoli 2014). Moreover, patients with rare migraines subtypes: hemiplegic migraine, migraine with brainstem aura, frequent, prolonged, or uncomfortable aura symptoms or migrainous infarction should also consider preventative treatment (Dodick 2018). Medication that can be used to treat migraine prevention include drugs from different groups like β blockers (propranolol), calcium channel blockers and anticonvulsants (flunarizine , valproic acid, topiramate) or antidepressants (amitriptyline). Newer drugs also used for prophylaxis are calcitonin gene-related peptide (CGRP) antagonists like Rimegepant or humanized monoclonal antibodies directed against human CGRP e.g. Fremanezumab and Erenumab (Dodick 2018; Stephen D. Silberstein et al. 2017).

Treatment for acute headache focuses on drug usage and behavioral therapy. Some general rules that improve patients outcomes are: administering acute medication early while the pain is mild and choosing the proper dose and route of administration. For example, non-oral medication like nasal sprays or injections, can prove to be useful in patients experiencing vomiting in the early phases or the ones' who pain progresses rapidly e.g. within 30 minutes (Dodick 2005). Moreover, patients who do not receive a fast pain relief or have another headache within 24-48 hours might benefit from combining acute drugs with different action mechanisms (Becker 2015). Another general rule concerns educating patients experiencing frequent headaches about medication-overuse headache, so that they take simple analgesics like non-steroidal anti-inflammatory drugs (NSAID), paracetamol less than 15 days per month,

and triptans, ergots, or combination analgesics less than 10 days per month ('Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition' 2018b; Diener et al. 2012). As mentioned, acute headache is treated with analgesics like: paracetamol, salicylic acid (NSAID), ergots, triptans or their combination (Ailani 2021).

Advanced medications

New treatment options have appeared for treating acute phase of migraines. They include medication from two groups CGRP receptor antagonists and serotonin (5-HT) 1F receptor agonists (Zobdeh et al. 2021).

Zavegepant is a CGRP receptor antagonist that is registered under the name Zavzpret. Its'administration route is a nasal spray which provides option for patients experiencing nausea and vomiting, those who do not tolerate oral medications or the drugs itself are ineffective or slow-acting (Khan et al. 2023). The mechanism of this drug targets pain pathways. After activating the trigeminovascular system, pain-inducing neuropeptides are released. That causes dilatating extracranial vessels, which leads to the throbbing sensation of a migraine headache (Riesco et al. 2020). Vasodilation is triggered by neuropeptides e.g. calcitonin gene related peptide (CGRP) (Khan et al. 2023). Recent double-blind, randomised, placebo-controlled, multicentre phase 3 trial, conducted at 90 academic medical centres has found that more participants in the zavegepant group has reported pain relief that the placebo group (Richard B. Lipton et al. 2023). Another randomized, placebo-controlled, dose-ranging, phase 2/3 clinical trial was conducted to determine the safety and efficacy of different doses of zavegepant. The doses used in the trial were 5mg, 10mg, 20mg and the placebo group. As for the primary outcome measures of efficacy, 19.6% of the participants in the 5 mg group, 22.5% in 10 mg, 23.1% in 20 mg and 15.5% in the placebo group reported freedom from pain two hours post dose (Croop et al. 2022).

Rimegepant is another CGRP receptor antagonist administered orally and used for acute treatment. It uses similar mechanism like zavegepant, but the administration is oral. It is sold as the orally disintegrating tablet (ODT) formulation, which provides significantly faster absorption than standard tablet formulation. It is contraindicated in patients with end stage renal disease (ESRD) or dialysis as it has not been researched yet (Scott 2020). In a recent multicenter, double-blind, phase 3 trial people were assigned to rimegepant orally at a dose of

75 mg and placebo for the treatment of a single migraine attack. End results found that treatment of a migraine attack with the oral calcitonin gene-related peptide receptor antagonist rimegepant resulted in a higher percentage of patients who were free of pain and free from their most bothersome symptom than placebo (Richard B. Lipton et al. 2019).

Lasmiditan is the first serotonin (5-HT) 1F receptor agonist for acute migraine treatment administered orally. Its' mechanism is based on activating 5-HT1F receptors on presynaptic trigeminal nerve terminals. This inhibits the release of calcitonin gene-related peptide (CGRP) from trigeminal nerve endings and thereby suppresses activation of the trigeminovascular system. What is more, it does not result in vasoconstriction, making lasmiditan a migraine-specific acute treatment option for those with cardiovascular risk factors (Labastida-Ramírez et al. 2020; Parikh 2021). This quality is potentially a great asset of Lasmiditan as most of the drugs e.g. triptans and dihydroergotamine induce vasoconstriction by binding to the serotonin 5-HT_{1B} receptor type on smooth muscle cells in the coronary and cerebral arteries (Ong and De Felice 2018). Thus both of these drugs are not suitable for patients with cardiovascular disease, which gives Lasmiditan an advantage (Mathew and Klein 2019). The clinical trial run in 2018 in phase 3 randomized patients into 3 groups: oral lasmiditan 200 mg, lasmiditan 100 mg, or placebo. All of the patients had more than one cardiovascular risk factors. The end point analysis showed that compared with placebo, more patients dosed with lasmiditan 200 mg were free of headache pain at 2 hours after dosing similar to those dosed with lasmiditan 100 mg (Kuca et al. 2018).

Conclusion

Without a doubt migraine is an extremely debilitating disease, which takes toll on patients. It reduces their health related quality of life and negatively impacts their personal, occupational and social lives. Adequate and effective treatment gives patients opportunity for a better quality of life. Apart from widely used drugs newer medications targeting specific receptor emerge. This gives an opportunity for a more effective medication with less side effects. Further research is needed in order to better establish safety, efficacy and efficiency of the new medications.

Disclosures

Author's contribution:

Conceptualization: KS, AE-Ł, PK; Methodology: KS, AE-Ł, PK, AF, AM; Software: not applicable; Check: AS, EK, JG, MG; Formal analysis: KK, AF, KS, AM; Investigation: AS, EK; Resources: not applicable; Data curation: AF, AM, AS, EK; Writing - rough preparation: JG, MG, KK, AE-Ł; Writing - review and editing: PK, KS, AF, AM ; Visualization: EK, JG; Supervision: MG, KK; Project administration: KS; Receiving Funding: not applicable

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This Research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

Acknowledgments: Not applicable.

Conflicts of Interests: The authors declare no conflict of interest.

Bibliography:

Abu Bakar, Norazah, Surat Tanprawate, Giorgio Lambru, Mariam Torkamani, Marjan Jahanshahi, and Manjit Matharu. 2016. 'Quality of Life in Primary Headache Disorders: A Review'. *Cephalalgia: An International Journal of Headache* 36 (1): 67–91. https://doi.org/10.1177/0333102415580099.

Aguilar-Shea, Antonio L., Javier A. Membrilla Md, and Javier Diaz-de-Teran. 2022. 'Migraine Review for General Practice'. *Atencion Primaria* 54 (2): 102208. https://doi.org/10.1016/j.aprim.2021.102208.

Ailani, Jessica. 2021. 'Acute Migraine Treatment'. *Continuum (Minneapolis, Minn.)* 27 (3): 597–612. https://doi.org/10.1212/CON.0000000000000956.

Ashina, Messoud, Zaza Katsarava, Thien Phu Do, Dawn C. Buse, Patricia Pozo-Rosich, Aynur Özge, Abouch V. Krymchantowski, et al. 2021. 'Migraine: Epidemiology and Systems of Care'. *Lancet (London, England)* 397 (10283): 1485–95. https://doi.org/10.1016/S0140-6736(20)32160-7.

Bartsch, T., and Peter J. Goadsby. 2003. 'The Trigeminocervical Complex and Migraine: Current Concepts and Synthesis'. *Current Pain and Headache Reports* 7 (5): 371–76. https://doi.org/10.1007/s11916-003-0036-y.
Becker, Werner J. 2015. 'Acute Migraine Treatment'. *Continuum (Minneapolis, Minn.)* 21 (4 Headache): 953–72. https://doi.org/10.1212/CON.0000000000000192.
Bigal, Marcelo E., Michel Ferrari, Stephen D. Silberstein, Richard B. Lipton, and Peter J. Goadsby. 2009. 'Migraine in the Triptan Era: Lessons from Epidemiology, Pathophysiology, and Clinical Science'. *Headache* 49 Suppl 1 (February):S21-33. https://doi.org/10.1111/j.1526-4610.2008.01336.x.
Bose, Pyari, Nazia Karsan, and Peter J. Goadsby. 2018. 'The Migraine Postdrome'. *Continuum (Minneapolis, Minn.)* 24 (4, Headache): 1023–31. https://doi.org/10.1212/CON.0000000000000626.
Burch, Rebecca C., Dawn C. Buse, and Richard B. Lipton. 2019. 'Migraine: Epidemiology, Burden, and Comorbidity'. *Neurologic Clinics* 37 (4): 631–49. https://doi.org/10.1016/j.ncl.2019.06.001.
Burstein, Rami, Rodrigo Noseda, and David Borsook. 2015. 'Migraine: Multiple Processes, Complex Pathophysiology'. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 35 (17): 6619–29. https://doi.org/10.1523/JNEUROSCI.0373-15.2015.
Cernuda-Morollón, Eva, Davinia Larrosa, César Ramón, Juan Vega, Pablo Martínez-Camblor, and Julio Pascual. 2013. 'Interictal Increase of CGRP Levels in Peripheral Blood as a Biomarker for Chronic Migraine'. *Neurology* 81 (14): 1191–96. https://doi.org/10.1212/WNL.0b013e3182a6cb72.
Croop, Robert, Jennifer Madonia, David A. Stock, Alexandra Thiry, Micaela Forshaw, Abigail Murphy, Vladimir Coric, and Richard B. Lipton. 2022. 'Zavegepant Nasal Spray for the Acute Treatment of Migraine: A Phase 2/3 Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Trial'. *Headache* 62 (9): 1153–63. https://doi.org/10.1111/head.14389.
Diener, Hans-Christoph, David W. Dodick, Peter J. Goadsby, Richard B. Lipton, Jes Olesen, and Stephen D. Silberstein. 2012. 'Chronic Migraine--Classification, Characteristics and Treatment'. *Nature Reviews. Neurology* 8 (3): 162–71. https://doi.org/10.1038/nrneurol.2012.13.
Dodick, David W. 2005. 'Triptan Nonresponder Studies: Implications for Clinical Practice'. *Headache* 45 (2): 156–62. https://doi.org/10.1111/j.1526-4610.2005.05031.x.
———. 2018. 'Migraine'. *Lancet (London, England)* 391 (10127): 1315–30. https://doi.org/10.1016/S0140-6736(18)30478-1.
GBD 2016 Headache Collaborators. 2018. 'Global, Regional, and National Burden of Migraine and Tension-Type Headache, 1990-2016: A Systematic Analysis for the Global Burden of Disease Study 2016'. *The Lancet. Neurology* 17 (11): 954–76. https://doi.org/10.1016/S1474-4422(18)30322-3.
Goadsby, Peter J., Philip R. Holland, Margarida Martins-Oliveira, Jan Hoffmann, Christoph Schankin, and Simon Akerman. 2017. 'Pathophysiology of Migraine: A Disorder of Sensory Processing'. *Physiological Reviews* 97 (2): 553–622. https://doi.org/10.1152/physrev.00034.2015.
Golden L. Peters, PharmD. 2019. 'Migraine Overview and Summary of Current and Emerging Treatment Options', Current, New, and Emerging Therapies for the Prevention and Management of Migraine, 25 (January). https://www.ajmc.com/view/migraine-overview-and-summary--of-current-and-emerging-treatment-options.

‘Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition’. 2018a. *Cephalalgia: An International Journal of Headache* 38 (1): 1–211. https://doi.org/10.1177/0333102417738202.
‘———’. 2018b. *Cephalalgia: An International Journal of Headache* 38 (1): 1–211. https://doi.org/10.1177/0333102417738202.
Khan, Zainab Z., Usman Ahmed, Faizan Shahzad, Muaz Ali, Kashif Tousif, Usman Ahmed, Qazi Muhammad Safwan, et al. 2023. ‘Safety and Efficacy of Zavegepant in Treating Migraine: A Systematic Review’. *Cureus* 15 (7): e41991. https://doi.org/10.7759/cureus.41991.
Kissoon, Narayan R., and Fred Michael Cutrer. 2017. ‘Aura and Other Neurologic Dysfunction in or with Migraine’. *Headache* 57 (7): 1179–94. https://doi.org/10.1111/head.13101.
Kuca, Bernice, Stephen D. Silberstein, Linda Wietecha, Paul H. Berg, Gregory Dozier, Richard B. Lipton, and COL MIG-301 Study Group. 2018. ‘Lasmiditan Is an Effective Acute Treatment for Migraine: A Phase 3 Randomized Study’. *Neurology* 91 (24): e2222–32. https://doi.org/10.1212/WNL.0000000000006641.
Labastida-Ramírez, Alejandro, Eloísa Rubio-Beltrán, Kristian A. Haanes, Kayi Y. Chan, Ingrid M. Garrelds, Kirk W. Johnson, Alexander H. J. Danser, Carlos M. Villalón, and Antoinette MaassenVanDenBrink. 2020. ‘Lasmiditan Inhibits Calcitonin Gene-Related Peptide Release in the Rodent Trigeminovascular System’. *Pain* 161 (5): 1092–99. https://doi.org/10.1097/j.pain.0000000000001801.
Leonardi, Matilde, Timothy J. Steiner, Ann T. Scher, and Richard B. Lipton. 2005. ‘The Global Burden of Migraine: Measuring Disability in Headache Disorders with WHO’s Classification of Functioning, Disability and Health (ICF)’. *The Journal of Headache and Pain* 6 (6): 429–40. https://doi.org/10.1007/s10194-005-0252-4.
Lipton, R. B., M. E. Bigal, M. Diamond, F. Freitag, M. L. Reed, W. F. Stewart, and AMPP Advisory Group. 2007. ‘Migraine Prevalence, Disease Burden, and the Need for Preventive Therapy’. *Neurology* 68 (5): 343–49. https://doi.org/10.1212/01.wnl.0000252808.97649.21.
Lipton, Richard B., Robert Croop, David A. Stock, Jennifer Madonia, Micaela Forshaw, Meghan Lovegren, Linda Mosher, Vladimir Coric, and Peter J. Goadsby. 2023. ‘Safety, Tolerability, and Efficacy of Zavegepant 10 Mg Nasal Spray for the Acute Treatment of Migraine in the USA: A Phase 3, Double-Blind, Randomised, Placebo-Controlled Multicentre Trial’. *The Lancet Neurology* 22 (3): 209–17. https://doi.org/10.1016/S1474-4422(22)00517-8.
Lipton, Richard B., Robert Croop, Elyse G. Stock, David A. Stock, Beth A. Morris, Marianne Frost, Gene M. Dubowchik, Charles M. Conway, Vladimir Coric, and Peter J. Goadsby. 2019. ‘Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine’. *The New England Journal of Medicine* 381 (2): 142–49. https://doi.org/10.1056/NEJMoa1811090.
Loder, Elizabeth, and Paul Rizzoli. 2018. ‘Pharmacologic Prevention of Migraine: A Narrative Review of the State of the Art in 2018’. *Headache* 58 Suppl 3 (November):218–29. https://doi.org/10.1111/head.13375.
Maniyar, Farooq H., Till Sprenger, Teshamae Monteith, Christoph J. Schankin, and Peter J. Goadsby. 2015. ‘The Premonitory Phase of Migraine--What Can We Learn from It?’ *Headache* 55 (5): 609–20. https://doi.org/10.1111/head.12572.
Mathew, Paul G., and Brad C. Klein. 2019. ‘Getting to the Heart of the Matter: Migraine, Triptans, DHE, Ditans, CGRP Antibodies, First/Second-Generation Gepants, and Cardiovascular Risk’. *Headache* 59 (8): 1421–26. https://doi.org/10.1111/head.13601.
Nicholson, Robert A., Dawn C. Buse, Frank Andrasik, and Richard B. Lipton. 2011. ‘Nonpharmacologic Treatments for Migraine and Tension-Type Headache: How to Choose

and When to Use'. *Current Treatment Options in Neurology* 13 (1): 28–40. https://doi.org/10.1007/s11940-010-0102-9.
Noseda, Rodrigo, and Rami Burstein. 2013. 'Migraine Pathophysiology: Anatomy of the Trigeminovascular Pathway and Associated Neurological Symptoms, Cortical Spreading Depression, Sensitization, and Modulation of Pain'. *Pain* 154 Suppl 1 (December):S44-53. https://doi.org/10.1016/j.pain.2013.07.021.
Noseda, Rodrigo, Moshe Jakubowski, Vanessa Kainz, David Borsook, and Rami Burstein. 2011. 'Cortical Projections of Functionally Identified Thalamic Trigeminovascular Neurons: Implications for Migraine Headache and Its Associated Symptoms'. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 31 (40): 14204–17. https://doi.org/10.1523/JNEUROSCI.3285-11.2011.
Ong, Jonathan Jia Yuan, and Milena De Felice. 2018. 'Migraine Treatment: Current Acute Medications and Their Potential Mechanisms of Action'. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics* 15 (2): 274–90. https://doi.org/10.1007/s13311-017-0592-1.
Parikh, S. 2021. 'Lasmiditan for Acute Treatment of Migraine'. *Drugs of Today (Barcelona, Spain: 1998)* 57 (2): 89–100. https://doi.org/10.1358/dot.2021.57.2.3238326.
Penzien, Donald B., Frank Andrasik, Brian M. Freidenberg, Timothy T. Houle, Alvin E. Lake, Gay L. Lipchik, Kenneth A. Holroyd, et al. 2005. 'Guidelines for Trials of Behavioral Treatments for Recurrent Headache, First Edition: American Headache Society Behavioral Clinical Trials Workgroup'. *Headache* 45 Suppl 2 (May):S110-132. https://doi.org/10.1111/j.1526-4610.2005.4502004.x.
Peres, Mario Fernando Prieto, Juliane P. P. Mercante, Patricia R. Tobo, Helder Kamei, and Marcelo Eduardo Bigal. 2017. 'Anxiety and Depression Symptoms and Migraine: A Symptom-Based Approach Research'. *The Journal of Headache and Pain* 18 (1): 37. https://doi.org/10.1186/s10194-017-0742-1.
Riesco, Nuria, Eva Cernuda-Morollón, Pablo Martínez-Camblor, Sara Pérez-Pereda, and Julio Pascual. 2020. 'Peripheral, Interictal Serum S100B Levels Are Not Increased in Chronic Migraine Patients'. *Headache* 60 (8): 1705–11. https://doi.org/10.1111/head.13919.
Rizzoli, Paul. 2014. 'Preventive Pharmacotherapy in Migraine'. *Headache* 54 (2): 364–69. https://doi.org/10.1111/head.12273.
Scott, Lesley J. 2020. 'Rimegepant: First Approval'. *Drugs* 80 (7): 741–46. https://doi.org/10.1007/s40265-020-01301-3.
Seng, Elizabeth K., and Kenneth A. Holroyd. 2014. 'Behavioral Migraine Management Modifies Behavioral and Cognitive Coping in People with Migraine'. *Headache* 54 (9): 1470–83. https://doi.org/10.1111/head.12426.
Silberstein, S. D., S. Holland, F. Freitag, D. W. Dodick, C. Argoff, E. Ashman, and Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. 2012. 'Evidence-Based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society'. *Neurology* 78 (17): 1337–45. https://doi.org/10.1212/WNL.0b013e3182535d20.
Silberstein, Stephen D., David W. Dodick, Marcelo E. Bigal, Paul P. Yeung, Peter J. Goadsby, Tricia Blankenbiller, Melissa Grozinski-Wolff, Ronghua Yang, Yuju Ma, and Ernesto Aycardi. 2017. 'Fremanezumab for the Preventive Treatment of Chronic Migraine'. *The New England Journal of Medicine* 377 (22): 2113–22. https://doi.org/10.1056/NEJMoa1709038.
Steiner, T. J., L. J. Stovner, R. Jensen, D. Uluduz, Z. Katsarava, and Lifting The Burden: the Global Campaign against Headache. 2020. 'Migraine Remains Second among the World's

Causes of Disability, and First among Young Women: Findings from GBD2019'. *The Journal of Headache and Pain* 21 (1): 137. https://doi.org/10.1186/s10194-020-01208-0.
Varkey, Emma, Asa Cider, Jane Carlsson, and Mattias Linde. 2011. 'Exercise as Migraine Prophylaxis: A Randomized Study Using Relaxation and Topiramate as Controls'. *Cephalalgia: An International Journal of Headache* 31 (14): 1428–38. https://doi.org/10.1177/0333102411419681.
Zobdeh, Farzin, Aziza Ben Kraiem, Misty M. Attwood, Vladimir N. Chubarev, Vadim V. Tarasov, Helgi B. Schiöth, and Jessica Mwinyi. 2021. 'Pharmacological Treatment of Migraine: Drug Classes, Mechanisms of Action, Clinical Trials and New Treatments'. *British Journal of Pharmacology* 178 (23): 4588–4607. https://doi.org/10.1111/bph.15657.