Nordic Migraine Symposium 23

Summary Report

Pearls and Pitfalls in Migraine Management

5th Nordic Migraine Symposium, 10 – 11 November 2023

teva

This Symposium Report was published by John Wiley & Sons Ltd, in association with and with sponsorship from Teva Nordic and Benelux Medical Affairs.

This Report highlights the presentations that were held during the Nordic Migraine Symposium 2023, sponsored by Teva Nordic Medical Affairs, which was held on 10 and 11 November 2023 in Copenhagen.

Medical Writer
Steve Titmarsh

Design and Layout
Michael Smith

Publisher
John Wiley & Sons Ltd
The Atrium,
Southern Gate
Chichester
West Sussex,
PO19 8SQ, UK
WILEY

Sponsor
teva
Teva Denmark A/S
Vandtårnsvej 83A
2860 Søborg,
Denmark

Promomat approval no: AJO-DK-00059

CONTENTS

MIGRAINE IS NOT ONLY HEADACHE 4

The interictal phase: Neither symptom-free nor burden-free 4

Neck pain and dizziness, and their relation to migraine 6

Prolonged migraine aura or TIA/stroke? 8

TREATMENT PEARLS AND PITFALLS 9

Challenges in navigating the treatment landscape 9

Combinations of new migraine therapies - Pros & Cons 12

Nerve blockade in headaches – The scientific rationale 14

HORMONES AND MIGRAINE 16

Impact of sex hormones in migraine 16

Menstrual migraine – Diagnosis & management 18

Pregnancy & lactation in migraine 19

LIFESTYLE CHANGES IMPACTING MIGRAINE 21

The role of sleep in migraine 21

Migraine and diet 23

Does increased exercise decrease migraine? 25

DIFFICULT-TO-TREAT HEADACHES 27

Continuous headache post Covid 27

Management of patients with more than one headache diagnosis 28

Anti-CGRPs, should I stay or should I go? 29

The interictal phase: neither symptom-free nor burden-free

Timothy Steiner PhD,
Affiliate Professor of Neurology, Danish Headache Center, Denmark; Honorary Consultant Physician, Imperial College Healthcare NHS Trust, London; Director, Global Campaign Against Headache, Lifting The Burden

Episodic migraine is characterised by attacks, which are symptomatic episodes that occur regularly or randomly over time. The so-called interictal period, between attacks, begins at the end of the preceding attack and ends at the beginning of the following attack. Thus, the definition of interictal period depends on how the attack itself is defined. The International Classification of Headache Disorders (ICHD) describes the attack as a symptomatic phase characterised by headache lasting 4 to 72 hours; there may or may not be one or more associated symptoms, but it is the headache that is the defining symptom.[1] In a minority of attacks in a minority of people, headache is preceded by aura (so-called migraine with aura), in which case ICHD defines the attack as the aura phase plus the headache phase. ICHD also describes a premonitory phase (ICHD 3 uses the term 'prodromal'), lasting up to 48 hours before the onset of pain or, if it occurs, the onset of aura, and a postdromal phase, which again is up to 48 hours in duration and occurs after resolution of pain. Quite clearly, the premonitory and postdromal phases are excluded from the attack in ICHD.[1]

Nonetheless, both are symptomatic. ICHD describes the most common symptoms of the premonitory phase as fatigue, mood changes and difficulty with concentration, and very similar symptoms are attributed to the postdromal phase – feeling tired or weary and difficulty with concentration.[1] Many publications purport to describe symptoms of either the premonitory or postdromal phases, but many of those symptoms are non-specific: in particular they include nausea, vomiting, neck pain, phonophobia and photophobia, all of which are also associated symptoms of the headache phase. It becomes a little difficult, therefore, to be clear about which symptoms are associated with which phases.

The focus here, is on the non-headache symptoms, and, by definition, the postdromal, interictal and premonitory phases are all headache-free.

Of the numerous publications describing the symptoms of these phases, almost all have been of patients from tertiary headache care centres, highly unrepresentative of the general population of people with migraine.[2-4] We cannot extrapolate from those findings to understand what the symptoms of these phases might be. Although it is now quite old – the data were published in 2016 but the survey they are from was carried out some years before that - this was the only major sample available that was largely population-based.

Eurolight was a cross-sectional survey of 8,400 participants conducted in nine countries representing 55% of the adult population of the European Union. It used a variety of sampling methods that differed between the countries. Although, therefore, the Eurolight sample is far from being perfectly representative of the general population, it is a much better sample than is obtained from tertiary headache clinics.

It produced data from almost 3,000 participants with migraine. Over a quarter (26%) of these reported that they were not entirely free of all symptoms on their last headache-free day. Over 10% reported interictal anxiety and nearly 15% reported some degree of interictal avoidance. Those are not large proportions, but it must be remembered that most of the time is spent in the interictal phase. In this survey, on average, 87% of all time was spent by the migraine respondents in the interictal phase.[5]

People with moderate headache were almost three times as likely to describe interictal anxiety as those with mild headache, and those with severe headache were 7.6 times as likely to report interictal anxiety. People with over 90 headache days per year, that is approaching 2 per week, were over six times as likely to report interictal anxiety as those with fewer than 12 per year. Similar though less marked differences were seen for interictal avoidance: people with severe headache were three times as likely to report interictal avoidance as those with mild headache, and people with frequent headache were about 2.5 times as likely to report interictal avoidance as those with infrequent headache.[5]

Anxiety about the next attack, and, in particular, avoidance of things that people would otherwise do, leads to lifestyle compromises. They may not have the glass of red wine, and they may not go to the party. These might appear trivial, but repeated avoidance of what people would otherwise wish to do reduces their quality of life.

Stigma is another important consequence of migraine. It was measured by asking people whether they avoided telling others they had migraine, and whether family, friends and colleagues who knew they had migraine understood exactly what that meant. Almost one-third of people with migraine had some sense of stigma, preferring not to tell others. About 10% felt that their family did not understand what it meant to have

migraine and almost 12% felt the same of their employers and work colleagues.[6]

Perhaps the most important of all the non-headache symptoms is cumulative burden: the burden of migraine that adds up over a lifetime of missed opportunities because of chronic recurring disability: in education and later in employment. About 12% of people with migraine said it had impaired their education in some way: it altered their educational choices or perhaps caused them to abandon education earlier than they might have done. As a result, over 7% reported that their careers had suffered in some way; 2% had taken easier jobs and 1.4% were on long-term sick leave. Nearly 6% of people with migraine reported that their lifetime earnings were reduced as a consequence of their migraine.[5]

Finally, 17.6% of survey respondents said that migraine had in some way affected their love lives: 1% said that having migraine affected their decisions about how many children they had, either fewer or none at all; 0.5% blamed migraine for marital separation, and 0.2% blamed migraine for divorce.[5] These might be small proportions, but they were very profound impacts.

In conclusion, interictal symptoms in migraine are common and they are associated with various forms of burden, all amplified by the fact that 87% of all time is spent in the interictal state, while some part of burden is cumulative over a lifetime. The 2016 iteration of the Global Burden of Disease (GBD) study estimated that migraine was the highest single cause of disability in adults aged 50 years or under ('disability' being expressed as years lived with disability (YLDs), which are actually a measure of lost health).[6] The disability weight used to calculate YLDs for migraine was applied to the ictal state, so this estimate – that migraine is the first cause of lost health – was based solely on ictal symptoms. It took no account of interictal symptoms or any of the other non-headache symptoms. Much work is needed to quantify these symptoms in such a way that they can be added to GBD estimates.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38(1):1–211.
2. Peng KP, May A. Redefining migraine phases – a suggestion based on clinical, physiological, and functional imaging evidence. Cephalalgia 2020;40(8):866–70.
3. Eigenbrodt AK, Christensen RH, Ashina H, et al. Premonitory symptoms in migraine: a systematic review and meta-analysis of observational studies reporting prevalence or relative frequency. J Headache Pain 2022:23:140.
4. Giffin NJ, Lipton RB, Silberstein SD, et al. The migraine postdrome: An electronic diary study. Neurology 2016;87(3):309–13.
5. Lampl C, Thomas H, Stovner LJ, et al. Interictal burden attributable to episodic headache: findings from the Eurolight project. J Headache Pain 2016;17:9.
6. Steiner TJ, Stovner LJ, Vos T, et al. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain 2018;19:17.

Neck pain and dizziness, and their relation to migraine

Sait Ashina,
Director, BIDMC Comprehensive Headache Center; Assistant Professor of Neurology and Anesthesia, Harvard Medical School, Boston, USA

Migraine is not just a headache – there are different phases, and there are also different symptoms. The classification of migraine describes it as a headache that lasts from four hours to 72 hours. However, headaches can be temporal, frontal, occipital, and patients may experience neck pain; they can also report tenderness in the muscles, or dizziness, which makes diagnosis challenging.

Vestibular migraine is a very important subtype of migraine. Preclinical studies help understand occipital headache and occipital migraines can be explained by preclinical models. Noseda *et al*. performed two studies, one anatomical and one neurophysiological study. They found that the occipital dura overlaying the cerebellum had receptive fields for the C2-DRG neurons. The tendons of the occipital neck muscles also have receptive fields. They also found occipital continuous areas behind the ear in animals, which also have receptive fields for C2-DRG neurons. The C2-DRG neurons enter the calvaria through the foramina, and also the suture lines to innervate the occipital dura. Therefore, the dura has innervation from both intracranial nerve fibers, and extracranial nerve fibers.[1]

These findings may help explain why patients respond to occipital nerve blocks. An interesting study from the Tertiary Headache Center by Kelman and Rains examined 1,283 patients with migraine presenting to the clinic and found that 40% of patients reported pain frequently located in the occipital and neck regions, occurring more than one third of the time. These occipital headaches occurring during migraine were often triggered by neck pain. In other words, one third of patients with migraine may report headaches in the occipital region.[2]

In Denmark, a population-based sample was used to look at the prevalence of self-reported neck pain in patients with primary headaches. It included patients with migraine, tension-type headache and co-existent headaches. The patients were invited to clinic for further examination and measurement of pain thresholds as well as the tenderness. Self-reported neck pain was frequent in patients with primary headaches. It was more frequent in co-existent headache, followed by pure tension-type headache, then by pure migraine and then headache. The study demonstrated that self-reported neck pain was present in approximately 70–80% of patients with primary headache disorders, such as migraine and tension-type headache. This contrasts markedly with the general population not reporting headache, where only about 40% reported experiencing neck pain. This difference highlights the prevalence of neck pain among those with primary headache disorders compared with those without such conditions.[3]

A meta-analysis in Denmark by Dr Al-khazali, found that up to 77% of patients in the migraine group had reported neck pain in contrast with 23.2% in a non-headache control group.[4] Moreover, Dr Buchgreitz found that pericranial tenderness, a common feature of patients with migraine and tension-type headache, was very prevalent in patients with headaches. It was more common in patients with chronic tension-type headache, followed by frequent episodic tension-type headache, and then migraine and then those with no headache. Interestingly, it was more common in females than males, and

in the younger population. One limitation was that there were no patients with chronic migraine identified in this study due to the questionnaire used.[5] If patients with a chronic migraine had been included, the frequency of tenderness could have been higher in patients with migraine. So, we would probably have seen similar findings to those found in chronic tension-type headache.

Another pertinent question addresses the role of neck pain in the pathophysiology of headaches, particularly its involvement in nociception. To explore this, Dr Ashina conducted a study using the same population sample, categorizing patients into groups with and without neck pain.[6] In one of his studies, he observed that those with neck pain exhibited more

pronounced pericranial tenderness. His findings suggest that neck pain is not just a concurrent symptom of migraine, but likely contributes to sensitization, potentially through both peripheral and central mechanisms. This study indicates that, given the underlying pathological mechanisms, treating patients with coexisting neck pain in clinical practice could pose challenges.

Dr Burstein proposed a theory regarding muscle tenderness in relation to headaches. He suggests that muscle tenderness occurring before the onset of a headache, or associated with tension headaches, should be considered primary. This type of tenderness likely originates from peripheral structures or nociceptors. On the contrary, muscle tenderness that develops after the onset of a headache is likely to be secondary, potentially arising from pain referral.[7]

Some studies have looked at the relative frequency of dizziness in patients with migraine. For example, Iljazi *et al*. found that up to 35% of migraine patients experience concurrent vertigo or dizziness during both the premonitory and headache phases.[8] Another study focusing on the premonitory, headache, and postdromal phases reported dizziness in almost 30% of patients during the headache phase. Dizziness was also commonly observed in the postdromal phase, along with neck stiffness, which can be a prominent feature of migraine.[9]

Vestibular migraine has been recognized in the International Classification of Headache Disorders (ICHD) as an appendix criterion. In cases of vestibular migraine, patients might not always experience a full-blown migraine. They may suffer from mild headaches, but can also exhibit symptoms like photophobia or phonophobia. Visual aura is less common, occurring in only one-third of these patients.

A research team from Ohio, USA, conducted a study to identify patients with a history of migraine with vestibular symptoms. They performed a research-specific chart review and categorized patients into two groups: those with migraines accompanied by vestibular symptoms and those with migraines without such symptoms. The study found that all patients with vestibular symptoms experienced occipital headaches, a result that differed from those without vestibular symptoms. Interestingly, a trend observed both in this study and in clinical settings is that vestibular migraines tend to manifest at an older age. There was also a correlation between the onset of dizziness and the age at which the headache began. In addition, a higher incidence of motion sickness was reported in the group with vestibular migraines, along with a significant family history of motion sickness. However, difference in the family history regarding the type and frequency of headaches between the two groups was not found.[10]

It is proposed that cortical spreading depolarization in the cerebellum could account for the dizziness observed in patients with occipital headache. The cerebellum plays a crucial role in our perception due to its complexity and capability for multisensory processing. It is connected with cognitive, autonomic, and visceral regions of the brain, and has links to the trigeminal pain pathways. This association makes it a key player in the emotional, cognitive, and motor regulation of pain.[1] Moreover, it is well established that the cerebellum plays a role in other types of migraines. However, detecting cerebellar dysfunction can be challenging. Assessment of cerebellar function is primarily clinical, encompassing both objective and subjective elements, and we currently lack a definitive test for it. Yet, it is observed that patients with migraine might exhibit certain symptoms between migraine attacks, such as interictal coordination issues, abnormal nystagmus, and other cerebellar abnormalities.[11]

Conclusion

In conclusion, neck pain is highly prevalent in patients with migraine, with occipital headaches being a significant feature in one-third of cases. Moreover, a third of all migraine patients experience initial tenderness in the neck and shoulder area that evolves into a low-grade occipital headache. Migraine often includes symptoms such as dizziness, vertigo and decreased motor coordination, among others. The role of the cerebellum in modulating these symptoms warrants further investigation through both preclinical and human studies.

References

1. Noseda R, Melo-Carrillo A, Nir RR, Strassman AM, Burstein R. Non-Trigeminal Nociceptive Innervation of the Posterior Dura: Implications to Occipital Headache. J Neurosci 2019;39(10):1867–80.
2. Kelman L, Rains JC. Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. Headache 2005;45(7):904–10.
3. Ashina S, Bendtsen L, Lyngberg AC, et al. Prevalence of neck pain in migraine and tension-type headache: a population study. Cephalalgia 2015;35(3):211–9.
4. Al-Khazali HM, Ashina H, Christensen RH, et al. An exploratory analysis of clinical and sociodemographic factors in CGRP-induced migraine attacks: A REFORM study. Cephalalgia 2023;43(10):3331024231206375.
5. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: a population study. Pain 2006;123(1-2):19–27.
6. Ashina S, Bendtsen L, Burstein R, et al. Pain sensitivity in relation to frequency of migraine and tension-type headache with or without coexistent neck pain: an exploratory secondary analysis of the population study. Scand J Pain 2022;23(1):76–87.
7. Burstein R, Blake P, Schain A, Perry C. Extracranial origin of headache. Curr Opin Neurol 2017;30(3):263–71.
8. Iljazi A, Chua A, Rich-Fiondella R, et al. Unrecognized challenges of treating status migrainosus: An observational study. Cephalalgia 2020;40(8):818–27.
9. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: an electronic diary study. Neurology 2003;60(6):935–40.
10. Wattiez AS, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. Expert Opin Ther Targets 2020;24(2):91–100.
11. Vincent M, Hadjikhani N. The cerebellum and migraine. Headache 2007;47(6):820–33.

Prolonged migraine aura or TIA/stroke?

Ville Artto, MD, PhD
Senior Neurologist, Department of Neurology, Helsinki University Hospital, Finland

The relationship between migraine and ischaemic stroke has long been recognised, with a particular emphasis on the increased risk associated with migraine with aura.

Numerous epidemiological studies and meta-analyses consistently highlight the connection between migraine with aura and an increased risk of ischaemic stroke, approximately two times higher than in individuals without this migraine subtype.[1]

While the rare occurrence of migraine-induced ischaemic events, such as migrainous infarcts, offers some explanation, traditional stroke risk factors in migraineurs suggest a more nuanced association. Microembolism emerges as a potential shared mechanism contributing to both migraine with aura and ischaemic stroke.

Insights from recent studies

A recent study conducted in Helsinki, involving 347 young stroke patients and a similar number of matched stroke-free controls, revealed a more than threefold increase in the risk of stroke in subjects with migraine with aura.[2] Notably, this elevated risk appeared independent of vascular risk factors, challenging conventional understanding and necessitating a deeper exploration of the mechanisms underlying this association.[3,4]

Clinical differentiation

The challenge lies in distinguishing between migraine aura and ischaemic events, especially considering the overlap in symptoms. For example, stroke might be associated with epileptic seizures or space-occupying lesions, functional disorders or psychiatric symptoms. For more than 1% of patients in the emergency room who are there due to stroke-like symptoms, migraine seems to be the main cause of those.[5] Those patients may be exposed to demanding treatment such as thrombolysis or anticoagulation. If, on the other hand, they are mistakenly diagnosed with migraine, they may not receive life-saving stroke prevention and other stroke treatments. Therefore, an accurate diagnosis is fundamental.[6,7]

In most cases, the diagnosis – deciding whether the patient is having migraine or stroke – is relatively easy, and there is no need for imaging. However, if stroke is suspected imaging is needed.

While MRI is considered optimal, the practicality of CT, particularly CT angiogram and perfusion imaging, means it may be used more often. The main finding in migraine is that it is a perfusion deficit not limited to specific vascular territory, whereas with stroke it is definitely limited to one specific vascular territory.[8]

References

1. Hu X, Zhou Y, Zhao H, Peng C. Migraine and the risk of stroke: an updated meta-analysis of prospective cohort studies. Neurol Sci 2017;38(1):33–40.
2. Martinez-Majander N, Artto V, Ylikotila P, et al; SECRETO Study Group. Association between Migraine and Cryptogenic Ischemic Stroke in Young Adults. Ann Neurol 2021;89(2):242–53.
3. Sacco S, Amin FM, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update. J Headache Pain 2022;23(1):67.
4. Sen S, Androulakis XM, Duda V, et al. Migraine with visual aura is a risk factor for incident atrial fibrillation: A cohort study. Neurology 2018;91(24):e2202–e2210.
5. Terrin A, Toldo G, Ermani M, et al. When migraine mimics stroke: A systematic review. Cephalalgia 2018;38(14):2068–78.
6. Kallela M, Lindsberg PJ. Miten erotan migreeniauran TIA-kohtauksesta? [How do I distinguish migraine aura from TIA attack?]. Duodecim 2012;128(9):971–7.
7. Lebedeva ER, Gurary NM, Gilev DV, et al. Explicit diagnostic criteria for transient ischemic attacks to differentiate it from migraine with aura. Cephalalgia 2018;38(8):1463–70.
8. Förster A, Wenz H, Kerl HU, et al. Perfusion patterns in migraine with aura. Cephalalgia 2014;34(11):870–6.

Challenges in navigating the treatment landscape

Gisela Terwindt,
Professor of Neurology, Department of Neurology, Leiden University Medical Centre;
Director of the Leiden Headache Center

Patients attending the Leiden Headache Centre all receive a headache screening questionnaire. An automatic algorithm calculates whether it is likely that a patient suffers from migraine. Those who are thought to be likely to suffer from migraine will receive an additional questionnaire on migraine-specific questions and are automatically invited to fill out a daily e-headache diary. This e-diary is visible on patients' mobile phones but can also be seen by health care professionals via webviewer within the electronic patient file of any clinical system. Based on the diary data, a validated algorithm makes a range of calculations, including the number of migraine days.[1]

With that information, 500 women were asked to fill out a questionnaire for at least three months. Using this validated tool, it could be shown that during the menstruation period, but also during a hormone-free interval for those who use the contraceptive pill, there is a peak incidence of the migraine attacks.[2]

The study also showed that these perimenstrual attacks lasted longer than the non-perimenstrual attacks and there were more recurrences compared with the one attack that was outside the perimenstrual period.[2] Also compared with men, perimenstrual and non-perimenstrual attacks in women are of longer duration, but also are more often accompanied by associated symptoms.[3]

In terms of treatment, compared with men, although women have a similar headache response to triptans, they more often experience recurrences. That is because they have longer attacks and they have perimenstrual attacks. They also report more side-effects because peak drug concentration and total drug absorption is higher compared with men.[1]

GPs prescribe a lower dosage of triptan to try to reduce side-effects, but that means these women are prone to more recurrences, leading to more doses of triptans being needed to control symptoms. This may partly explain why women more often have chronic migraine and are therefore more likely to experience medication overuse headache.[4–9]

Other risk factors for chronic migraine include depression and anxiety, another being allodynia.[8,10–12]

Patients with chronic migraine and medication overuse headache can be treated as outpatients with the simple advice to withdraw medication. They can be supported by a headache nurse. Inpatient treatment is less common and usually reserved for those with complicating characteristics. Education and behavioural intervention might be worthwhile, and there is discussion whether supportive preventive medication during the withdrawal process may be useful.[4,10]

Despite the opioid crisis in the US, opioids are still used. For example, for half of the emergency room visits by patients with acute migraine, opioids were provided.[13–15] That is quite alarming because opioids are less effective than triptans, and opioid use has been associated with increased risk of progression to chronic migraine.[13,16]

A web-based Dutch population-based cohort was examined to assess the situation in Europe.[17] Perhaps surprisingly, 13% of patients had used opioids, some for a prolonged time. Strikingly, although probably not intended by the physicians, of the opioid users, 16% took opioids as preventive treatment, and 2% of users indicated they had used opioids, even without a prescription.[17]

Nevertheless, there is still a huge difference between the US and the Dutch populations and that may be due partly to the guidelines. The American Academy of Neurology guideline recommends opioids for rescue medication, whereas the European Headache Federation and the European Academy of Neurology have advised that opioids should be avoided.

The CHARM study aimed to investigate whether patients with chronic migraine (CM) who were advised to acutely withdraw from medication overuse required additional preventive medication. In this randomized double-blind controlled trial, all patients stopped acute medication, with half receiving Botox and the other half receiving a placebo. Botox is believed to reduce nociceptive input and neurotransmission in central pathways. To maintain blinding in the placebo group, a minimal amount of Botox was

administered to the forehead. Both treatment and placebo groups exhibited a similar decrease in headache days, of around 6 to 7 days (p=0.68). The study concluded that acute withdrawal alone was highly effective, and supplementary medication was not necessary.[18]

Anti-CGRP monoclonal antibodies are also effective in CM, even when medication overuse headache (MOH) plays a role.[19-23] However, data from the CHARM study show that withdrawal alone is as effective as providing additional treatments to those who suffer from CM and MOH.[18] Thus, further studies are needed on CGRP mAbs and CM and MOH.

The effect of medication withdrawal and additional support for 12 weeks was studied as part of the CHARM study. Participants were randomised to receive maximal support (an initial half-hour consultation, followed by weekly calls) from a nurse or minimal support (one 15-minute consultation with a nurse).[18] After the withdrawal, there was a significant benefit for those who received maximal intervention compared with those who received minimal intervention at 24 weeks. However, by 36 weeks there was no difference between the groups because there was no further support from the headache nurses (Fig. 1).[18] Behavioural intervention is thus effective but needs to be maintained in those who had CM and MOH to prevent relapse. Migraine is a risk factor for stroke, but there is no proof that more attacks are associated with more damage, or greater risk of stroke.[24,25]

It is thought that CGRP antagonists are unlikely to lead to medication overuse headache, as blockade of CGRP was shown to reduce the risk of cutaneous allodynia.[26] Also, CGRP antagonists can be used as acute medication and as preventive medication. However, CGRP antagonists block vasodilation and thus may raise questions about safety and side-effects.[27] Real-world data for people with chronic migraine or high-frequency episodic migraine, who failed on 2–4 previous prophylactic medications, show it is difficult to achieve 50% reduction in monthly migraine days.[28] In terms of safety, there was an increase in blood pressure when people were treated with erenumab or fremanezumab. Monitoring blood pressure in patients is important as a 5mmHg increase in systolic blood pressure is associated with a 10% increase in stroke risk.[29]

Potential indicators of response to CGRP antagonists may include drug levels, as higher blockade levels with erenumab correlate with a greater likelihood of response. Successful blockade of the trigeminovascular response to capsaicin post-erenumab treatment increases the likelihood of being a responder.[30] Responders are also more likely to experience a decrease in visual hypersensitivity after treatment.[31] Notably, depression serves as a negative predictor for response, and a reduction in depressive symptoms is associated with decreased migraine occurrence. Treatment with monoclonal antibodies has an additional effect of reducing depressive symptom scores compared with placebo, independently of migraine reduction.[32]

For women, anti-CGRP antibodies have been found effective for non-perimenstrual attacks and for perimenstrual attacks.[33]

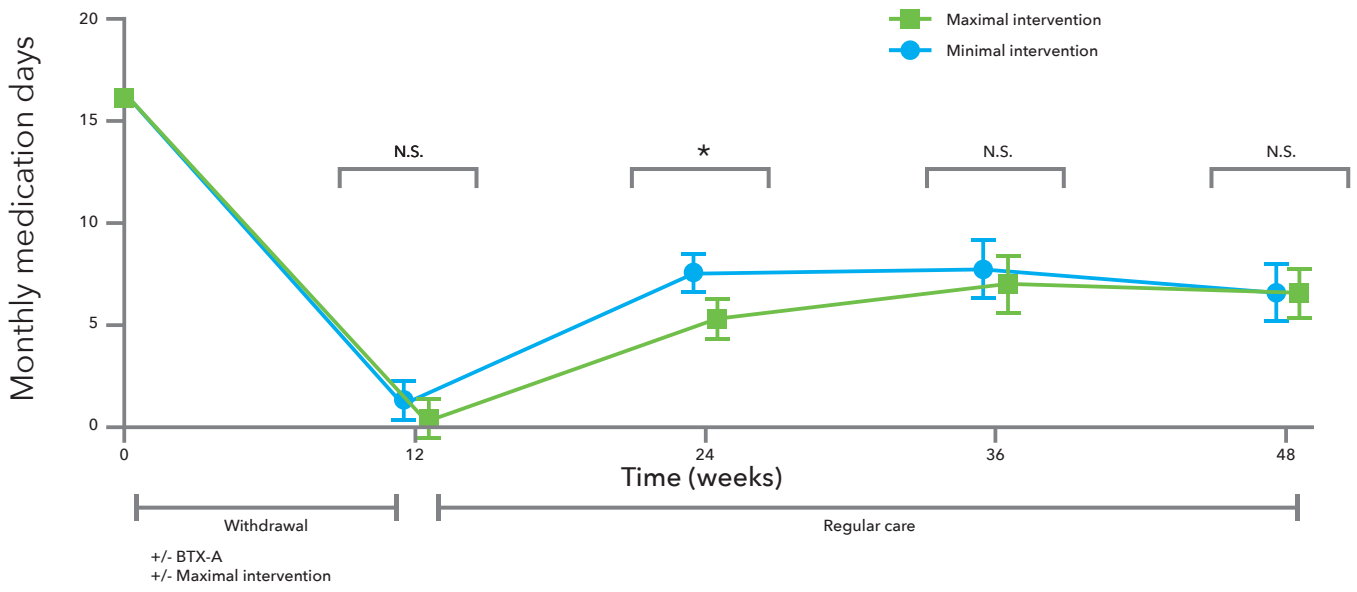


Figure 1 Effect of maximal versus minimal behavioural intervention (for the first period of 12 weeks) on acute medication use, during withdrawal and after the withdrawal period in Pijpers et al. (2022).[18]

References

1. van Casteren DS, Verhagen IE, de Boer I, et al. E-diary use in clinical headache practice: A prospective observational study. Cephalalgia 2021;41(11-12):1161–71.
2. Verhagen IE, Spaink HA, van der Arend BW, et al. Validation of diagnostic ICHD-3 criteria for menstrual migraine. Cephalalgia 2022;42(11–12):1184–93.
3. Van Casteren DS, Kurth T, Danser AHJ, et al. Sex Differences in Response to Triptans: A Systematic Review and Meta-analysis. Neurology 2021;96(4):162–70.
4. Ashina S, Terwindt GM, Steiner TJ, et al. Medication overuse headache. Nat Rev Dis Primers 2023;9(1):5.
5. May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. Nat Rev Neurol 2016;12(8):455–64.
6. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine Progression: A Systematic Review. Headache 2019;59(3):306–38.
7. Detke HC, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91(24):e2211–e2221.
8. Silberstein SD, Blumenfeld AM, Cady RK, et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci 2013;331(1-2):48–56.
9. Diener HC, Bussone G, Van Oene JC, et al; TOPMAT-MIG-201(TOP-CHROME) Study Group. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia 2007;27(7):814–23.
10. Diener HC, Dodick D, Evers S, et al. Pathophysiology, prevention, and treatment of medication overuse headache. Lancet Neurol 2019;18(9):891–902.
11. Louter MA, Fernandez-Morales J, de Vries B, et al. Candidate-gene association study searching for genetic factors involved in migraine chronification. Cephalalgia 2015;35:500–7.
12. Louter MA, Wardenaar KJ, Veen G, et al. Allodynia is associated with a higher prevalence of depression in migraine patients. Cephalalgia 2014;34:1187–92.
13. Langer-Gould AM, Anderson WE, Armstrong MJ, et al. The American Academy of Neurology's top five choosing wisely recommendations. Neurology 2013;81:1004–11
14. Joules. Emerg Med Australas 2021;33:1133–4.
15. Wells S, Stiell IG, Vishnyakova E, et al. Optimal management strategies for primary headache in the emergency department. CJEM 2021;23:802–11.
16. Bigal ME, Lipton RB. Excessive opioid use and the development of chronic migraine. Pain 2009;142:179–82.
17. van Welie RF, van Welie FC, de Vries Lentsch S, et al. Characterizing opioid use in a Dutch cohort with migraine. Cephalalgia 2023;43(5):3331024231174160.
18. Pijpers JA, Kies DA, van Zwet EW, et al. Behavioural intervention in medication overuse headache: A concealed double-blind randomized controlled trial. Eur J Neurol 2022;29:1496–1504.
19. Tepper S Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017;16:425–34.
20. Tepper SJ , Diener HC, Ashina M, et al. Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. Neurology 2019;92:e2309–e2320.
21. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med 2017;377:2113–22.
22. Ferrari MD , Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet 2019;394:1030–40.
23. Detke HC, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91(24):e2211-e2221.
24. Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427–34.
25. Palm-Meinders IH, Koppen H, Terwindt GM, et al. Structural brain changes in migraine. JAMA 2012;308:1889–97.
26. Kopruszinski CM, Xie JY, Eyde NM, et al. Prevention of stress- or nitric oxide donor-induced medication overuse headache by a calcitonin gene-related peptide antibody in rodents. Cephalalgia 2017;37:560–70.
27. de Vries T, Villalon CM, MaassenVanDenBrink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. Pharmacol Ther 2020;2011:107528.
28. de Vries Lentsch S, Verhagen IE, van den Hoek TC, et al. Treatment with the monoclonal calcitonin gene-related peptide receptor antibody erenumab: A real-life study. Eur J Neurol 2021;28:4194–4203.
29. de Vries Lentsch S, van der Arend BWH, Maassen VanDenBrink A, Terwindt GM. Blood Pressure in Patients With Migraine Treated With Monoclonal Anti-CGRP (Receptor) Antibodies: A Prospective Follow-up Study. Neurology 2022;99(17):e1897–e1904.
30. de Vries Lentsch S, Garrelds IM, Danser AHJ, et al. Serum CGRP in migraine patients using erenumab as preventive treatment. J Headache Pain 2022;23(1):120.
31. de Vries Lentsch S, Perenboom MJL, Carpay JA, et al. Visual hypersensitivity in patients treated with anti-calcitonin gene-related peptide (receptor) monoclonal antibodies. Headache 2023;63(7):926–33.
32. de Vries Lentsch S, Louter MA, van Oosterhout W, et al. Depressive symptoms during the different phases of a migraine attack: A prospective diary study. J Affect Disord 2022;297:502–7.
33. Verhagen IE, de Vries Lentsch S, van der Arend BWH, et al. Both perimenstrual and nonperimenstrual migraine days respond to anti-calcitonin gene-related peptide (receptor) antibodies. Eur J Neurol 2023;30(7):2117–21.

Combinations of new migraine therapies – pros and cons

Anne Christine Poole,
General Practitioner and Headache Specialist, Oslo Headache Centre, Norway

Treatment of migraine with a combination of modern therapies has recently gained attention, particularly for some difficult-to-treat patients who, according to the consensus of the definition proposed by the European Headache Federation, encompass three scenarios.[1] First are patients with resistant migraine. That refers to patients who have failed at least three prophylactic medications – they still have eight debilitating headache days a month for the last three months without progression. Then there are refractory migraine patients who have failed all classes of the prophylactic medication and still have eight headache days a month, and that has been going on for six months. Thirdly are those with debilitating migraine who failed at least two triptans and still have serious impairments to daily activities.[1]

There is no global consensus about how to treat these patients, but there are national guidelines in some countries. In Norway, we have web-based guidelines, but they are not national guidelines. We follow the European guidelines whenever we update our web pages. Many doctors are driven by the reimbursement rules, as they are told to use three different oral medications before they can move to more modern medicines.

The combination of Botox and CGRP monoclonal antibodies (mAbs) can be suitable for severe chronic migraine, and has only a few side-effects. However, many patients say they experience a wearing-off effect of the medication a couple of days or even a week or two weeks before the next dose of Botox or mAb, which can be seen from their headache diaries. A combination of Botox and mAbs may be able to bridge this wearing off effect through a synergistic effect of the medicines, which have different modes of action. MAbs exert their effects principally via the alpha-delta nerve fibers, the slow myelinated fibers, and Botox blocks CGRP release in the C fibers.[2,3]

The gepants are small molecule antagonists that block the CGRP receptors. Erenumab blocks the

receptor, whereas eptinezumab, fremanezumab and galcanezumab bind to the CGRP ligand and thereby prevent it from binding its target receptors.

Combining mAbs and Botox is associated with minimal drug interaction, again because they have different modes of action. Also, they are generally well-tolerated in terms of side-effects compared with traditional oral prophylactic medication. They are regarded as expensive. However, it could be argued that the social costs of not using them are greater.

Blumenfeld *et al*. found that 45.1% of patients treated with a combination of Botox and mAbs had a clinically meaningful improvement in their migraine-related disability (≥5 point reduction in MIDAS score) after around six months.[4]

However, a retrospective chart review found the opposite. In patients with chronic migraine treated with erenumab alone (n=70) or as an add on to Botox (n=73), it was found that the probability of achieving a ≥50% reduction in monthly headache days was lower with dual therapy (odds ratio 0.57).[5]

Therefore, there is still a long way to go. There are limited data on safety and more research is needed to establish the long-term benefits and potential risks of the combination.

Turning to the combination of ligand-binding mAbs and gepants, they target distinct components within the CGRP pathway and that such a dual approach could potentially enhance symptom relief for certain individuals. For example, combination therapy with mAbs for prevention and gepants for acute treatment could be a potential strategy to manage severe migraine headache. However, there are no data on effect or safety of long-term combination of mAbs and prophylactic use of gepants.

In 2019, the European Headache Federation developed a new guideline, recommending the discontinuation of oral medication before starting mAbs in episodic migraine.[6] For chronic migraine, mAbs could be added to oral prophylactic medication, whereas Botox should be stopped before starting mAbs. Updated guidelines in 2022 now say use of Botox is optional, for individual consideration.[7]

References

1. Sacco S, Braschinsky M, Ducros A, et al. European headache federation consensus on the definition of resistant and refractory migraine: Developed with the endorsement of the European Migraine & Headache Alliance (EMHA). J Headache Pain 2020;21(1):76.
2. Ashina M, Katsarava Z, Do TP, et al. Migraine: epidemiology and systems of care. Lancet 2021;397(10283):1485–95.
3. Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nat Rev Neurol 2018;14(6):338–50.
4. Blumenfeld AM, Frishberg BM, Schim JD, et al. Real-World Evidence for Control of Chronic Migraine Patients Receiving CGRP Monoclonal Antibody Therapy Added to OnabotulinumtoxinA: A Retrospective Chart Review. Pain Ther 2021;10(2):809–26.
5. Jaimes A, Gómez A, Pajares O, Rodríguez-Vico J. Dual therapy with Erenumab and OnabotulinumtoxinA: no synergistic effect in chronic migraine: a retrospective cohort study. Pain Pract 2023;23(4):349–58.
6. Sacco S, Bendtsen L, Ashina M, et al European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain 2019;20(1):6.
7. Sacco S, Amin FM, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update. J Headache Pain 2022;23(1):67.

Nerve blockade in headaches – the scientific rationale

Koen Paemeleire, Prof., MD, PhD
Department of Neurology, Ghent University Hospital, Ghent, Belgium

Peripheral nerve blocks are popular acute and prophylactic headache treatments, despite a paucity of evidence, and no real standard procedures. Although recently, there have been attempts at carrying out randomised controlled trials (RCTs), mainly in migraine and cluster headache. These nerve blocks are also used as diagnostic tools, for occipital neuralgia, for example.

Nerve blocks are used in a variety of headache disorders, including primary headache disorders such as migraine and cluster headache, secondary headaches such as cervicogenic headache and medication overuse headache, as well as cranial neuralgias.

More than 10 RCTs, many small, have looked at symptomatic relief in primary headache disorders. The primary result, is that local anaesthesia is driving the effect in migraine. Whereas in cluster headache, the steroid drives the effect – but there are only two RCTs.

Mode of action

Local anaesthetics reduce the afferent tone, thus reducing activity at the first synapse of the nociceptive pathway because there is always some baseline firing in the nerve. However, what is seen throughout the migraine data is that the effect is much longer than the effect of the local anaesthesia. So, there is some long-term relief (hours to days, sometimes even longer) in migraine. The long-term relief with local anaesthetics cannot be simply explained by a block. Theoretically, there may be a winding down of central sensitisation, or a change in central descending pain modulation, but there is a lot of work that needs to be done to really understand what is happening.[1]

For cervicogenic headache, the C2-C3 facet is quite well accepted as a potential source of the headache, so that can be blocked before doing another intervention.[1]

For peripheral neuropathic pain such as occipital neuropathic pain, local anaesthetic provides some short-term relief.[1]

So, the mechanism of action of local anaesthetics is quite well understood, except for long-term relief.

When we think of local steroids, the mechanism of action in primary headache disorder is unknown. The initial hypothesis, based on data in rats with high dosages of steroids locally applied, was that there was a demyelination of nerve fibers.[2] However, later research, mainly in anaesthesiology, showed that locally applied steroids in limited, normal amounts have no long-term effects on structure or on electrical properties of peripheral nerves.[3,4] However, there is one interesting publication using methylprednisolone locally applied in an animal model, that showed that corticosteroids suppressed transmission in C fibers, but not in A delta fibers. C fibers are unmyelinated, and the authors suggested that corticosteroid had a direct membrane effect.[5] Though, it is very limited evidence.

These treatments have been popular for a very long time, and delving back into the literature shows that the relationship between occipital nerve tenderness and headache disorders was first reported in 1947, where Dr Perelson was looking at over 300 patients who had tenderness on pressure application on the occipital nerves with varying clinical forms of headache. Interestingly, at that time, the hypothesis of a trigeminocervical complex had already been conceived because the author mentions in the discussion that there may be a relationship between the spinal nucleus of the trigeminal nerve and the central termination of the greater and lesser occipital nerves in the dorsal horn of the upper cervical cord.[6]

This brings us to the concept of a convergence of nociceptive information from the front and the back of the head. The greater occipital nerve is mainly derived from C2 with a contribution from C3 and there is a convergence with nociceptive input via the trigeminal nerve that leads to a loss of spatial specificity. From there, the information is projected upwards. There are a lot of data behind the concept of a (functional rather than anatomical) trigeminocervical complex including a paper by Bartsch and Goadsby that corroborates its existence. Through a hole drilled in a rat's skull, they stimulated the dura mater over the middle meningeal artery. A second stimulator was used to stimulate the greater occipital nerve in the animal's neck, and a recording from the C2 segment of the cervical spine was made. Stimulation of dura

mater elicited an early latency response within the A-fibre range. Increasing the stimulation recruits further A-fibre as well as C-fibre latency responses. Stimulation of the greater occipital nerve also shows A-fibre and C-fibre latency responses. So, the receptive fields of these neurons are in both the greater occipital nerve territory and in the trigeminal nerve territory.[7,8]

There is also human experimental evidence documented. When sterile water is injected at the exit of the greater occipital nerve, a majority of patients will not only report pain in the greater occipital nerve territory, but also in the ophthalmic division of the trigeminal nerve.[9] The phenomenon was alluded to as long ago as 1944. When noxious stimulation is applied to the basal occipital periosteum or the interspinous muscles C1-C2 and C2-C, patients report pain locally but also in the ophthalmic division of the trigeminal nerve.[10,11]

The mechanism by which steroid injections exert their effect in the greater occipital nerve area is not known. An RCT in patients with cluster headache, given a steroid mixture plus a local anaesthetic versus an anaesthetic alone as the placebo control demonstrated that the steroid was the active component. The researchers then suggested that the steroid might act systemically, and that there may be no real advantage to injecting occipitally. To test the idea, they proposed a double-blind trial to compare suboccipital and intramuscular injections of the same mixture.[12] However, so far, the study has not been done.

There are systemic side-effects associated with steroid injections at the greater occipital nerve, specifically with serial applications, for example, Cushing syndrome[13] and very rarely avascular necrosis.[14] The original reference on cluster headache by Michael Anthony involved greater occipital nerve blocks with steroids and aesthetics in both cluster headache and in migraine. In the cluster headache study, there were five patients in the control group showing there was no effect with an intramuscular injection. He did the same in a group of 20 migraine patients given Depo-Medrol intramuscularly, and they showed that the effect they observed with occipital infiltration was not seen with the intramuscular injection.[15,16] A (partial) systemic effect has not been looked at enough.

References

1. Afridi SK, Shields KG, Bhola R, Goadsby PJ. Greater occipital nerve injection in primary headache syndromes – prolonged effects from a single injection. Pain 2006;122(1-2):126–9.
2. Selby R. Complications from Depo-Medrol R. Surg Neurol 1983;19(4):393–4.
3. Johansson A, Hao J, Sjölund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. Acta Anaesthesiol Scand 1990;34(5):335–8.
4. Johansson A, Dahlin L, Kerns JM. Long-term local corticosteroid application does not influence nerve transmission or structure. Acta Anaesthesiol Scand 1995;39(3):364–9.
5. Johansson A, Bennett GJ. Effect of local methylprednisolone on pain in a nerve injury model. A pilot study. Reg Anesth 1997;22(1):59–65.
6. Perelson HN. Occipital nerve tenderness; a sign of headache. South Med J 1947;40(8):653–6.
7. Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. Brain 2002;125(Pt 7):1496–509.
8. Bartsch T, Goadsby PJ. Increased responses in trigeminocervical nociceptive neurons to cervical input after stimulation of the dura mater. Brain 2003;126(Pt 8):1801–13.
9. Piovesan EJ, Kowacs PA, Tatsui CE, et al. Referred pain after painful stimulation of the greater occipital nerve in humans: evidence of convergence of cervical afferences on trigeminal nuclei. Cephalalgia 2001;21(2):107–9.
10. Bogduk N, Govind J. Cervicogenic headache: an assessment of the evidence on clinical diagnosis, invasive tests, and treatment. Lancet Neurol 2009;8(10):959–68.
11. Campbell DG, Parsons CM: Referred head pain and its concomitants. J Nerv Ment Dis 1944;99:544–51.
12. Ambrosini A, Vandenheede M, Rossi P, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain 2005;118(1-2):92–6.
13. Lavin PJ, Workman R. Cushing syndrome induced by serial occipital nerve blocks containing corticosteroids. Headache 2001;41(9):902–4.
14. Rozen TD. High-Volume Anesthetic Suboccipital Nerve Blocks for Treatment Refractory Chronic Cluster Headache With Long-Term Efficacy Data: An Observational Case Series Study. Headache 2019;59(1):56–62.
15. Anthony M. Headache and the greater occipital nerve. Clin Neurol Neurosurg 1992;94(4):297–301.
16. Anthony M. Arrest of attacks of cluster headache by local steroid injections of the occipital nerve. In: Clifford Rose F, ed. Migraine: clinical and research advances. Basel: Karger, 1985:168–73.

Impact of sex hormones in migraine

Bianca Raffaelli,
Neurologist, Postdoctoral Researcher, Danish Headache Center, University of Copenhagen, Rigshospitalet Glostrup, Denmark

Migraine prevalence in women is two to three times higher than in men.[1] That is especially true for women of childbearing age. Migraine also has some specific characteristics in women. For example, migraine attacks in women are longer than in men and migraine attacks may be more severe in women than in men.[2] That, together with the higher prevalence in women, results in a higher burden of disease in women compared with men.[1]

Data from the Netherlands show that around 80% of women reported menstruation to be a trigger of their migraine attacks.[3,4] Migraine frequency usually decreases during pregnancy. Some investigations show that up to 90% of women reported an improvement during pregnancy. However, it is important to note that migraine can also worsen in some women and there is a possibility of a new onset of migraine, especially in patients with migraine with aura, and there is a peak in migraine incidence after giving birth. In fact, 55% of women report a return of attacks postpartum, within one month. Finally, there is a peak in migraine incidence during the perimenopause and then at an older age but at a lower incidence level.[3,5]

The peaks in migraine incidence seem to all occur after a decline in oestrogen.[3] This observation has led to a theory called the 'oestrogen withdrawal hypothesis', a theory formulated in 1972 by an Australian neurologist, Brian Somerville, who carried out a pivotal study in which estradiol was given to only six women before menstruation. The study showed that administration of estradiol postponed an expected migraine.[6]

Researchers at the Danish Headache Center (with other colleagues) looked at the theory in a little more detail and were quite surprised how limited the evidence was.[7] Animal experiments investigating the influence of oestrogen on pain perception employed a range of stimuli – heat, cold, ischaemia or pressure, for example – to stimulate different areas. Although, of course, the hormonal cycle in mice and rats is different than in humans. Nevertheless, some investigations showed an increased pain sensitivity during low-oestrogen phases. However, there were an equal number of investigations showing the opposite.[8,9]

So, animal experiments do not really help to draw any specific conclusions. Human studies also vary in their use of pain stimuli, cohorts, timing and nomenclature.[10]

In an electrophysiological study by an Italian group, the right superorbital zone was simulated with a laser, which is painful.

They measured the evoked potential after that, once in the premenstrual phase and then in the late luteal phase of the menstrual cycle. In patients with migraine, in particular, there was an increased amplitude and a decreased habituation of this potential,[11] which could point to a pro-nociceptive status during the premenstrual phase.

Another investigation involving participants taking combined oral contraception for three weeks with a one-week break, showed similar results. They measured how much electricity applied to the back was needed to provoke a withdrawal reaction. The amount of electricity needed was lower during the hormone-free interval compared with the time when hormones were being taken.[12] Again, they concluded that oestrogen withdrawal or at least a phase with low oestrogen could be associated with a pro-nociceptive response.

One theory that may help explain the link between oestrogen levels and migraine attacks involves CGRP, which has been shown to be important in migraine pathophysiology. It is known that oestrogen can influence CGRP and the CGRP pathway. However, the relationship is very complex.[13] In some studies, oestrogen led to an increase in CGRP while in others, there was a decrease.

Raffaelli and colleagues measured CGRP levels in plasma and in tear fluid, which is nearer to the trigeminal system in women with migraine and without migraine with different hormonal profiles. They found that patients with migraine had higher CGRP levels during menstruation, compared with healthy controls without migraine. In the middle of the menstrual cycle, these levels were numerically higher but this did not reach statistical significance. They interpreted the results as potentially indicating that there is a hormone-dependent dysfunction in the modulation of the CGRP pathway.[14] More work is needed in the area.

Turning to exogenous hormones, they can have a variable effect on migraine: it depends on factors such as the formulation, dosage, indication and duration of treatment. Hormonal contraception with oestrogen is associated with an increased risk of ischaemic stroke, particularly true in women with migraine. For women aged 20 to 44 years who do not have migraine and are not taking contraception, the absolute risk of ischaemic stroke is 2.5 per 100,000. For women who have migraine with aura and who are taking hormonal contraception, the absolute risk is 36.9 per 100,000.[15,16]

Exogenous hormones work best in patients with menstrual-related migraine and they work best if we suppress the hormonal fluctuation, for example, by giving hormones in an extended cycle. On the other side, the safety recommendation we should really pay attention to are the other vascular risk factors such as smoking or arterial hypertension. Particular caution is needed when treating patients with migraine with aura.

A study from the Netherlands compared migraine prevalence in male to female transgender individuals with genetic females and genetic males, and found that the migraine prevalence in transfeminine individuals was similar to that for genetic females.[17] The finding was confirmed by a recent investigation with a small sample size that found that transfeminine individuals taking oestrogen had a six-times higher probability of having headache compared with transfeminine individuals who were not taking oestrogen.[18]

References

1. Vetvtik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol 2017;16(1):76–87.
2. Wöber-Bingöl C, Wöber C, Karwautz A, et al. Clinical features of migraine: a cross-sectional study in patients aged three to sixty-nine. Cephalalgia 2004;24:12–17.
3. Sacco S, Ricci S, Degan D, Carolei A. Migraine in women: the role of hormones and their impact on vascular diseases. J Headache Pain 2012;13(3):177–89.
4. Van Casteren DS, Verhagen IE, Onderwater GL, et al. Sex differences in prevalence of migraine trigger factors: A cross-sectional study. Cephalalgia 2021;41(6):643–8.
5. Negro A, Delaruelle Z, Ivanova TA, et al. Headache and pregnancy: a systematic review. J Headache Pain 2017;18(1):106.
6. Somerville BW. The role of estradiol withdrawal in the etiology of menstrual migraine. Neurology 1972;22(4):355–65.
7. Raffaelli B, Do TP, Chaudhry BA, et al. Menstrual migraine is caused by estrogen withdrawal: revisiting the evidence. J Headache Pain 2023;24(1):131.
8. Kayser V, Berkley KJ, Keita H, et al. Estrous and sex variations in vocalization thresholds to hindpaw and tail pressure stimulation in the rat. Brain Res 1996;742(1–2):352–4.
9. Martin VT, Lee J, Behbehani MM. Sensitization of the trigeminal sensory system during different stages of the rat estrous cycle: implications for menstrual migraine. Headache 2007;47(4):552–63.
10. Sherman JJ, LeResche L. Does experimental pain response vary across the menstrual cycle? A methodological review. Am J Physiol Regul Integr Comp Physiol 2006;291(2):R245–56.
11. de Tommaso M, Valeriani M, Sardaro M, et al. Pain perception and laser evoked potentials during menstrual cycle in migraine. J Headache Pain 2009;10(6):423–9.
12. De Icco R, Cucinella L, De Paoli I, et al. Modulation of nociceptive threshold by combined hormonal contraceptives in women with oestrogen-withdrawal migraine attacks: a pilot study. J Headache Pain 2016;17(1):70.
13. Labastida-Ramírez A, Rubio-Beltrán E, Villalón CM, MaassenVanDenBrink A. Gender aspects of CGRP in migraine. Cephalalgia 2019;39(3):435–44.
14. Raffaelli B, Storch E, Overeem LH, et al. Sex Hormones and Calcitonin Gene-Related Peptide in Women With Migraine: A Cross-sectional, Matched Cohort Study. Neurology 2023;100(17):e1825–e1835.
15. Sacco S, Merki-Feld GS, Ægidius KL, et al. Hormonal contraceptives and risk of ischemic stroke in women with migraine: a consensus statement from the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC). J Headache Pain 2017;18(1):108.
16. Nappi RE, Tiranini L, Sacco S, et al. Role of Estrogens in Menstrual Migraine. Cells 2022;11(8):1355.
17. Pringsheim T, Gooren L. Migraine prevalence in male to female transsexuals on hormone therapy. Neurology 2004;63(3):593–4.
18. Hralniovic JA. Headache prevalence in transgender and gender diverse youth: A single-center case-control study. Headache 2023;63(4):517–22.

Menstrual migraine – diagnosis and management

Anna Sundholm, MD, PhD
Head of Section 'Junior Doctors' ME Neurology, Karolinska University Hospital, Sweden

Approximately 4–8% of all females have menstrual migraine: approximately 1% have pure menstrual migraine, and approximately 6–7% have menstrual-related migraine. Of all women who have migraine, around 22% have menstrual migraine.[1,2]

Pure menstrual migraine fulfils the diagnosis criteria for migraine with or without aura, with migraine attacks two days before to three days after the first day of menstruation for two out of three menstrual cycles and at no other times during the menstrual cycle. Menstrual-related migraine has the same definition but with attacks at other times during the menstrual cycle as well.[3]

They have different characteristics. In menstrual migraine, attacks occur mainly without the aura even in women who have attacks with aura at other times. Attacks are more severe, more disabling, they last longer, and they are harder to treat.[4,5]

Some studies have found an association between menstrual migraine and dysmenorrhea where symptoms are thought to be due to prostaglandins. Migraine frequency and severity often increase during perimenopause – particularly in women with menstrual migraine.[4,5]

Diagnosis of menstrual migraine should be restricted to women in whom there is more than a chance association between migraine and menstruation. Women should keep a headache diary and record their menstrual periods to help confirm the diagnosis.[6]

Menstrual migraine is harder to confirm in patients with very frequent migraine but a statistical association between migraine and menstruation has also been shown in this patient group.[6]

Oestrogen has a range of influences on menstrual migraine.[7] It has been shown that migraine is significantly more likely to occur in association with falling oestrogen levels in the late luteal/early follicular phase of the menstrual cycle, which supports the hypothesis of oestrogen 'withdrawal' triggering migraine.[8]

In terms of treating menstrual migraine, a holistic approach is needed: a number of strategies have been adopted.

Acute therapies include triptans and NSAIDs to treat the attack itself, along with hormonal therapy, nutraceuticals and medical devices which are options for mini-prophylaxis where patients are treated during their menstrual period. Options for long-term prevention include standard medications used for prevention, and hormonal therapy.[9]

On an individual basis, treatment choice will be guided to some extent by whether menstrual migraine is frequent or not and whether patients experience long duration or symptoms that respond poorly to acute therapy, if attacks are predictable or not. Other considerations such as vascular risk factors, regularity of menstruation, whether there is a menstrual disorder, comorbidities such as depression and sleep disorders as well as the need for contraception and personal preference also play a part.[10]

Triptans have been shown to provide relief from pain when used acutely also in menstrual migraine. There is some evidence for the use of short-term prophylactic treatments such as naproxen, triptans, oestrogen patches and magnesium, given around the time of menstruation, starting two days before bleeding starts.[10,11]

References

1. Vetvik KG, Macgregor EA, Lundqvist C, Russell MB. Prevalence of menstrual migraine: a population-based study. Cephalalgia 2014;34(4):280–8.
2. Ashina M, Katsarava Z, Do TP, et al. Migraine: epidemiology and systems of care. Lancet. 2021;397(10283):1485–95.
3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38(1):1–211.
4. MacGregor EA. Menstrual migraine. Curr Opin Neurol 2008;21(3):309–15.
5. MacGregor EA. Menstrual and perimenopausal migraine: A narrative review. Maturitas 2020;142:24–30.
6. Barra M, Dahl FA, MacGregor EA, Vetvik KG. Identifying menstrual migraine- improving the diagnostic criteria using a statistical method. J Headache Pain 2019;20(1):95.
7. Cupini LM, Corbelli I, Sarchelli P. Menstrual migraine: what it is and does it matter? J Neurol 2021;268:2355–63.
8. MacGregor EA, Frith A, Ellis J, et al. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. Neurology 2006;67(12):2154–8.
9. Ansari T, Lagman-Bartolome AM, Monsour D, Lay C. Management of Menstrual Migraine. Curr Neurol Neurosci Rep 2020;20(10):45.
10. Maasumi K, Tepper SJ, Kriegler JS. Menstrual Migraine and Treatment Options: Review. Headache 2017;57(2):194–208.
11. Burch R. Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review. Headache 2020;60(1):200–16.

Pregnancy and lactation in migraine

Marja-Liisa Sumelahti, MD, PhD
Associate Professor, Tampere University; Neurologist, Terveystalo Tampere, Finland

Addressing treatment safety for women of childbearing age is crucial, particularly when initiating preventive medications. Careful consideration about the use of medications and other therapies for migraine is needed in the context of pregnancy planning.

Migraine in pregnancy

Migraine is the most common headache during pregnancy, overshadowing secondary headaches caused by factors such as sinus thrombosis, preeclampsia, and hypertension.[1,2] Pregnant women with migraine face an increased risk of preeclampsia, especially when compounded by obesity.[3,4]

A common feature is new or more frequent aura symptoms with or without headache. The risk for aura relates to a rise in pregnancy hormones where oestrogen levels can be over 100-fold higher than in non-pregnant women.[3,4]

However, evidence suggests that migraine, in general, does not significantly impact pregnancy outcomes.

In cases of a migraine without aura, most women notice their migraines either go away or greatly improve in the second or third trimester when hormone levels stabilise. However, less than 10% of migraineurs do not experience this break. The increasing oestrogen level is a substrate for aura, which may appear for the first time during pregnancy. Other attack triggers include increasing blood volume and some lifestyle-related factors. Therefore, before deciding if a medication is needed to help prevent or treat migraines, it may be best to consider the safest interventions, which are lifestyle changes likely to reduce the frequency and severity of migraine.[5-8]

It is important to encourage discussions about alternative migraine therapies in pregnancy. Feverfew and St. John's Wort, otherwise considered safe, are to be avoided in pregnancy. Non-drug therapies such as relaxation techniques, sleep, massage, ice packs and bio-feedback are regarded as safe. Clear proof of effectiveness has not been found for acupuncture and when used in pregnancy, there can be an increased risk of miscarriage depending on the location of the needle placements. Non-invasive stimulation devices such as transcutaneous supraorbital nerve stimulation are thought to be safe. Greater occipital nerve

block can alleviate pain and reduce the number of headache days and medication consumption. Also, oral corticosteroids are considered safe but parenteral dexamethasone is not recommended due to foetal exposure.

Drug treatments can be grouped into three classes according to the evidence for their use: those known to cause foetal harm in humans or animals; those for which no harm has been found to date, and those that have been studied extensively through testing and/or patient and infant follow-ups with no increase in foetal or infant defects. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are regarded as the safest medicines for migraine attacks. However, NSAIDs should be stopped during the last trimester to avoid early closure of ductus arteriosus.[4]

The choice of preventives is very limited. If prophylaxis is indicated in pregnancy or lactation, the lowest effective dosage of propranolol or amitriptyline are the options.[9]

Triptans, commonly used for migraines, seem relatively safe during pregnancy, with studies showing no significant increase in risk for major malformations or adverse outcomes compared with the general population. A systematic review showed that the adjusted risk ratio for major malformations, low birth weight and preterm labour showed no risk for triptan users compared with the general population.[10] Two other studies showed triptan safety among infants exposed to triptans and among pregnant users. These results support information from sumatriptan and naratriptan pregnancy register dated up to 2008. Furthermore, there was no risk for stillbirth or early labour of migraineurs with or without migraine medication.[10]

In conclusion, these studies support the relative safety of triptans in pregnancy. They do not appear to increase the risk of pregnancy outcomes when compared with the general population and results support the use of sumatriptan.[10–12] However, it may be indicated for severe attacks that do not respond to paracetamol or an NSAID.

Post-delivery

After childbirth, women typically return to their pre-pregnancy migraine patterns. Breastfeeding provides a protective effect against migraines until menstruation resumes. While there are no specific recommendations for preventive medications during lactation, a database of medication safety studies for nursing mothers is available.[9]

Safety analyses on monoclonal antibodies, including calcitonin gene-related peptide monoclonal antibodies, suggest no consistent signals of foetal-maternal toxicity. However, current labels advise against their use during pregnancy due to their long half-life, recommending discontinuation at least five months before conception.[13,14]

Conclusion

In summary, managing migraines during pregnancy involves a nuanced approach, emphasizing non-drug therapies and carefully considering medication risks and benefits. While some options are available, ongoing research is essential to expand our understanding of safe treatments during pregnancy and lactation.[14–17] It is crucial for health care providers to engage in open discussions with patients, tailoring treatment plans to individual needs and circumstances.

References

1. Robbins MS, Farmakidis C, Dayal AK, Lipton RB. Acute headache diagnosis in pregnant women: a hospital-based study. Neurology 2015;85(12):1024–30.
2. Raffaelli B, Siebert E, Körner J, et al. Characteristics and diagnoses of acute headache in pregnant women – a retrospective cross-sectional study. J Headache Pain 2017;18(1):114.
3. Tanos V, Raad EA, Berry KE, Toney ZA. Review of migraine incidence and management in obstetrics and gynaecology. Eur J Obstet Gynecol Reprod Biol 2019;240:248–55.
4. Burch R. Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review. Headache 2020;60(1):200–16.
5. Allais G, Castagnoli Gabellari I, Airola G, et al. Is migraine a risk factor in pregnancy? Neurol Sci 2007;28(Suppl 2):S184–7.
6. Calhoun AH. Migraine Treatment in Pregnancy and Lactation. Curr Pain Headache Rep 2017;21(11):46.
7. Sanchez SE, Williams MA, Pacora PN, et al. Risk of placental abruption in relation to migraines and headaches. BMC Womens Health 2010;10:30.
8. Chen HM, Chen SF, Chen YH, Lin HC. Increased risk of adverse pregnancy outcomes for women with migraines: a nationwide population-based study. Cephalalgia 2010;30(4):433–8.
9. LactMed (www.ncbi.nlm.nih.gov/books/NBK501922; accessed December 2023)
10. Dudman DC, Tauqeer F, Kaur M, et al. A systematic review and meta-analyses on the prevalence of pregnancy outcomes in migraine treated patients: a contribution from the IMI2 ConcePTION project. J Neurol 2022;269:742–9.
11. Marchenko A, Etwel F, Olutunfese O, et al. Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis. Headache 2015;55(4):490–501.
12. Spielmann K, Kayser A, Beck E, et al. Pregnancy outcome after anti-migraine triptan use: A prospective observational cohort study. Cephalalgia 2018;38(6):1081-1092.
13. Noseda R, Bedussi F, Gobbi C, et al. Safety profile of monoclonal antibodies targeting the calcitonin gene-related peptide system in pregnancy: Updated analysis in VigiBase. Cephalalgia 2023;43(4):3331024231158083.
14. Sances G, Granella F, Nappi RE, et al. Course of migraine during pregnancy and postpartum: a prospective study. Cephalalgia 2003;23(3):197–205.
15. Källén B, Lygner PE. Delivery outcome in women who used drugs for migraine during pregnancy with special reference to sumatriptan. Headache 2001;41(4):351–6.
16. Olesen C, Steffensen FH, Sørensen HT, et al. Pregnancy Outcome Following Prescription for Sumatriptan. Headache 2000;40:20–4.
17. MacGregor EA. Migraine in pregnancy and lactation. Neurol Sci 2014;35 Suppl 1:61–4.

The role of sleep in migraine

Piero Barbanti, MD, PhD
Director, Headache and Pain Unit, Associate Professor of Neurology, San Raffaele University, Rome, Italy

Sleepiness may precede, follow or accompany a migraine attack. Migraine chronobiology is closely tied to the sleep-wake cycle and sleep disorders are more frequent in patients with migraine than the general population. Sleep affects migraine and migraine affects sleep.

Many of the areas of the brain involved in sleep and migraine overlap, for example, the superchiasmatic nucleus, tuberomammillary nucleus, locus coeruleus and raphe nucleus. There is also an overlap of neurotransmitters; for example, norepinephrine, serotonin, dopamine, histamine, pituitary adenylate cyclase-activating polypeptide (PACAP), orexine (which is crucial for the treatment of sleep disorders), adenosine and melatonin.[1,2]

Regardless of the migraine attack, patients with migraine do not sleep well. About half of them report having frequent, very frequent or occasional trouble falling asleep or staying asleep.[3]

In terms of sleep disorders, as opposed to complaints, episodic insomnia affects 30% of the population, but only 6% of the population has chronic insomnia. In migraine, chronic insomnia affects around 26% of patients with an odds ratio of 2,[4-6] and the odds of having insomnia increases with migraine frequency. A meta-analysis by Stanyer *et al*. found that the Pittsburgh Sleep Quality (PSQI) score was higher in people with migraine – mostly those with chronic migraine, but also those with episodic migraine[7] – indicating that people with migraine do not sleep well.

People with migraine also report restless legs syndrome (RLS), which has a prevalence of 13.7–25% (odds ratio 2.65). Other disorders seen in people with migraine include shift worker disorder (prevalence 11.3%, odds ratio 1.6)[4-6]

The link between these various disorders seems to be serotonin.[10-14]

In case-controlled studies done more than 15 years ago, patients with migraine were found to be three times more likely to have excessive daytime somnolence, mostly because they were bad sleepers, as indicated by a PSQI score of over five.[8,9] Somnolence is a dopaminergic symptom, and dopaminergic symptoms by definition are present in migraine, for example, but in some patients they are extremely pronounced, evidenced by yawning and somnolence prodromally, and mood swings in the postdromal phase. The theory was that dopaminergic activity is reduced interictally in patients with migraine, which accounts for an upregulation of dopamine receptors. At the very beginning of the upregulation, there is a slight increase in dopaminergic tone, which stimulates presynaptic dopaminergic terminals, resulting in an anti-dopaminergic effect because presynaptic stimulation reduces the outflow of the neurotransmitter, leading to somnolence and yawning.[14]

However, the most likely link between sleep and migraine is the glymphatic system, which has a role in clearing excitatory and inflammatory waste as well as brain-wide cerebral

metabolism, delivering glucose and transporting lipid, signalling molecules and apolipoprotein E.[15–17] Burstein and colleagues also demonstrated that cortical spreading depression (an animal model of migraine aura) experimentally induced in mice, closes the paravascular space and impairs glymphatic load, providing all the elements needed to trigger pain.[18] However, in children under eight years old, sleep may stop migraine attacks.[19]

In adults, the transition from non-REM to REM sleep, cooling and warming, and accompanying changes in brain metabolism may be the trigger for a migraine attack.[20–22]

A global sample of 11,000 patients using the Migraine Buddy app involved in a study that used a Bayesian cross-sectional approach, found that sleep interruptions and deviation from the users' mean sleep were significant predictors of a migraine attack the following day. Very painful attacks are correlated with sleeping for longer afterwards but just having a migraine attack was not.[23]

A prospective study of 98 patients with episodic migraine was designed to try to untangle some of what is happening. Participants completed an eDiary regarding migraine and sleep twice a day and wore a wrist actigraph for six months. The odds of having headache the day immediately after the sleep period zero was not affected by the duration or quality of sleep according to the diary. However, somewhat surprisingly, the odds of having a migraine the day after poor sleep, was reduced, according to the actigraphy data. Then, the next day, the odds ratio of headache following diary-reported low efficiency was 39% higher.[24]

In conclusion, patients with migraine are at an increased risk of developing insomnia and patients with insomnia are at an increased risk of developing migraine. Therefore, migraine needs to be treated but sleep hygiene should be an inherent part of migraine management.[25]

References

1. Ashina M, Hansen JM, Do TP, et al. Migraine and the trigeminovascular system-40 years and counting. Lancet Neurol 2019;18(8):795–804.
2. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005;437(7063):1257–63.
3. Kelman L, Rains JC. Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. Headache 2005;45(7):904–10.
4. Kim J, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK. Impact of migraine on the clinical presentation of insomnia: a population-based study. J Headache Pain 2018;19(1):86.
5. Bjorvatn B, Pallesen S, Moen BE, et al. Migraine, tension-type headache and medication-overuse headache in a large population of shift working nurses: a cross-sectional study in Norway. BMJ Open 2018;8(11):e022403.
6. Arruda MA, Guidetti V, Galli F, et al. Childhood periodic syndromes: a population-based study. Pediatr Neurol 2010;43(6):420–4.
7. Stanyer EC, Creeney H, Nesbitt AD, et al. Subjective Sleep Quality and Sleep Architecture in Patients With Migraine: A Meta-analysis. Neurology 2021;97(16):e1620–e1631.
8. Barbanti P, Fabbrini G, Aurilia C, et al. A case-control study on excessive daytime sleepiness in episodic migraine. Cephalalgia 2007;27(10):1115–9.
9. Barbanti P, Aurilia C, Egeo G, et al. A case-control study on excessive daytime sleepiness in chronic migraine. Sleep Med 2013;14(3):278–81.
10. Charbit AR, Akerman S, Goadsby PJ. Comparison of the effects of central and peripheral dopamine receptor activation on evoked firing in the trigeminocervical complex. J Pharmacol Exp Ther 2009;331(2):752–63.
11. Charbit AR, Akerman S, Goadsby PJ. Trigeminocervical complex responses after lesioning dopaminergic A11 nucleus are modified by dopamine and serotonin mechanisms. Pain 2011;152(10):2365–76.
12. Hajak G, Geisler P. Orchestrating sleep-wake functions in the brain. Nat Med 2003;9(2):170–1.
13. Messina A, Bitetti I, Precenzano F, et al. Non-Rapid Eye Movement Sleep Parasomnias and Migraine: A Role of Orexinergic Projections. Front Neurol 2018;9:95.
14. Barbanti P, Aurilia C, Egeo G, et al. Dopaminergic symptoms in migraine: A cross-sectional study on 1148 consecutive headache center-based patients. Cephalalgia 2020;40(11):1168–76.
15. Lohela TJ, Lilius TO, Nedergaard M. The glymphatic system: implications for drugs for central nervous system diseases. Nat Rev Drug Discov 2022;21(10):763–79.
16. Fultz NE, Bonmassar G, Setsompop K, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. Science 2019;366(6465):628–31.
17. Yi T, Gao P, Zhu T, Yin H, Jin S. Glymphatic System Dysfunction: A Novel Mediator of Sleep Disorders and Headaches. Front Neurol 2022;13:885020.
18. Schain AJ, Melo-Carrillo A, Strassman AM, Burstein R. Cortical Spreading Depression Closes Paravascular Space and Impairs Glymphatic Flow: Implications for Migraine Headache. J Neurosci 2017;37(11):2904–15.
19. Aaltonen K, Hämäläinen ML, Hoppu K. Migraine attacks and sleep in children. Cephalalgia 2000;20(6):580–4.
20. Fox AW, Davis RL. Migraine chronobiology. Headache 1998;38(6):436–41.
21. Ungurean G, Barrillot B, Martinez-Gonzalez D, et al. Comparative Perspectives that Challenge Brain Warming as the Primary Function of REM Sleep. iScience 2020;23(11):101696.
22. Lewis LD. The interconnected causes and consequences of sleep in the brain. Science 2021;374(6567):564–8.
23. Stanyer EC, Brookes J, Pang JR, et al J. Investigating the relationship between sleep and migraine in a global sample: a Bayesian cross-sectional approach. J Headache Pain 2023;24:123.
24. Bertisch SM, Li W, Buettner C, et al. Nightly sleep duration, fragmentation, and quality and daily risk of migraine. Neurology 2020;94(5):e489–96.
25. Tiseo C, Vacca A, Felbush A, et al. Migraine and sleep disorders: a systematic review. J Headache Pain 2020;21(1):126.

Migraine and diet

Parisa Gazerani, Pharm PhD
Professor, Department of Life Sciences and Health Faculty of Health Sciences, Oslo, Metropolitan University, Norway

There is some evidence that migraine can be influenced by diet, and migraine can influence the choice of diet. For example, migraine patients may choose foods based on their symptoms. So they may have cravings for some foods or may not be able to tolerate others because of feelings of nausea, for example.[1–3] So, there may be a bidirectional connection between diet and migraine.

Some dietary components can trigger migraine, but it seems to be very individual.[4]

A systematic review in 2021 identified caffeine and alcohol as major triggers of migraine.[1] Other foods may trigger migraine but evidence for a widespread effect is lacking.

Elimination diets can help people manage their migraine symptoms, but because the effect of different foods is so individual and because it is important to avoid nutritional deficits when eliminating foods from a diet (beyond alcohol and caffeine), it is important that the strategy is carried out under medical supervision with expert advice.

Average-quality evidence shows that the ketogenic diet (KD) and the Dietary Approaches to Stop Hypertension (DASH) are effective in reducing the frequency, duration, and severity of migraine headaches in adult patients.[1] The DASH diet emphasises plant-based foods high in potassium, calcium, and magnesium, and minimises foods high in saturated fat, cholesterol, sodium, and sugar. The KD is a regimen that mimics fasting and induces ketone body production through carbohydrate restriction, with the aim of decreasing insulin secretion and increasing glucagon secretion along with the mobilisation of fatty acids and production of ketone bodies.[5,6]

The gut microbiome may have a part to play. Prebiotics and probiotics modulate the gut-brain axis and thus have some impact on migraine symptoms.[1,7] Although evidence for probiotic supplementation, for example, has been negative with no effect on frequency and severity of migraine headaches.[8]

Dietary fatty acids have been studied in relation to migraine. Headaches were less frequent and of shorter duration among those on diets high

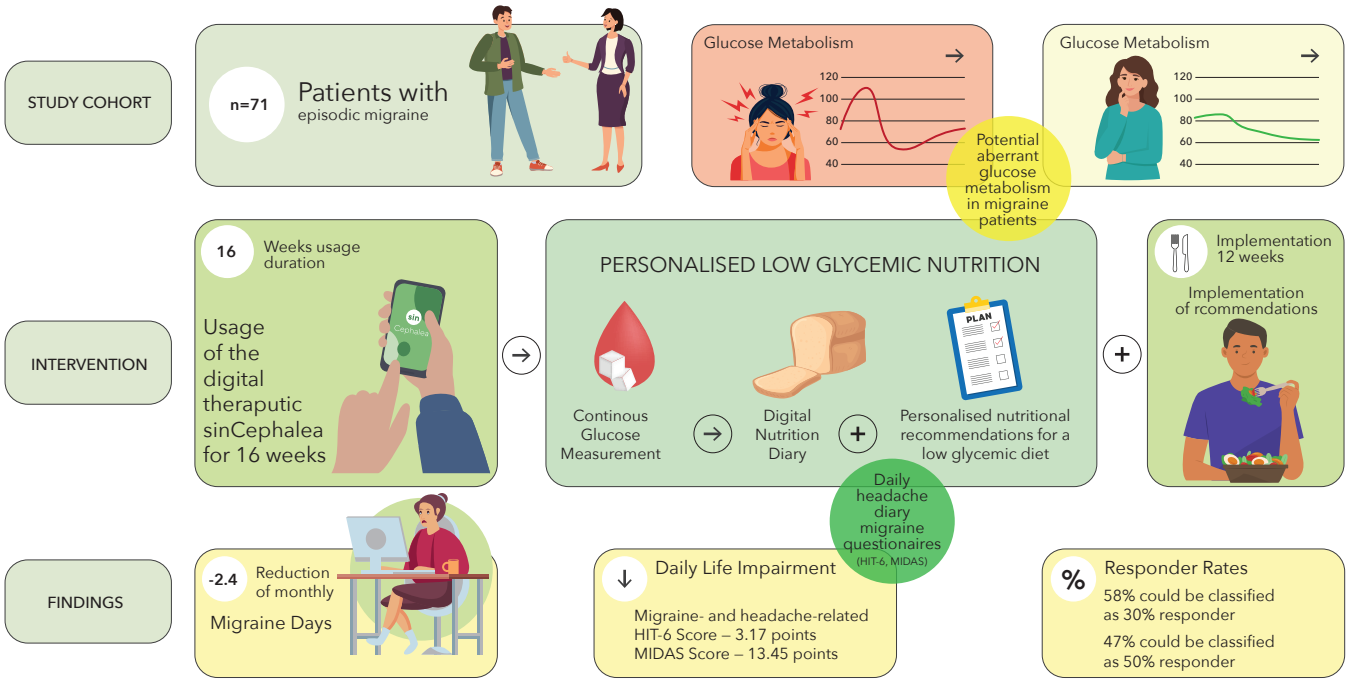


Figure 1: sinCephalea, a non-pharmacological, digital migraine prophylaxis in Lelleck et al. (2022)[11]

in omega-3 and omega-6 or high in omega-3 but with lower levels of omega-6 compared with people on diets with typical levels of the fats.[9]

Another study looking at levels of vitamins and other nutrients, found a significant relationship with Visual Analogue Scale (VAS) and pain duration, as well as Migraine Disability Score (MIDAS).[10]

Digital technology may be able to help people take advantage of personalised dietary modification to improve control of migraine symptoms or even prevent migraines occurring. For example, the digital therapeutic sinCephalea provides an individualised low-glycaemic diet based on continuous glucose measurement. It has been shown to reduce monthly migraine days by 2.40 days (95% confidence interval (CI) [−3.37; −1.42]), improve Headache Impact Test-6 (HIT-6) by 3.17 points (95% CI [−4.63; −1.70]) and MIDAS by 13.45 points (95% CI [−22.01; −4.89]) (Fig. 1).[11]

References

1. Gazerani P. A Bidirectional View of Migraine and Diet Relationship. Neuropsychiatr Dis Treat 2021;17:435–51.
2. Gazerani P. Diet and migraine: what is proven? Curr Opin Neurol 2023;36(6):615–21.
3. Gazerani P. Migraine and Diet. Nutrients 2020;12(6):1658.
4. European Brain Council (EBC). Disease Fact Sheets (www.braincouncil.eu/disease-fact-sheets; accessed 13 February 2024).
5. Jibril AT, Shab-Bidar S, Djafarian K, et al. Effect of Major Dietary Interventions on Migraine: a Systematic Review of Randomized Control Trials. SN Compr Clin Med 2022;4:185.
6. Neri LCL, Ferraris C, Catalano G, et al. Ketosis and migraine: a systematic review of the literature and meta-analysis. Front Nutr 2023;10:1204700.
7. Spekker E, Nagy-Grócz G. All Roads Lead to the Gut: The Importance of the Microbiota and Diet in Migraine. Neurol Int 2023;15(3):1174–90.
8. Parohan M, Djalali M, Sarraf P, et al. Effect of probiotic supplementation on migraine prophylaxis: a systematic review and meta-analysis of randomized controlled trials. Nutr Neurosci 2022;25(3):511–8.
9. Ramsden CE, Zamora D, Faurot KR, et al. Dietary alteration of n-3 and n-6 fatty acids for headache reduction in adults with migraine: randomized controlled trial. BMJ 2021;374:n1448.
10. Bahrampour N, Mirzababaei A, Yarizadeh H, et al. The relationship between dietary nutrients patterns and intensity and duration of migraine headaches. Br J Nutr 2023;129(6):947–54.
11. Lelleck VV, Schulz F, Witt O, et al. A Digital Therapeutic Allowing a Personalized Low-Glycemic Nutrition for the Prophylaxis of Migraine: Real World Data from Two Prospective Studies. Nutrients 2022;14(14):2927.

Does increased exercise decrease migraine?

Lotte Skytte Krøll, Physiotherapist, MPH, PhD
Department of Neurology, Danish Headache Center, Rigshospitalet, Glostrup, Denmark

According to the World Health Organization (WHO) recommendation for physical activity people should do aerobic exercise at a moderate intensity level, for at least 30 minutes, five days a week. Or, aerobic exercise three times a week for at least 25 minutes at a vigorous intensity level. For additional health benefits, strength exercise at a moderate or greater intensity at least twice a week is recommended.[1]

The recommendations would be quite hard to follow for many people, particularly for patients significantly affected by their headache.

Cross-sectional studies have found a positive association between physical activity levels and migraine prevalence. For example, an increased odds ratio of 4.4 for having migraine and coexisting tension-type headache with a low level of physical activity.[2] Hagen *et al.* found an increased odds ratio of 3.7 for having migraine with a low level of physical fitness.[3] Varkey *et al*. found an increased odds ratio of 1.4 for having migraine with a low level of physical activity compared with a high level of physical activity.[4]

Of course, we cannot draw causal relationships from these results. We need to look at longitudinal studies because we do not know whether engaging in a high level of physical activity will reduce migraine. There are a number of systematic reviews looking at the effect of aerobic exercise on migraine. An umbrella review by Varangot-Reille *et al.* published in 2022, was a systematic review of systematic reviews with or without meta-analysis. They found that with aerobic exercise, there was a moderate strength of evidence for migraine frequency, limited strength of evidence for duration and pain, and unclear evidence for quality of life.[5]

Beier *et al.* published a clinical guideline with a systematic review and a meta-analysis in 2021, with the aim of producing recommendations for or against a treatment strategy. They reviewed only randomised controlled trials (RCT) studies published after the release of the second version of The International Classification of Headache Disorders (ICHD) in 2004. They considered physical activity as one item, so, it could be a mixture of aerobic exercise, strength training, yoga, and Tai Chi, etc. Although, they actually found only studies of aerobic exercise. They found that physical activity might have a positive effect on quality of life, but it was a very low certainty of evidence. No adverse events were reported, and there were no negative effects. Patient preferences were taken into account when formulating the recommendations.[6] In 2023, La Touche *et al.* published a clinical practice guideline. Their aim was to formulate recommendations for prescribing exercise. They included a wide range of study designs, with no restrictions. They found a grade B recommendation for moderate-intensity aerobic exercise three times a week, which was likely to improve migraine frequency, might improve pain intensity and remotely improve duration and quality of life. They also found a grade B recommendation for yoga three times a week, which was likely to improve migraine frequency and disability and remotely improve pain and duration.[7]

The biological mechanism behind exercise-induced pain reduction is not fully understood. Some studies suggest the release of endorphins may result in pain reduction.[8] Release of endorphins may also make people feel happy or have a feeling of well-being. Exercising may make people feel they have a higher level of energy that then might reduce the negative impact of migraine on daily activities.[9] Fear of pain plays a huge role in the level of physical activity; migraine patients have shown to have a greater fear of pain compared with patients with tension-type headache.[10] That may lead to avoidance of physical activity, or a very low level of physical activity.[11] Exercise was reported as a migraine trigger for about 20% of patients with migraine.[12] Experimental studies have shown a higher proportion after doing a maximum exercise test, but two-thirds of participants did not develop migraine.[13,14]

So, it is possible to exercise between attacks. Indeed Ambrose *et al*. state that physical activity should be promoted, migraine or not,[15] because being sedentary might not necessarily improve migraine anyway, and may result in loss of strength and physical functioning.

Suddenly starting a high level of aerobic or high-intensity exercise may trigger a migraine.[14] Even so, there are other factors that may be to blame for the migraine – poor

sleep, stress, etc. Therefore, the recommendation is to start exercising gradually[15,16] supervised by health professionals who are knowledgeable about headache and exercising.[6] It is also important to educate patients and explain that flare-ups or aggravation are normal at the beginning. It is not dangerous and it is not a sign of new damage.[16,17]

The key is to start low and go slow.[15] Patients should begin with an activity they are actually motivated to do, such as brisk walking. The intensity level can be judged by the degree of breathing.[18] Headache patients experience good and bad periods and it is important to have a plan B for bad periods by reducing, for instance, walking distance or the intensity level.

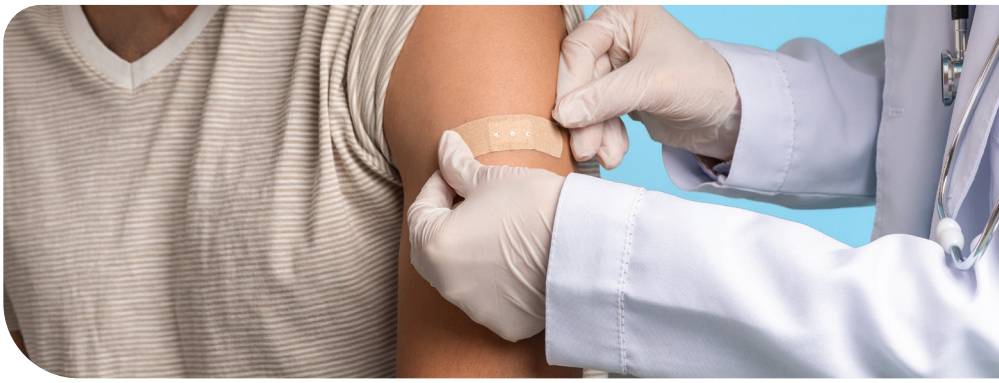
References

1. World Health Organization (WHO). Physical activity
2. (www.who.int/news-room/fact-sheets/detail/physical-activity; accessed December 2023).
3. Krøll LS, Hammarlund CS, Westergaard ML, et al. Level of physical activity, well-being, stress and self-rated health in persons with migraine and co-existing tension-type headache and neck pain. J Headache Pain 2017;18(1):46.
4. Hagen K, Wisløff U, Ellingsen Ø, et al. Headache and peak oxygen uptake: The HUNT3 study. Cephalalgia 2016;36(5):437–44.
5. Varkey E, Hagen K, Zwart JA, Linde M. Physical activity and headache: results from the Nord-Trøndelag Health Study (HUNT). Cephalalgia 2008;28(12):1292–7.
6. Varangot-Reille C, Suso-Martí L, Dubuis V, et al. Exercise and Manual Therapy for the Treatment of Primary Headache: An Umbrella and Mapping Review. Phys Ther 2022;102(3):pzab308.
7. Beier D, Callesen HE, Carlsen LN, et al. Manual joint mobilisation techniques, supervised physical activity, psychological treatment, acupuncture and patient education in migraine treatment. A systematic review and meta-analysis. Cephalalgia 2022;42(1):63–72.
8. La Touche R, Fierro-Marrero J, Sánchez-Ruíz I, et al. Prescription of therapeutic exercise in migraine, an evidence-based clinical practice guideline. J Headache Pain 2023;24(1):68.
9. Amin FM, Aristeidou S, Baraldi C, et al; European Headache Federation School of Advanced Studies (EHF-SAS). The association between migraine and physical exercise. J Headache Pain 2018;19(1):83.
10. Krøll LS, Sjödahl Hammarlund C, Gard G, et al. Has aerobic exercise effect on pain perception in persons with migraine and coexisting tension-type headache and neck pain? A randomized, controlled, clinical trial. Eur J Pain 2018. doi: 10.1002/ejp.1228 [Epub ahead of print].
11. Black AK, Fulwiler JC, Smitherman TA. The Role of Fear of Pain in Headache. Headache 2015;55:669–79.
12. Adams LM, Turk DC. Psychosocial factors and central sensitivity syndromes. Curr Rheumatol Rev 2015;11(2):96–108..
13. Pellegrino ABW, Davis-Martin RE, Houle TT, Turner DP, Smitherman TA. Perceived triggers of primary headache disorders: A meta-analysis. Cephalalgia 2018;38(6):1188–98.
14. Hougaard A, Amin FM, Hauge AW, et al. Provocation of migraine with aura using natural trigger factors. Neurology 2013;80(5):428–31.
15. Varkey E, Grüner Sveälv B, Edin F, et al. Provocation of Migraine after Maximal Exercise: A Test-Retest Study. Eur Neurol 2017;78(1–2):22–7.
16. Ambrose KR, Golightly YM. Physical exercise as non-pharmacological treatment of chronic pain: Why and when. Best Pract Res Clin Rheumatol 2015;29(1):120–30.
17. Woldeamanuel YW, Oliveira ABD. What is the efficacy of aerobic exercise versus strength training in the treatment of migraine? A systematic review and network meta-analysis of clinical trials. J Headache Pain 2022;23(1):134.
18. Rice D, Nijs J, Kosek E, et al. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. J Pain 2019;20(11):1249–66.
19. Krøll LS, Hammarlund CS, Linde M, et al. The effects of aerobic exercise for persons with migraine and co-existing tension-type headache and neck pain. A randomized, controlled, clinical trial. Cephalalgia 2018;38(12):1805–16.

Continuous headache post Covid

Anne Hege Aamodt,
Chief Physician at the Headache Clinic, Associate Professor, Department of Neurology, Oslo University Hospital, Rikshospitalet, Oslo; Chair of the Scientific Advisory Board, The Norwegian Centre for Headache Research, Department of Neuromedicine and Movement Science, NTNU, Trondheim, Norway

Headache is the fourth most common neurological symptom in COVID-19 and it usually occurs very early on.[1] The intensity and frequency of headache is commonly worse in association with the vaccine against SARS-CoV-2.[2,3]



Headache can last for some time after COVID-19 infection. For example, a multicentre nine-month follow up study for tertiary-level hospitals with more than 900 patients, found that the median duration of post-COVID-19 persistent headache lasted for a median 14 (6–39) days but persisted after 3 months in 19% (95% confidence interval (CI): 16.5–21.8%) and after 9 months in 16% (95% CI: 13.7–18.7%) of participants. Headache intensity during the acute phase was associated with a more prolonged duration of headache (hazard ratio (HR) 0.66; 95% CI 0.58–0.74).[4] A case series of 31 patients with new or worsening headaches after COVID-19 found a headache duration of 7.4±4.8 months after infection: 74% met The International Classification of Headache Disorders ICHD-3 criteria for migraine and 65% for chronic migraine – only 16% met these criteria before COVID-19 infection.[5]

There are many reports that headache is among the most common symptoms after vaccination against SARS-CoV-2 and that they can occur after the first or the second dose.[6] However, there is not much information regarding long-lasting headache after vaccination.[7,8]

Headache attributed to SARS-CoV-2 infection has a prevalence of 50% in the acute phase, and headache attributed to SARS-CoV-2-vaccination has a prevalence of 40%, both are most prevalent in the young. Prevalence is highest in females with long-lasting headache and after vaccination, and it is more common in people with previous headache.[3] New-onset headache after COVID-19 infection has also been documented.[9]

In Norway, a multicentre prospective observational study of neurological symptoms in COVID-19 positive patients has been undertaken. Results are yet to be published, but the aim is to study the natural course and to characterise the long-term functional impairment of patients with neurological symptoms 6 and 12 months after COVID-19 infection. A substudy of headache 6 and 12 months after COVID-19 infection is also planned.

Another study (CovaxHEAD; NCT05235776) aims to describe the characteristics of severe new-onset headache after COVID-19 vaccine and the treatment effects.

References

1. García-Azorín D, Abildúa MJA, Aguirre MEE, et al. Neurological presentations of COVID-19: Findings from the Spanish Society of Neurology neuroCOVID-19 registry. J Neurol Sci 2021;423:117283.
2. Kuan AS, Chen SP, Wang YF, Wang SJ. Prolonged headache with vaccine- and dose-specific headache pattern associated with vaccine against SARS-CoV-2 in patients with migraine. Cephalalgia 2023;43(10):3331024231208110.
3. Caronna E, van den Hoek TC, Bolay H, et al. Headache attributed to SARS-CoV-2 infection, vaccination and the impact on primary headache disorders of the COVID-19 pandemic: A comprehensive review. Cephalalgia 2023;43(1):3331024221131337.
4. Garcia-Azorin D, Layos-Romero A, Porta-Etessam J, et al. Post-COVID-19 persistent headache: A multicentric 9-months follow-up study of 905 patients. Cephalalgia 2022;42(8):804–9.
5. Moskatel LS, Smirnoff L. Protracted headache after COVID-19: A case series of 31 patients from a tertiary headache center. Headache 2022;62(7):903–7.
6. Castaldo M, Waliszewska-Prosół M, Koutsokera M, et al. Headache onset after vaccination against SARS-CoV-2: a systematic literature review and meta-analysis. J Headache Pain 2022;23(1):41.
7. Cocores AN, Goadsby PJ, Monteith TS. Post-vaccination headache reporting: Trends according to the Vaccine Adverse Events Reporting System. Headache 2023;63:275–82.
8. van der Arend BWH, Bloemhof MM, van der Schoor AG, et al. Effect of COVID vaccination on monthly migraine days: a longitudinal cohort study. Cephalalgia 2023;43(9):3331024231198792.
9. Torrente A, Alonge P, Di Stefano V, et al. New-onset headache following COVID-19: An Italian multicentre case series. J Neurol Sci 2023;446:120591.

Management of patients with more than one headache diagnosis

Faisal Mohammad Amin,
Chief Consultant Neurologist and Associate Professor, Danish Headache Center,
Department of Neurology, Copenhagen University Hospital - Rigshospitalet, Denmark

There are no randomised clinical trials of patients with more than one primary headache diagnosis. Therefore, Professor Amin explained that his views were based on clinical experience, rather than formal evidence. First, it is important that clinicians know the headache criteria by heart, so they are able to easily and accurately diagnose the different types of headaches in their patients.

In clinic, we typically see patients with overlapping tension-type headache, medication overuse headache and migraine. Indeed, medication overuse headache is diagnosed only in the context of an existing primary headache disorder. So, by definition, it is always a co-diagnosis. In fact, it is not strictly correct to say there are no studies looking at two headache diagnoses at the same time, because patients who participated in medication overuse headache trials had, by definition, two headache diagnoses. Indeed, it is very rare to see a patient with only tension-type headache or a patient with migraine without a tension-type headache. Thus, in migraine and tension-type headache studies, most patients will have both diagnoses, but only one is typically evaluated.

In clinical practice, amitriptyline is used for both migraine and tension-type headache. Amitriptyline is therefore the drug of choice in patients with concomitant migraine and tension-type headache. However, one might wonder how strong the evidence is. A novel meta-analysis by the European Headache Federation looked at amitriptyline and its value in migraine prevention, and found that it may have a prophylactic role in migraine patients,[1] but the studies were not robust. A large-scale, randomised clinical trial is needed to test how it really affects patients with migraine. A study published almost 30 years ago by Bendtsen *et al*. found that amitriptyline was effective in chronic tension-type headache, reducing the number of headache days per month from a baseline of 24.7 days to 18.6 days. On the other hand, placebo reduced the headache days to 21.7. Nevertheless, there was a small, but statistically significant difference between amitriptyline and placebo.[2]

Many patients ask for botulinum toxin A, when conventional treatments fail for migraine and tension-type headache. While there is robust evidence for the effect of botulinum toxin A for migraine, the effect of botulinum toxin A on tension-type headache is still a matter of debate. A 24-week study of botulinum toxin A found that it reduced the number of headache days by 8.4 and migraine days by 8.2 compared with, respectively, 6.6 and 6.2 days for placebo.[3] A meta-analysis showed botulinum toxin A to be effective in tension-type headache reducing the number of headache days by 2.8 per month.[4] However, the number of participants in the studies included were small, numbering 11, 12 and 14 in three of them, for example.

Turning to CGRP monoclonal antibodies a real-world study from the Danish Headache Center found that 65% (n=58) of patients treated with fremanezumab achieved at least a 30% reduction in monthly migraine days, 51% (n=45) had at least a 50% reduction, and 24% (n=21) had at least a 75% reduction. These patients started with a mean (SD) of 18.5 (±7.4) migraine days per month and 24.3 (±5.8) headache days each month. There was a similar reduction in monthly headache days as well.[5] Another larger real-world study involving 273 patients with chronic migraine treated with erenumab found similar results.[6] Taken together, these results suggest that CGRP monoclonal antibodies only reduce migraine days and not days with, for instance, tension-type headache.

References

1. Lampl C, Versijpt J, Amin FM, et al. European Headache Federation (EHF) critical re-appraisal and meta-analysis of oral drugs in migraine prevention-part 1: amitriptyline. J Headache Pain 2023;24(1):39.
2. Bendtsen L, Jensen R, Olesen J. A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. J Neurol Neurosurg Psychiatry 1996;61(3):285–90.
3. Dodick DW, Turkel CC, DeGryse RE, et al; PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50(6):921–36.
4. Dhanasekara CS, Payberah D, Chyu JY, et al. The effectiveness of botulinum toxin for chronic tension-type headache prophylaxis: A systematic review and meta-analysis. Cephalalgia 2023;43(3):3331024221150231.
5. Cullum CK, Chaudhry BA, Do TP, Amin FM. Real-world efficacy and tolerability of fremanezumab in adults with chronic migraine: a 3-month, single-center, prospective, observational study. Front Neurol 2023;14:1226591.
6. Cullum CK, Do TP, Ashina M, et al. Real-world long-term efficacy and safety of erenumab in adults with chronic migraine: a 52-week, single-center, prospective, observational study. J Headache Pain 2022;23(1):61.

Anti-CGRPs, should I stay or should I go?

Messoud Ashina,
Professor of Neurology, Danish Headache Center and Department of Neurology, University of Copenhagen, Rigshospitalet Glostrup, Denmark

Tailoring treatment to individual patient profiles is a growing focus in medicine. A real-world study by Raffaelli and colleagues identified clinical characteristics in responders and non-responders to CGRP receptor monoclonal antibodies (CGRP receptor mAbs), such as unilateral headache and nausea.[1] Dr Sait Ashina also found that 79% of galcanezumab responders did not have allodynia, compared with 21% who did.[2]

A scoping review and meta-analysis by Hong reported a good response to triptans as predictive of a positive response to CGRP receptor mAbs. Moreover, the number of prior preventive medications seems to inversely correlate with the likelihood of responding to a CGRP receptor mAb.[3] However, patients with two to four previous therapy failures often respond well in clinical practice.

Psychiatric comorbidities like anxiety, depression, and sleep disorders are more common in individuals with migraine.[4,5] These comorbidities might indicate lower treatment efficacy.[3] The UNITE study, a randomized controlled trial, evaluated fremanezumab's efficacy in patients with migraine and major depressive disorder (MDD), demonstrating significant migraine reduction.[6,7]

In a real-world study, fremanezumab showed efficacy within one month, improving over six months, even in patients with challenging migraine profiles.[8] However, guidelines for CGRP mAbs vary internationally, with different criteria for prescribing and continuing therapy.[9–13]

CGRP mAbs are categorized as anti-ligand (galcanezumab, fremanezumab, eptinezumab) and anti-receptor (erenumab). Some studies suggest anti-ligand mAbs may be more effective.[14] Switching from receptor- to ligand-targeting CGRP pathway mAbs might reduce migraine frequency, as indicated by recent studies.[15,16] Updated European Headache Federation guidelines recommend individualized treatment decisions, considering the patient's history, comorbidities, and disease burden.[17] They suggest including CGRP pathway mAbs as a first-line treatment option and considering antibody switch in case of inadequate response. However, caution is advised in patients with vascular risk factors, Raynaud's phenomenon, or severe constipation.[17]

This body of research underscores the complexity of migraine treatment and the need to consider individual patient profiles, previous treatment responses, and comorbidities when prescribing CGRP mAbs.

References

1. Raffaelli B, Fitzek M, Overeem LH, et al. Clinical evaluation of super-responders vs. non-responders to CGRP(-receptor) monoclonal antibodies: a real-world experience. J Headache Pain 2023;24(1):16.
2. Ashina S, Melo-Carrillo A, Szabo E, et al. Pre-treatment non-ictal cephalic allodynia identifies responders to prophylactic treatment of chronic and episodic migraine patients with galcanezumab: A prospective quantitative sensory testing study (NCT04271202). Cephalalgia 2023;43(3):3331024221147881.
3. Hong JB, Lange KS, Overeem LH, et al. A Scoping Review and Meta-Analysis of Anti-CGRP Monoclonal Antibodies: Predicting Response. Pharmaceuticals (Basel) 2023;16(7):934.
4. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. Neurol Clin 2019;37(4):631–49.
5. Smitherman TA, Penzien DB, Rains JC. Migraine and Psychiatric Comorbidity. Psychiatric Times 2013;30.
6. Lipton R, Barbanti P, Ramirez Campos V, et al. Efficacy of fremanezumab in reducing depression in patients with migraine and major depressive disorder: results of the UNITE study. Headache 2023;63(Suppl 1):133.
7. Lipton RB, Ramirez Campos V, Galic M, et al. A Phase 4 Study of Fremanezumab for Preventive Migraine Treatment in Patients With Major Depressive Disorder: Baseline Patient Characteristics in UNITE. Cephalalgia 2022;42(1S):99.
8. Driessen MT, Cohen JM, Thompson SF, et al. Real-world effectiveness after initiating fremanezumab treatment in US patients with episodic and chronic migraine or difficult-to-treat migraine. J Headache Pain 2022;23(1):56.
9. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17(11):954–76.
10. Lundbeck Seattle BioPharmaceuticals Inc. Vyepti (package insert) 2022.
11. Ashina M, Lanteri-Minet M, Pozo-Rosich P, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol 2022;21(7):597–607.
12. Silberstein S, Tfelt-Hansen P, Dodick DW, et al; Task Force of the International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia 2008;28(5):484–95.
13. Tassorelli C, Diener HC, Dodick DW, et al; International Headache Society Clinical Trials Standing Committee. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. Cephalalgia 2018;38(5):815–32.
14. Schiano di Cola F, Bolchini M, Ceccardi G, et al. An observational study on monoclonal antibodies against calcitonin-gene-related peptide and its receptor. Eur J Neurol 2023;30(6):1764–73.
15. Straube A, Broessner G, Gaul C, et al. Real-world effectiveness of fremanezumab in patients with migraine switching from another mAb targeting the CGRP pathway: a subgroup analysis of the Finesse Study. J Headache Pain 2023;24:59.
16. Lambru G, Caponnetto V, Hill B, et al. Long-Term Effect of Switching From an Anti-CGRP Receptor to an Anti-CGRP Ligand Antibody in Treatment-Refractory Chronic Migraine: A Prospective Real-World Analysis. Neurotherapeutics 2023;20:1284–93.
17. Sacco S, Amin FM, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update. J Headache Pain 2022;23(1):67.

Nordic Migraine Symposium 23

Teva Denmark A/S
Vandtårnsvej 83A
2860 Søborg,
Denmark

Teva Denmark