Nordic Migraine Symposium 24

Summary Report

Breaking Boundaries in Migraine Management: from Controversies to Innovations

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Anti-CGRP therapies: similar but not the same

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An understanding of the basic pharmacodynamics and pharmacokinetics of drugs can provide useful insights into the clinical effects and therefore their utility for patients.

Pharmacology has a number of important implications for clinical use of drugs. For example, drug half life determines how long a drug persists in the body after a course of treatment has finished. Calcitonin gene-related peptide (CGRP) receptor antagonists (gepants) have a plasma half-life of around 5–11 hours whereas the plasma half-life of anti-CGRP monoclonal antibodies can be around 4 weeks. Assuming a drug is cleared from the body in five half-lives, gepants can persist for 1-2 days compared with about 5 months for monoclonal antibodies. That information will be useful when considering drug treatment for women who plan to become pregnant, for example. [1,2]

Receptor binding is perhaps not as straightforward as it may seem. Gepants, for example, bind not only to CGRP receptors but also to receptors that resemble the CGRP receptor such as the amylin receptor. So even when CGRP receptors are not available the drugs may exert some effect via different receptors.[1-3] This may also explain why gepants added to treatment with erenumab[3] micromolar monoclonal antibody show an enhanced effect even though the two types of drug ostensibly target the same receptor, or an alternative explanation is that the drugs act differently at the same receptor. Clinically this information could suggest[4] that patients treated with erenumab might benefit from acute treatment with gepants. More research is needed in this area, particularly in terms of cardiovascular safety.

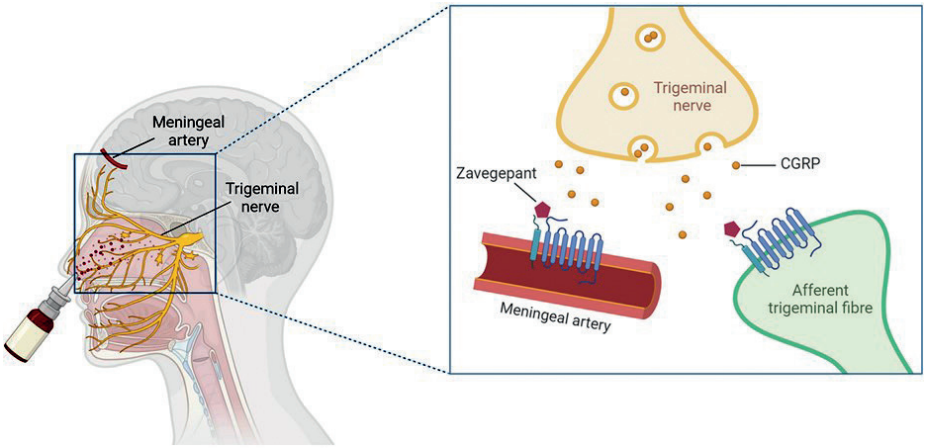

Figure 1. Does nasal administration of zavegepant have direct trigeminovascular effects? NB: Zavegepant is not approved in the EU. Reproduced from Boucherie et al. (2024)[5]

On the face of it the route of administration – oral or intranasal – does not seem to influence efficacy except perhaps in the case of a patient who is vomiting for whom the nasal route may be preferred. However, if systemic concentration of drug alone predicts efficacy then the efficacy of zavegepant should be lower than gepants given orally. However, the observed efficacy of zavegepant is similar to oral gepants. The finding implies that zavegepant may have a direct trigeminovascular effect in addition to a systemic effect.[5]

Basic research suggests that patient characteristics may also have a significant effect on the efficacy of anti-migraine drugs. Variation in receptor expression may explain differences in response to gepants between patients, particularly for patients who may have a higher expression of adrenomedullin receptors, which also mediate relaxation of human middle meningeal arteries, thought to play a role in the pathophysiology of migraine.[6]

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When to evaluate effectiveness? Anti-CGRPs and gepants

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There is no definitive guidance on when to evaluate the effectiveness of anti-migraine therapies, in part because of the lack of biomarkers.

European and American guidelines suggest anti-CGRP monoclonal antibodies should be evaluated after 3 months and after 6 months in selected patients. For gepants the US guidelines suggest evaluation after 8 weeks and switch treatment if they are not effective. Partial responders could benefit from 6–12 months treatment.[1,2]

A 5-year follow-up study of erenumab showed a mean change from baseline in monthly migraine days of 5.3 days, with most of the effect appearing to happen relatively early. The 50% response in last 2 years after the dosage adjustment was also quite stable.[3]

Real world data for fremanezumab suggest that we should wait 3 months before evaluation of efficacy at least for episodic migraine. Twelve-month extension data, with patients blinded to monthly or quarterly injections, showed that more than half of the patients with chronic migraine and approximately two-thirds of those with episodic migraine had a 50% reduction or more from baseline to month 12.[6] Comparing proportion of 50% responders at the third month with the 12th month of treatment there appears to be an increase of 9 percentage points in the chronic migraine group and 7 percentage points in the episodic migraine group.[5] However, it should be noted that due to the nature of the study, we do not have data on the therapeutic gain at these data points.

In terms of blinded data beyond 3 months treatment, the STRIVE study showed that the overall erenumab treatment resulted in a relatively modest reduction in the number of migraine days each month when comparing month 3 and month 6 data, with similar gains from treatment with 70 mg or 140 mg dosages. With a 140 mg dosage the difference between drug and placebo was 1.8 monthly migraine days at month 3 and 1.9 monthly migraine days at month 6.[6] So there is not much overall additional effect to be gained between month 3 and month 6.

The 50% responder rate in the 70 mg group in the STRIVE study increases from 41.3% to 47.1% and from 48.1% to 49.1% in the 140 mg group. Compared with placebo the therapeutic gain (i.e. difference in effect between placebo and drug) increases in 70 mg from 15 percentage points at month 3 to 17.7 percentage points at month 6. In contrast, for the 140 mg group, there was a reduction of 2.1 percentage points in the therapeutic gain during the same time interval.

In the EVOLVE-1 study of episodic migraine after 6 months treatment with galcanezumab 120mg the therapeutic gain was 1.8 fewer monthly migraine days than the placebo group, similar to the gain seen at month 3.[7]

Eptinezumab 100 mg and 300 mg dosages were compared with placebo in patients who had failed previous treatment for episodic or chronic migraine in the DELIVER study. Infusions were given at day 0 and week 12. At 3 months those who received eptinezumab 300 mg showed a therapeutic gain of 36% when comparing 50% responder rates. After 6 months the therapeutic gain was 35%.[9]

In a placebo-controlled 48-week PROMISE-1 study in patients with episodic migraine treatment with eptinezumab resulted in a decrease in monthly migraine days from baseline through to 48 weeks; 50% responder rates also increased over the same period. Looking at the therapeutic gap, however, there was no increase in the percentage response over the 48 weeks.[9,10]

Registry data from Italy on patients with chronic migraine show that 63.2% respond by week 12 of treatment with anti-CGRP monoclonal antibodies and a further 15.3% respond by week 24 of treatment. An additional 7.4% had a so-called ultra-late persistent response after week 24 up to week 48, with 6.4% having a non-persistent ultra-late response during the same period.[11]

Predicting response to treatment

There has been some work trying to predict response to anti-migraine treatments.

One group found that a 50% or greater response at 6 months was associated with:[12]

- Older age
- Unilateral headache
- Absence of depression
- Less concomitant oral medication

While another group found that late responders had:[13]
- Higher BMI
- More frequent treatment failures
- Psychiatric comorbidities
- Less common unilateral pain
- Unilateral cranial autonomic symptoms
- Allodynia

Effectiveness of gepants

In the ADVANCE study with atogepant for prevention in episodic migraine, there was a therapeutic gain for the 60 mg dosage at 12 weeks of 1.7 monthly migraine days compared with placebo.[14] An open label study of the drug in patients with episodic migraine showed a change from baseline of 5.2 monthly migraine days at 52 weeks for a dosage of 60 mg, with a sustained response over the 12 months of the study. The 50% responder rate also increases gradually from the first to the 12th month.[15]

Similar therapeutic gains are seen in patients with chronic migraine treated with atogepant 60 mg over 12 weeks.[16]

Contextual effects (including the effect of placebo) make a significant contribution to the benefit gained from treatment with anti-migraine drugs – estimated to be around two-thirds of the effect seen in trial involving anti-CGRP monoclonal antibodies according to some research.[17] If that is true then it may be difficult to predict the exact timing of the biological effects of drugs and as migraine is a fluctuating condition and patients tend to start treatment at the time of peak symptom frequency the effect of medication itself might be more difficult to interpret from open label data.

Based on the data we have there is a case for evaluating anti-CGRP monoclonal antibodies at 3 months, and for some patients there might be a case for evaluating the effects at 6 months. The data for gepants are less clear as most of the effect occurs in the first week, with limited evidence for an effect at month 2 or 3. For patients the effect of a drug may be measured in terms beyond just a reduction in migraine days (see Table 1).

1. Number of headache days (mild, moderate and severe)
2. Duration of attacks
3. Change in response to acute medication
5. Change in aura frequency (if relevant)
6. Change in postdromal symptoms (severity and duration) and interictal symptoms
7. Frequency reduction in month 3 compared with baseline
8. HIT-6
9. PGIC (seven-item patient global impression of change)

Table 1. Variables to consider when evaluating efficacy

Therefore clinicians need to use clinical knowledge as a basis for clinical craftmanship to individualize treatment for each patient. Also, until there are solid data proving otherwise, as the drugs in question have few side effects and migraine is a chronic disorder, we need to invest a few extra months of treatment in those patients where we see a pattern of response that both we and the patient acknowledge as meaningful.

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When to switch? Anti-CGRPs and gepants

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Guidelines and medicine licensing vary from country to country in Europe, however, in Germany switching between migraine treatments when there is a lack of response is recommended in guidelines. For example, it is recommended to switch in cases of failed response especially when the switch is between drug class such as from a CGRP receptor monoclonal antibody to a CGRP ligand monoclonal antibody.

Around a third of a group of 25 patients who switched after not responding to 3 months treatment with erenumab had a clinically meaningful response of more than a 30% reduction in monthly headache days after 3 months treatment with fremanezumab or galcanezumab. Among those who did not respond after switching treatment were patients with daily or continuous headache who are among the most challenging to treat.[1]

Patients who switched from fremanezumab or galcanezumab to erenumab showed a similar response with around a third of those who switched having a positive response of a reduction in monthly headache days of 30% or more.[2]

The FINESSE study looked at 153 patients who switched from erenumab or galcanezumab to fremanezumab (Figure 1). Of those who switched, 42.8% (n=59) saw a 50% or greater reduction in monthly migraine days from baseline – 48% (n=36) of those with episodic migraine and 36.5% (n=23) of those with chronic migraine.[3]

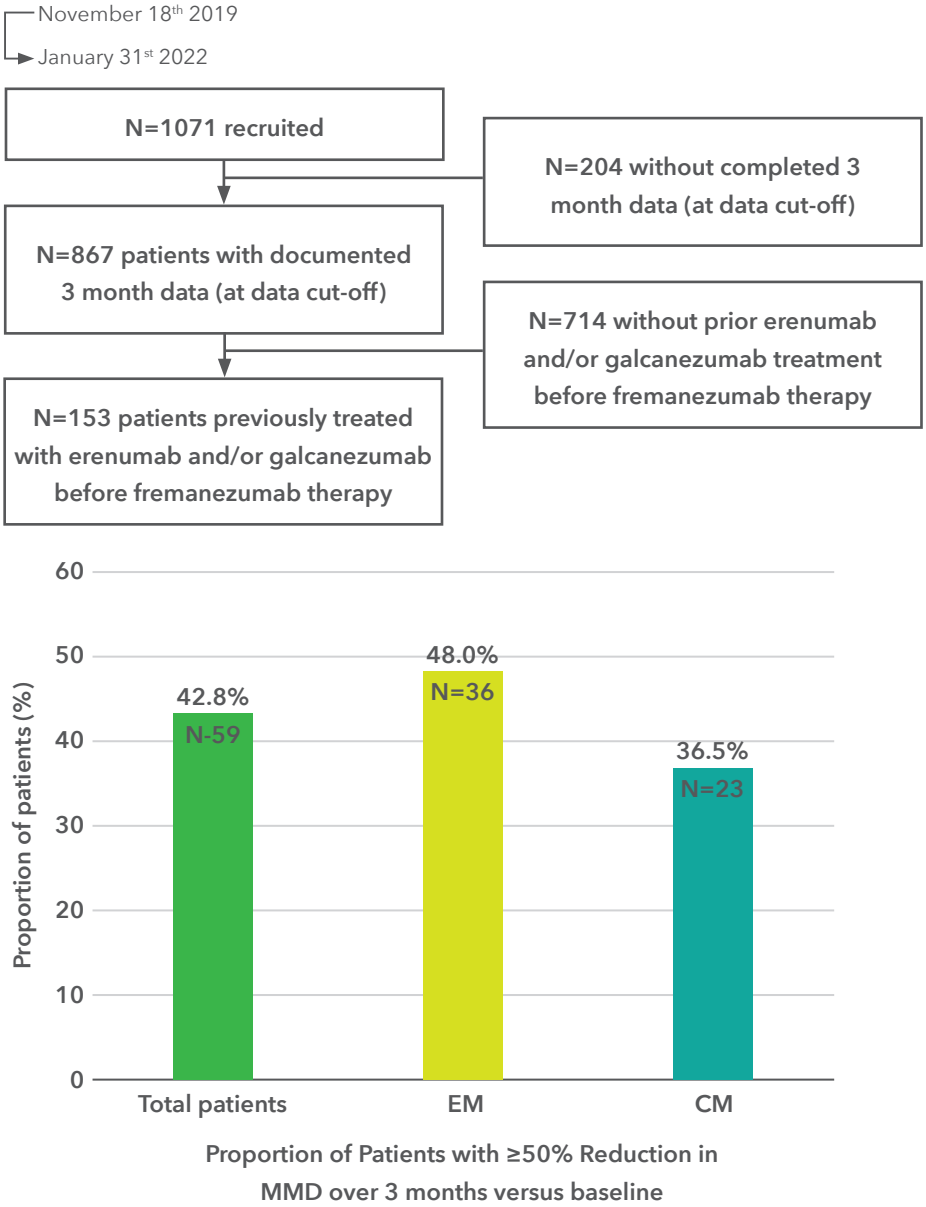

Figure 1. FINESSE study: switch from erenumab/galcanezumab to fremanezumab. Reproduced from Straube et al. (2023)[3]

Some patients who do not respond to erenumab and at least one CGRP ligand monoclonal antibody (i.e. galcanezumab and/or fremanezumab) may benefit from treatment with intravenous eptinezumab. For example, 41 patients treated with epitinezumab 100 mg, 38 of whom received a second infusion after week 12, when 29 received 300 mg and nine received 100 mg. Monthly migraine days decreased from 16.3 (SD ±8.0) at baseline to 15.4 (SD ±8.1) days during weeks 9–12 and 14.4 (SD ±8.0) days

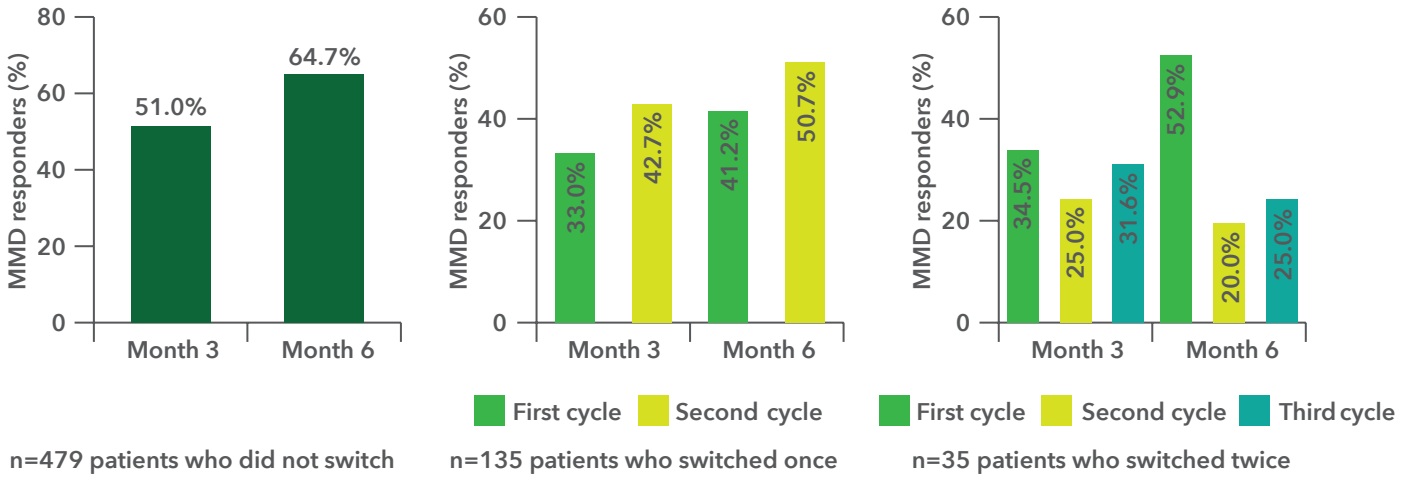

Figure 2. NTD Migraine Registry: response rates are lower in switchers than in non-switchers. Redrawn from Hong et al. (2024)[5]

during weeks 21–24 (p=0.07). Eleven patients (29.7%) reported a 30% or greater reduction in monthly migraine days during weeks 21–24 compared with baseline, with two patients (5.4%) achieving a reduction of 50% or more.[4]

Although switching treatment is helpful for some patients who have not responded to treatment there are some negatives. For example, overall response rates are lower in patients who switch treatment than they are among those who do not switch (Figure 2)[5] and response rates decrease with every switch.[6]

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Does vestibular migraine exist? A case in favour

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Migraine with vertigo was first described in the literature about 150 years ago by Edward Liveing[1] and the clinical features of migraine have been elucidated in several large case series, most of which have been published in the last 25 years.[2-8] So it is not new, just newly recognised.

The term vertigo encompasses different descriptions of what patients actually experience and must not be confused with dizziness.

Vestibular migraine is recognised as a diagnosis by the International Headache Society and the Barany Society, which promotes the development of an implementable classification of vestibular disorders. Symptoms associated with migraine can happen before, during or after the vestibular symptom and one symptom is enough during one episode and different symptoms can occur in different episodes – they do not have to be stereotypical. However, some patients with vestibular migraine do not have headache or they have mild headache and around a third of patients have isolated vertigo attacks.[9] The duration of episodes is highly variable – from seconds to several days.[5,8]

Vestibular migraine is the most common cause of spontaneous (non-positional) episodic vertigo. It has a lifetime prevalence in general adult population of 1–3%. Around 25% of adults with migraine could be diagnosed with vestibular migraine but the delay in diagnosis is as long as 8.4 years after the first onset of migraine. It can happen at any age and may be a precursor of migraine. In postmenopausal women migraine attacks can be replaced by isolated vertigo attacks. Being a young woman with comorbid anxiety or depression, and having a previous head trauma, significantly increases the odds for experiencing vestibular migraine.[6,10-12]

A meta-analysis in migraine patients showed that about one third of patients experienced dizziness (35.7%) or vertigo (33.9%) either in the prodromal or in the headache phase.[13]

Clinically it has been found that 8.6–66% of patients have central vestibular ocular motor abnormalities during the interictal phase. During attacks no difference have been observed in the distribution of central and peripheral vestibular signs but 70% of those with vestibular migraine had pathological nystagmus compared with 34% of patients with migraine.[14,15]

Migraine with brainstem aura is recognised as a distinct diagnosis in the headache classification. It requires at least two reversible brainstem symptoms, each lasting from 5 to 60 minutes (in addition to visual, sensory or dysphasic aura symptoms). When asked most (60%) patients say they have vertigo. Other symptoms include dysarthria, tinnitus, hypacusis, diplopia, ataxia not attributable to sensory deficit and decreased level of consciousness.[5] However, most patients do not mention other symptoms they have, so if clinicians do not ask them, this diagnosis will be missed.

Currently the diagnosis of vestibular migraine relies on the same principles as for the other subtypes of migraine: history of migraine; temporal association, and exclusion of other causes.[4,6-8,16] Differential diagnosis must be borne in mind when diagnosing vestibular migraine, including benign paroxysmal positional vertigo (BPPV), Meniere's disease, vertebrobasilar transient ischaemic attack (TIA), vascular compression of the eighth nerve, autoimmune inner ear disease, Schwannoma of the eighth nerve, anxiety disorder and functional neurological disorder.

In conclusion, although dizziness and vertigo are common in migraine, vestibular migraine is a separate disorder.

So it is important to diagnose vestibular migraine – it requires no additional (or repeated) testing and migraine therapy might be effective.

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Does vestibular migraine exist? A case against

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Vestibular migraine is not yet a validated entity, and has not earned its place in the core section of the Classification. Moreover, there is no robust discriminator for the disease.

Migraine, as we know, is not a single entity and dizziness and vertigo are hallmarks of the disease.[1] Dizziness or vertigo, for example, have been recorded as a premonitory symptom in a fifth to a third of patients with migraine.[2]

However, one of the grey zones in the criteria for vestibular migraine is the uncoupling of vestibular episodes and headache, where it is accepted that only 50% of the vestibular episodes should be accompanied by one or more migraine features.[3] That uncoupling is strange because it is not accepted for any other associated migraine symptom. Indeed, we see very few patients with isolated attacks of photo- or phonophobia or nausea. We do not accept that as being part of the migraine spectrum, so why would we accept that for vestibular episodes?

The concept of chronification does not seem to apply to vestibular migraine as it is defined as an episodic disorder.

One of the reasons given is that it is difficult to distinguish between so-called chronic vestibular migraine, motion sickness and comorbid persistent postural-perceptual dizziness, the latter being a functional disorder.[3]

There are very few randomized controlled trials in vestibular migraine. One of these is the PROVEMIG study with metoprolol, which was negative,[4] in contrast to the many trials with beta-blockers in patients with migraine.

The INVESTMENT trial looked at the effect of galcanezumab in vestibular migraine in 17 patients. The effect on vestibular migraine was positive but the drug also had a positive effect on headache test.[5] So it could be seen as a headache trial as well.

Accepting vestibular migraine as a valid diagnosis could be viewed as part of a slippery slope that changes clinical practice by accepting dizziness or vertigo as cardinal symptoms of migraine. That could conceivably lead to the misdiagnosis of conditions such as vertebral artery dissection where headache and dizziness are the two core features that may be misdiagnosed as vestibular migraine.[6]

The International Classification of Headache Disorders includes an appendix for a number of orphan disorders that need validation and that is perhaps where vestibular migraine belongs at present.[7]

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Do we need drug holidays? A case in favour

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Clinical experience shows drug holidays do benefit patients and in some countries they are mandatory. So the question is not should we have drug holidays but how should they be designed.

Most patients do not want to take a drug holiday so clinicians need to explain the reasons for them and treatment, including drug holidays, should be tailored to each individual patient. Initially in Denmark the requirement was for a drug holiday for 2 months every year but many patients found their migraine became worse so the requirement was changed to a 1-month drug holiday every 18 months.

Over time up to 10% of patients experience complete remission of their symptoms in a year no longer requiring treatment.[1] Partial remission, seen in around 3% of patients,[1] may be due to spontaneous improvement rather than drug treatment.[2,3]

There are a number of reasons why drug holidays should be considered. For example, there is no evidence that CGRP monoclonal antibodies are disease modifying so stopping treatment for periods of time will have no detrimental effect on patients.

Migraine patients are typically treated for long periods of time and as they age they are likely to experience other conditions, such as myocardial infarction, for which some antimigraine drugs may be problematic. Other life events that occur such as pregnancy may also be challenging for migraine treatment. Also, with prolonged use the potential for as yet unknown side effects to emerge increases.

It is important not to treat patients who will not benefit from treatment to avoid pathologizing them unnecessarily. Healthcare resources need to be optimised and waste reduced by using only medicines that are necessary for patients who need them.

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Do we need drug holidays? A case against

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Discontinuing treatment frequently leads to a significant increase in migraine frequency and medication use.

Patients who interrupted prophylactic treatment with an CGRP inhibitor for three months documented a marked increase in both migraine days and analgesic use, despite earlier clinical improvements.[1]

A study by Gantenbein et al. showed that the migraine days more than doubled 3 months after treatment interruption of CGRP inhibitor treatment.[2] Continuous prophylactic therapy should therefore be prioritised over periodic treatment cessation to maintain optimal disease control and prevent relapse.

The cost of CGRP inhibitors, which some people argue are expensive when used continuously, should be seen in the context of the cost of people being sick as a result of a drug holiday: so which is more expensive, a once-a-month injection or a day off sick leave from work?

These treatments are obviously beneficial, after all who would voluntarily inject themselves every month if they did not benefit.

The idea that long-term drug treatment increases the risks of side effects is countered by the observation that all CGRP inhibitors have good tolerability profiles and there is no evidence that prolonged use results in tolerance to the drugs.

Treatment interruption for good clinical reasons makes sense but patients should be involved in the decision – the idea of an enforced regular drug holiday was rejected by the patient organisation in Norway and the government agreed.

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Trigeminal autonomic cephalalgias or migraine?

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There is a degree of overlap in symptoms between trigeminal autonomic cephalalgia and migraine. Patient descriptions of their symptoms vary and there is evidence that a proportion of patients (5–75%) with migraine have cranial autonomic symptoms, which clinicians may miss because they may not specifically ask patients about them.[1,2]

Autonomic features are common in patients with cluster headache, but they also have migraine symptoms such as allodynia, photophobia, vomiting, etc.[3]

Despite the overlap in symptoms migraine and cluster headache are distinct diseases. Features such as duration and frequency of attacks are important in making the distinction.[4,5]

There are also reported sex differences in cluster headache, for example, in a study from Fourier 2023[6] female patients seem to have a more severe and longer cluster bouts compared to males. Also reported in this study is that as many as 13% report longer attacks than the 180 minutes that is maximum length in the diagnostic criteria for cluster headache. However, exact recognition of attack length might be difficult and affect these results, especially in cluster patients as the severe pain might impact focus on recognition of attack length.

So could cranial autonomic symptoms help with differential diagnosis and personalising treatment? For one thing, we need to consider that patients who do not respond to treatment or have an atypical presentation may actually have the wrong diagnosis.

Treatment response to triptans appears to maybe be better in those with cranial autonomic symptoms in some small studies. Evaluation of 10 responders and 10 non-responders to rizatriptan who were previously treatment naïve showed that autonomic signs or symptoms were seen only in treatment responsive patients.[7] In another study of 29 patients those who were treatment responsive to frovatriptan had more unilateral pain and had autonomic symptoms. Those who did not respond so well had severe pain, nausea and vomiting.[8]

There are other potential clues that may help determine who may respond and who may not. For example, there are anecdotal reports of people with severe migraine with cranial autonomic symptoms responding to oxygen (sometimes used for cluster headache). Cranial autonomic symptoms have been proposed as a possible positive predictor of positive treatment response with onabotulinum toxin A treatment in chronic. Cranial autonomic symptoms seem to be more common in chronic migraine compared with episodic migraine EM, and studies tend to suggest that migraineurs with cranial autonomic symptoms have more severe attacks, that are more frequent and perhaps last longer.[9-13]

To take the research further to elucidate whether cranial autonomic symptoms might be helpful in the diagnosis and management of migraine Christensen and colleagues have proposed criteria for migraine with cranial autonomic symptoms for use in genetic, epidemiological, clinical and pathophysiological studies.[2]

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Tension type headache or chronic migraine or both? Multiple diagnosis

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Individual patients can each experience many different types of headache – tension-type headache, migraine, etc. Physicians frequently find their patients puzzled by a diagnosis of chronic migraine when most of the headache they experience is more like a tension headache (they never use the term tension-type headache).

Chronic migraine did not appear in classification systems until 1995 and chronic daily headache was defined in 1996 as >15 headache days per month over more than 3 months and transformed migraine.[1-4]

Multiple headache diagnoses are common among headache clinic patients. A study in Texas found that 90% of patients admitted with chronic tension-type headache also had migraine. Indeed migraine was most prevalent in those with chronic headache and the transformation to migraine seemed to be spontaneous for many and perhaps induced by medication in others.[5]

So pure tension-type headache is rare and the recognition of chronic migraine has gradually increased. The first International Classification of Headache Disorders had no classification of transformed or chronic migraine.[6] However, chronic tension-type headache was acknowledged. Several chronic headache types were classified in the second classification:[3,7]
– Chronic migraine: defined as more than 15 migraine days per month over more than 3 months.
– ICHD-3: Chronic migraine: more than 3 months with more than 15 headache days per month of which there should be a minimum of 8 days with migraine.[8]

Additional features such as nausea, vomiting, photophobia and phonophobia are the factors that distinguish between migraine and tension-type headache.[8]

Even the pathophysiology of tension-type headache is not well understood.

The diagnosis may need to be reframed in terms of the impact of the disease on day-to-day life rather than purely a symptom profile.

Chronic migraine diagnostic criteria are as follows:[8]

A. Headache (migraine-like or tension-type-like) on 15 days/month for >3 months, and fulfilling criteria B and C below.
B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for migraine without aura and/or criteria B and C for migraine with aura.
C. On 8 days/month for >3 months, fulfilling any of the following:
1. criteria C and D for migraine without aura;
2. criteria B and C for migraine with aura;
3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.

D. Not better accounted for by another ICHD-3 diagnosis.

In 2002 Cady and colleagues commented that the similarities between migraine and tension-type headache outweigh the differences and hypothesized a common pathophysiology for the two diseases. The so-called convergence hypothesis suggests that 'successive symptoms experienced clinically reflect an escalating pathophysiological process, beginning with the premonitory period and progressing into tension-type headache and, if uninterrupted, finally into migraine'.[9] The idea has important implications for earlier recognition, diagnosis and treatment, they suggested.

From the patients' perspective it is probably more important to think about the burden of migraine, which is not part of the diagnostic landscape. We also need to consider when migraine becomes chronic migraine and whether there is a threshold for disability[10,11] and whether those factors require a change in the diagnostic criteria for migraine.[11] Indeed, Chalmer and colleagues have proposed a diagnostic criteria for chronic migraine, removing the tension-type headache element, as follows:[11]

A. Fulfils the diagnostic criteria for migraine without aura and/or for migraine with aura.
B. For at least 3 months, migraine headache day frequency according to criteria C has been 8 or more per month.
C. Each of the migraine days fulfils at least one of the following:

1. Criteria C and D for migraine without aura
2. Criteria B and C for migraine with aura
3. Believed by the patient to be migraine at onset and relieved by a triptan, an ergot derivative, a CGRP antagonist or a 5-HT IF agonist.

For now the conundrum of whether chronic migraine and tension-type headache are the same or separate diseases is unclear. That is confusing for patients who are diagnosed with chronic migraine while most of the headache they experience is tension-type headache, which is why a rethink about diagnostic criteria may be needed.

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...for treating in the prodromal phase?

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Evidence suggests the preictal or prodromal phase in migraine occurs up to 48 hours before an attack and the postictal or postdromal phase lasts for around 24 hours after an attack.[1,2]

Around 80% of patients experience premonitory symptoms, which include:[3,4]
- neck stiffness
- tiredness
- cognitive dysfunction
- sensory sensitivities
- mood change
- homeostatic symptoms: yawning, thirst, food cravings.

Over the last 30 years a number of drugs have been tested for treating patients during premonitory symptoms, including:[3]
- dopaminergic system: domperidone
- serotonergic system: naratriptan and dihydroergotamine
- CGRP system: ubrogepant*

In 1982 Waelkens and colleagues published data from a small placebo-controlled crossover trial in 19 migraine with aura patients on the effect of domperidone 30 mg used during the prodromal phase. It was found that the drug prevented 25 out of 38 attacks compared with 2 out of 38 attacks after placebo.[5]

Dihydroergotamine given as a nasal spray during the prodromal or aura phase has been found to prevent headache occurrence compared with placebo (36% versus 26%) in a double blind crossover trial.[6] And in an open label study with naratriptan 2.5 mg prevented 60% of headaches when taken during premonitory symptoms (reliably occuring 4–24 hours before a headache onset when patients felt that having a headache was inevitable). Naratriptan was more effective when treating early.[7]

In terms of the CGRP system Ubrogepant* 100 mg has been found to prevent the occurrence of moderate or severe headache within 24 hours of treatment in 46% (190/418) of prodrome events compared with 29% (121/423) of those treated with placebo (OR 2.09; 95%CI, 1.63–2.69) in a crossover trial. Of 480 patients who received at least one dose of the study drug only 17% (n=77/456) experienced any adverse event with ubrogepant* compared with 12% (55/462) after placebo administration.[8]

To conclude, premonitory symptoms are common, in many cases allow reliable prediction of the headache phase and provide an opportunity for early treatment. Evidence, albeit from small placebo-controlled trials, shows the efficacy of domperidone and dihydroergotamine administered during the prodromal phase,[5,6] and a larger more recent study shows the benefit of ubrogepant* for treatment of migraine attacks during the prodrome.[8]

*Not approved in the EU.

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… for using triptan during the aura phase?

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Evidence supporting the use of triptans to treat migraine during aura is scarce with only a few small studies evaluating the drugs' efficacy.

In 2021 in a review by Eigenbrodt *et al.* the authors said: 'Triptans are most effective when taken early in an attack, when the headache is still mild. However, no evidence supports the use of triptans during the aura phase of a migraine attack.'[1]

In 2010 Loder *et al.* commented that 'triptans do not prolong aura in the roughly 30% of patients with migraine who are subject to it, but it is uncertain whether efficacy is reduced or absent when the drug is given during the aura,' adding: 'The optimal timing of triptan use in relation to aura is in doubt. In the absence of firm evidence, patients with aura who take triptans should experiment with the timing of use to find the timing that works for them'.[2]

A network meta-analysis in the BMJ in 2024 revealed that while triptans are effective for acute treatment of migraine they are less effective in patients with aura compared with those who have migraine without aura.[3]

Three randomized controlled studies have looked at the effect of triptans in patients with migraine with aura. Sumatriptan given during the aura did not prevent headache development.[4] It was less effective in patients with aura compared with patients with no aura.[5] Another study showed some effect of zolmitriptan in which 19% (n=3/16) of patients responded based on diary entries made by participants compared with 0% in the placebo group.[6] A third study of eletriptan 80 mg compared the drug with placebo but found no effects during the aura phase.

Furthermore, a study with a four-way cross-over, open-label design in which patients were instructed to treat their next five attacks in the following order:[7]
– treat attack 1 at 4 hours after onset of headache (late phase)
– treat attacks 2 and 3 within 1 hour of onset of pain (early phase)
– treat attacks 4 and 5 during the aura before the onset of pain (aura phase)

In contrast with other studies of triptans in migraine the results showed that 'treating migraine with sumatriptan within the first 15 minutes of the aura phase proved extremely effective in pre-empting the onset of migraine headache'.[7]

There is now a good deal of evidence that the risks associated with taking triptans are probably low, even though the data do not necessarily relate specifically to taking the drugs during the aura phase.[8]

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...for neuroinflammation in migraine?

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Proinflammatory and vasodilatory agents such as prostaglandin and histamine induce migraine-like headaches in humans while also promoting neurogenic inflammation in animal models.[1-7] Data from animal studies support a link between inflammatory processes and migraine,[8-13] and show that the same inflammatory agents activate meningeal nociceptors that contribute to migraine pain.[4-7]

However, do the data translate to human physiology?

Recent imaging studies in humans suggest that patients with migraine with aura exhibit neuroinflammatory signals based on findings that cortical and parameningeal neuroinflammation could be detected when compared with healthy controls and with patients without aura.[8-10] However, in patient with migraine without aura the evidence is less certain. Studies show no difference in permeability of the blood brain barrier during migraine attacks without aura or after aura, or in macrophage activity on the pain side or the non-pain side (i.e. without or with sumatriptan treatment).[11-13] Nevertheless, these studies concentrated on the brain where pain cannot be felt, whereas pain-sensitive structures such as the meninges have gone largely uninvestigated.

The next question is whether neuroinflammation should be a treatment target. It is known that trigeminal nerves release certain substances that can contribute to nociceptive pain signalling acting in part perhaps through immune cells and vasculature. Non-steroidal anti-inflammatory drugs exert their effects through inhibiting prostaglandin synthesis and may inhibit the same compounds that trigger migraine attacks. It is also known that triptans inhibit so-called neurogenic inflammation and reduced the release of pro-inflammatory mediators. Added to that, it is known that CGRP is part of the neurogenic inflammatory process, hence the thinking behind targeting it with anti-CGRP drugs.

In conclusion, it is known that neuroinflammatory substances can trigger migraine attacks, especially those with a vasodilatory action. Neuroimaging suggests neuroinflammation occurs in migraine with aura, specifically relating to the visual cortex. Moreover, migraine treatments inhibit neurogenic inflammation. Although the role of anti-inflammatory compounds in the management of migraine remains unclear, the current evidence suggests it is a topic that needs further investigation.

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PACAP in migraine and cluster headache

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Migraine and cluster headache share many clinical features, although the severity of certain symptoms is often greater in cluster headache.[1] From an anatomical and pathophysiological perspective, the trigeminovascular system is a common denominator for both disorders, and several compounds have been implicated in induction of attacks.[2-4]

Both migraine and cluster headache can be experimentally induced by pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide.[5,6] PACAP exists in two forms in humans, PACAP38 and PACAP27, with PACAP38 being the predominant form. This observation prompted researchers to investigate whether blocking PACAP could yield therapeutic benefits for patients with these headache disorders.

In healthy volunteers, pre-treatment with Lu AG09222 – a compound under development – was shown to bind and neutralize exogenously administered PACAP38 and preventing PACAP38-induced vasodilatory responses and headache (Figure 1).[7]

Subsequently, a proof-of-concept trial of Lu AG09222 (HOPE) was designed to assess the efficacy, safety and tolerability of a single intravenous infusion of Lu AG09222 750mg for migraine prevention in adults with a history of two to four unsuccessful preventive treatments. This multinational, multi-site, randomized, double-blind, parallel-group, placebo-controlled phase 2 trial demonstrated that participants receiving Lu AG09222 experienced a mean reduction in migraine days over a 4-week period of 6.2±0.7 compared with 4.2±0.7 in the placebo group (p=0.02).[8] Although this study involved a limited number of participants, a subsequent 3-month trial (PROCEED) is currently underway to validate these findings and to evaluate the efficacy of subcutaneous formulation of the drug for migraine prevention.

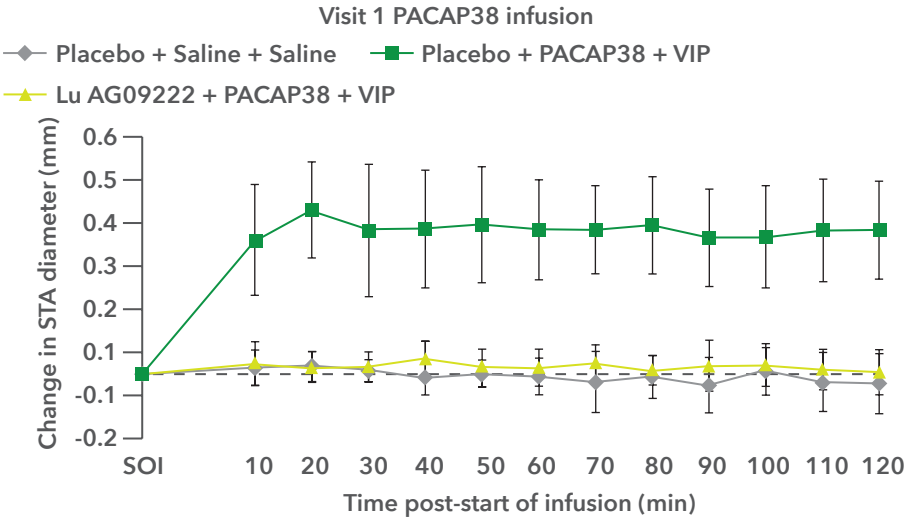

Figure 1. Mean change in STA diameter from start of PACAP38/VIP infusion. PACAP38, pituitary adenylate cyclase-activating polypeptide 38; STA, superficial temporal artery; VIP, vasoactive intestinal peptide. Reproduced from Rasmussen et al. (2023)[7]

In addition, both PACAP and vasoactive intestinal peptide have been shown to trigger cluster headache. In a study of 41 individuals, PACAP38 and vasoactive intestinal peptide induced cluster headache in patients with active episodic cluster headache (43% after PACAP38 and 36% after vasoactive intestinal peptide) and in those with chronic cluster headache (47% after both peptides), but not in patients whose cluster headache was in remission.[9] These findings suggest that PACAP and vasoactive intestinal peptide play a significant role in the pathophysiology of cluster headache.

Overall, these results indicate that PACAP is involved in the development of both migraine and cluster headache, and proof-of-concept studies suggest that blocking PACAP may be effective in preventing migraine attacks. Insights derived from human models, supported by preclinical data, provide a strong foundation for the development of targeted therapies for these debilitating conditions.

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Swedish digi-physical headache centre

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Years ago there was no publicly funded treatment for migraine in the second largest city in Sweden – Göteberg. Indeed, the disease was not even considered a neurological condition, despite its 15% prevalence, with most of the burden among young women.[1]

Following recommendations from an expert panel it was decided to reform the whole structure of migraine services from self-treatment to specialist care. Treatment guidelines were also developed,[2] and a new free digital course in migraine for physicians in the publicly funded healthcare system was made available.

Digital services are now recommended as first-line treatment with physical clinic appointments made available as needed. The idea being that healthcare is available close to where everyone is.

An app has been developed (Figure 1) to help people document their symptoms and to provide some educational features. It can track symptoms and medication use and

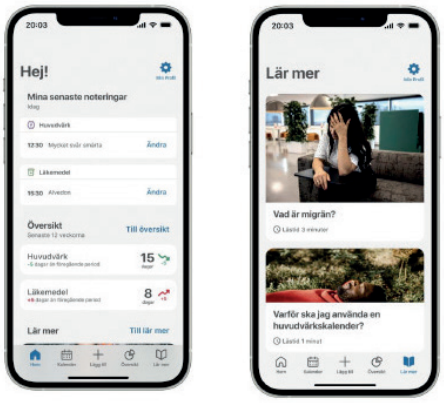

Figure 1. Screenshots from the migraine app.

suggest when people should consider visiting their doctor. The app undergoes continuous development based on feedback from users. The hope is that eventually information from the app will be shared with the healthcare system so physicians have access to the patient-generated data collected in the app.

However, not everyone has access to digi-physical care, those without smartphones or who have language difficulties, for example, so they are welcome to attend the migraine clinic in person. And the clinic itself has taken a novel approach to care with specialists from a range of disciplines working in close proximity with one another.[4] So if they need to consult a colleague about a specific aspect of care they can do so easily and efficiently. It is multidisciplinary care done in an interdisciplinary way – just another example of how migraine service is being developed in the area, with the hope that other regions may follow the examples being developed.

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Artificial intelligence in migraine management

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Artificial intelligence (AI) can be thought of as a machine that mimics natural intelligence. There are a number of forms of artificial intelligence, including:[1]
– Machine learning (ML): a subset of AI that aims to identify patterns from pre-existing data to teach a machine how to perform a specific task;
– Non-machine learning AI: a machine that mimics natural intelligence but operates on a specific set of rules (e.g. chess software);
– Predictive AI: uses ML algorithms to understand patterns and predict outcomes;
– Generative AI: uses ML to create original content or data (text, images, sound, video).

Machine learning can be divided into shallow learning and deep learning.[1]

Shallow learning includes:
– Supervised learning: learns a pattern from labelled data and uses it to predict the outcome of new data. It is used mostly for data classification;
– Unsupervised learning: finds patterns from unlabelled data. It is used for data reduction and clustering problems;
– Reinforcement learning: based on the Markov decision process. It does not need labelled data. The agent optimizes the decision-making process based on a feedback which acts as a reward.

Deep learning, on the other hand, utilizes multiple layers of neural networks. Data follow a chain of transformation from input to output that allows more in-depth analyses (e.g. in image analyses, one layer analyses colour, other shapes and other elements that are relevant to human perception, etc.). Deep learning includes a wide number of possible architectures (Convolutional Networks, Transformers, Recurrent Neural Networks, Restricted Boltzmann Machines, Deep Belief Networks).[1]

There is a range of potential applications for artificial intelligence in the diagnosis and management of migraine, which is common, creates a high burden of disease and is under-recognised.[2-4]

AI may have a role in diagnosis and patient profiling. For example, clinical data can be used as inputs to train AI models to correctly identify migraine patients. In one study, data from 400 medical records were used to train five different classification models, including a multilayer perceptron-type artificial, neural network (MLP), a logistic regression model, an SVM model, a nearest neighbour model and an optimized classification and regression tree (CART). The data were based on basic information clinicians would ask patients – duration and frequency of episodes, location of pain, pain intensity, concomitant symptoms, and so on. The researchers found there was a 97% diagnostic accuracy with 23 variables and 98% accuracy with 18 variables.[5]

Another potential application for AI is to provide support in distinguishing between migraine and tension-type headache. In one study, decision tree, random forest, logistic regression, gradient boosting algorithm and support vector machine (SVM) were used to create a model based on data from 173 patients.[6]

The model reached an accuracy of 0.84 in differentiating between the two primary headaches. The researchers found that the absence of nausea/vomiting and photophobia/phonophobia were the most important discriminating factors among those examined – which also included gender, pain quality and severity, change after activities and course of disease – with an accuracy of 0.74.[6]

A group in Japan found that AI could help improve diagnostic accuracy among non-specialist clinicians. Five non-headache specialists were asked to select the correct headache diagnosis for 50 patients based on questionnaires they had answered. With the help of an AI shallow learning model trained using the medical records from 4000 patients the diagnostic accuracy among the non-specialists rose from 46% to 83.2% with the help of AI.[7]

Comorbidities are another aspect of migraine where AI may find a place. For example, depression is associated with migraine and can affect response to treatment so it would be helpful to recognise the disease in patients with migraine, especially cases of mild depression that may go unnoticed. A shallow learning AI model was trained using the medical records of 178 patients diagnosed with migraine

without aura. Depression was assessed according to DSM-V criteria using the HAMD scale. Mild depression was defined as 2 or more weeks of mild symptoms (HAMD score ≤7). The study showed that AI can effectively predict the risk of mild depression based on headache characteristics.[8]

Patients who have migraine are known to be at greater risk for atrial fibrillation and stroke, however, monitoring patients with migraine for heart disease is not routinely feasible. ECGs with normal sinus rhythm from 40,002 migraine patients were examined with an AI-ECG algorithm that calculated the probability of paroxysmal or impending atrial fibrillation. Comparisons were made between those with migraine with aura and those with migraine without aura, adjusting for sex, age and other vascular comorbidities. Patients with migraine with aura had a significantly higher atrial fibrillation prediction model output (least square means of difference [95% CI] 0.7% [0.4%, 0.9%], p<0.001) especially in people aged 55 years or younger.[9]

AI might be of help in treatment selection. NSAIDS are considered first-line medications for migraine attacks. However, there are no biomarkers that can accurately predict response to treatment.

Patients diagnosed with episodic migraine according to ICHD 3rd edition criteria – 59 patients who were NSAID responders and 59 who were non-responders – underwent fMRI to train an AI-model based on six variables: percent amplitude of fluctuation (PerAF) of left insula and left transverse temporal gyrus; and grey matter volume (GMV) of right superior frontal gyrus, left postcentral gyrus, right postcentral gyrus, and left precuneus.[10]

The study found that an AI model could predict response to NSAIDS in people with migraine with a sensitivity of 0.976.[10]

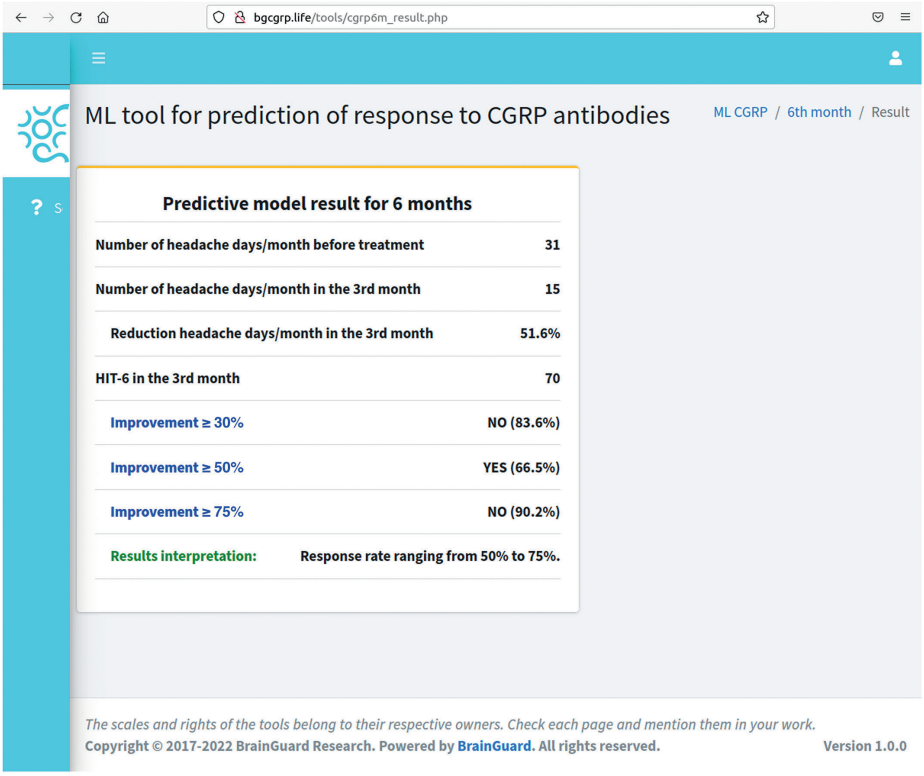

Figure 1. Machine-learning (ML) calculator tool for predicting anti-calcitonin gene-related peptide (CGRP) response at 6, 9 and 12 months. Predictive model result for 6 months. HIT-6, Headache Impact Test. Reproduced from Gonzalez-Martinez et al. (2023)[12]

The approach can be extended to preventive medicine.[11] Researchers in Spain have found that by using just three variables – headache days before the start of treatment, headache days 3 months after treatment started and HIT-6 score 3 months after treatment started – an AI model could predict response to treatment with anti-CGRP monoclonal antibodies at 6, 9 and 12 months (Figure 1).[12] The tool used by the researchers is available online through a link in the paper.

AI might find a role in the analysis of neuroimaging. White matter hyperintensities are known to commonly occur in people with migraine and knowing the localisation and number of these hyperintensities can be helpful in managing patients; periventricular white matter hyperintensities are associated with a decline in cognitive function and cerebral blood flow, and deep white matter hyperintensities are of hypoxic/ischaemic origin and are linked with a higher incidence of migraine. In a study of 148 people with migraine a deep neural network algorithm was used to quantify deep white matter hyperintensities, developing an automatic model that reached a true positive rate of 0.88 and a false discovery rate of 0.13, thus performing better than other existing models.[13]

Predicting migraine attacks could be another useful application of AI. Researchers are looking at ways of developing an app that could be used on smart phones to help predict migraine attacks. One approach has been to try to link weather conditions that may act as a trigger for migraine attacks to data from headache diaries to provide a prediction model. For example, weather conditions such as barometric pressure, temperature, humidity, rainfall, seasons and time zone can trigger migraine attacks.[14]

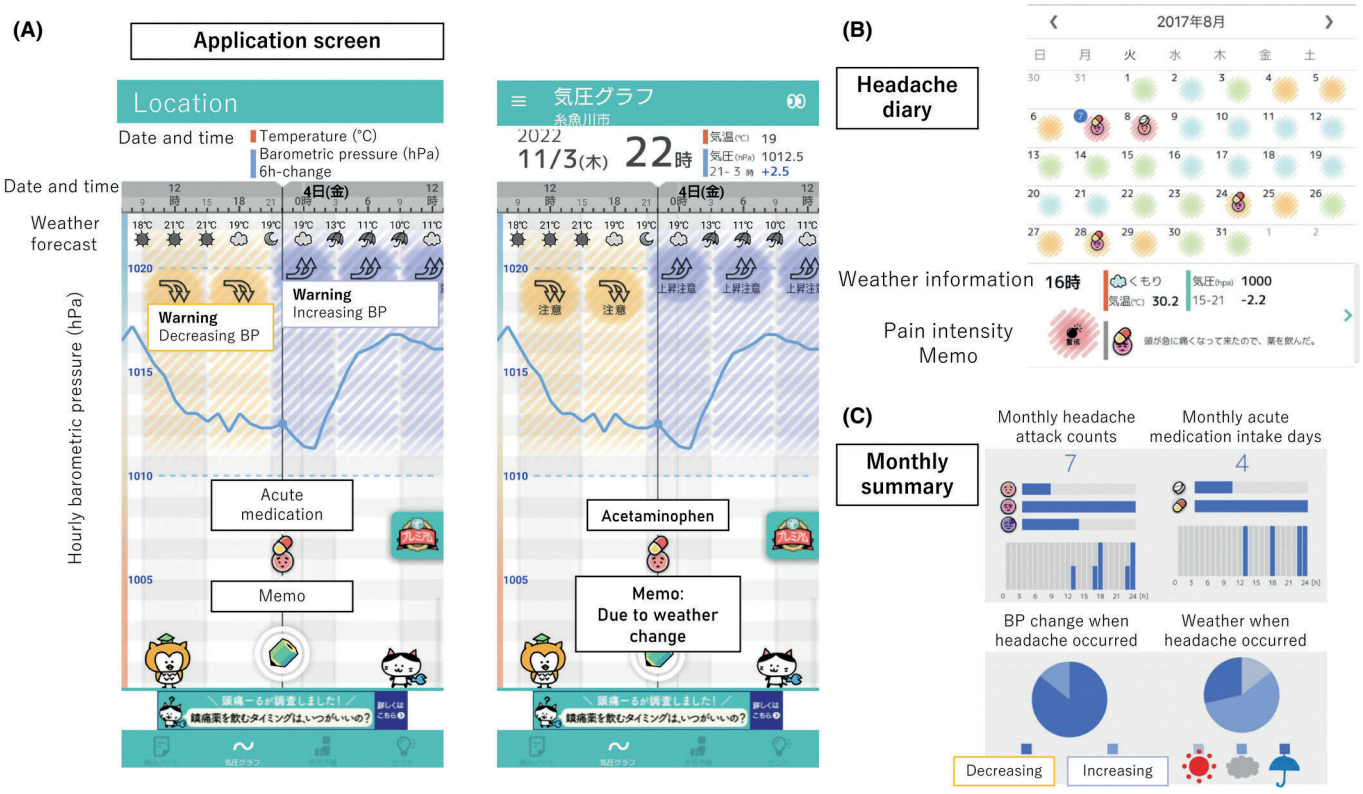

Figure 2. The application screen and its function. (A) Application screen. The users can observe hourly weather and barometric pressure (BP) changes, and the application tells users when severe BP changes will occur. Users can also keep a headache diary. (B) Electronic headache diary. (C) Monthly summary of headache attacks and weather when headache occurred. Reproduced from Katsuki et al. (2023)[14]

A retrospective observational cross-sectional study used data collected from 4375 people with migraine, which were analysed with deep learning-based models to assess the impact of weather conditions on migraine. The study found that low barometric pressure, barometric pressure changes, higher humidity, and rainfall were significantly temporally related to migraine attacks.[14]

In another study with 18 patients with migraine it was shown that migraine attacks could be predicted based on information reported by patients about headache intensity, impact on daily functioning, use of medication, premonitory symptoms and the amount of sleep and exercise within the last 24 hours. Machine learning was used to construct a predictive model (4:1 training-test ratio) that could correctly predict an acute attack with an area under the curve (AUC) of 0.62.[15] Although it is still early days in the development of AI models to aid diagnosis and management of migraine the studies discussed illustrate that steps are being made to achieve that goal. To reach it will require a homogeneity of approaches and larger study samples. More powerful deep learning techniques will need to be developed to analyse data. Perhaps then programs to implement AI in routine clinical practice can be developed.

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