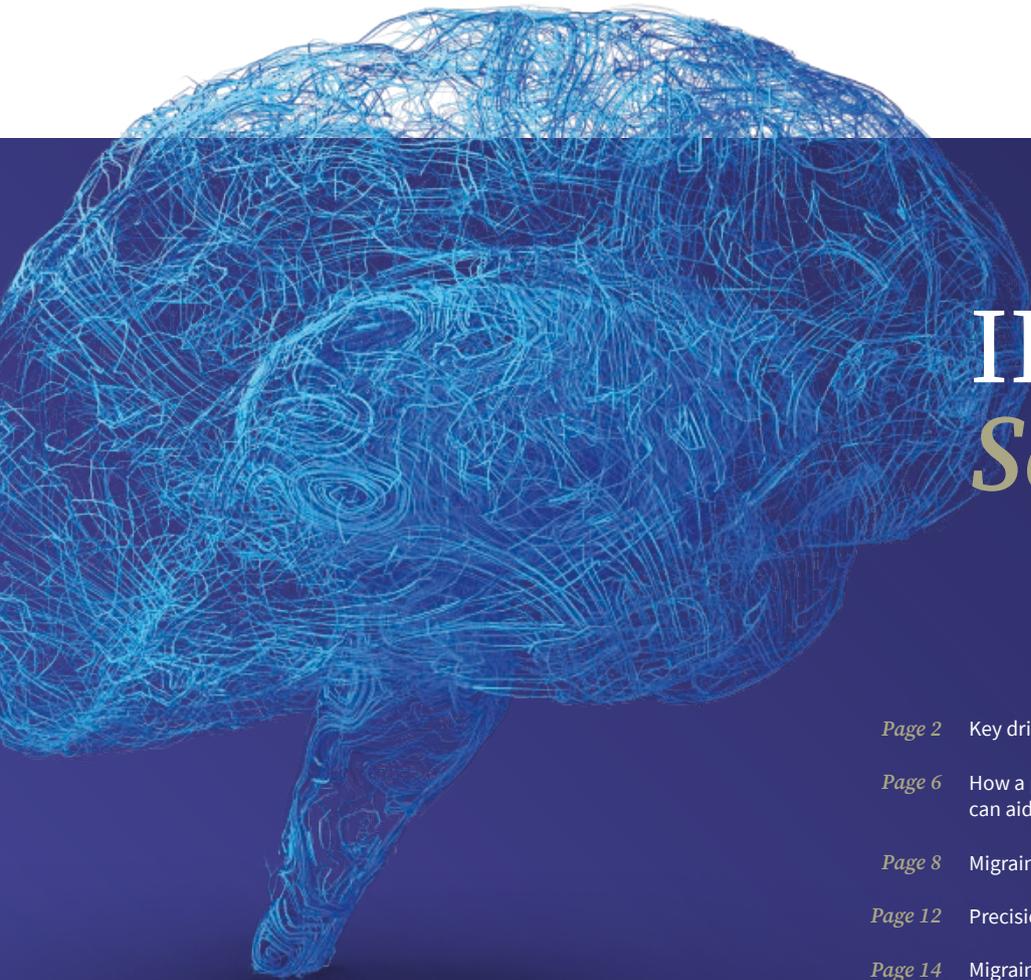


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IHC 2023

Seoul 14-17 September

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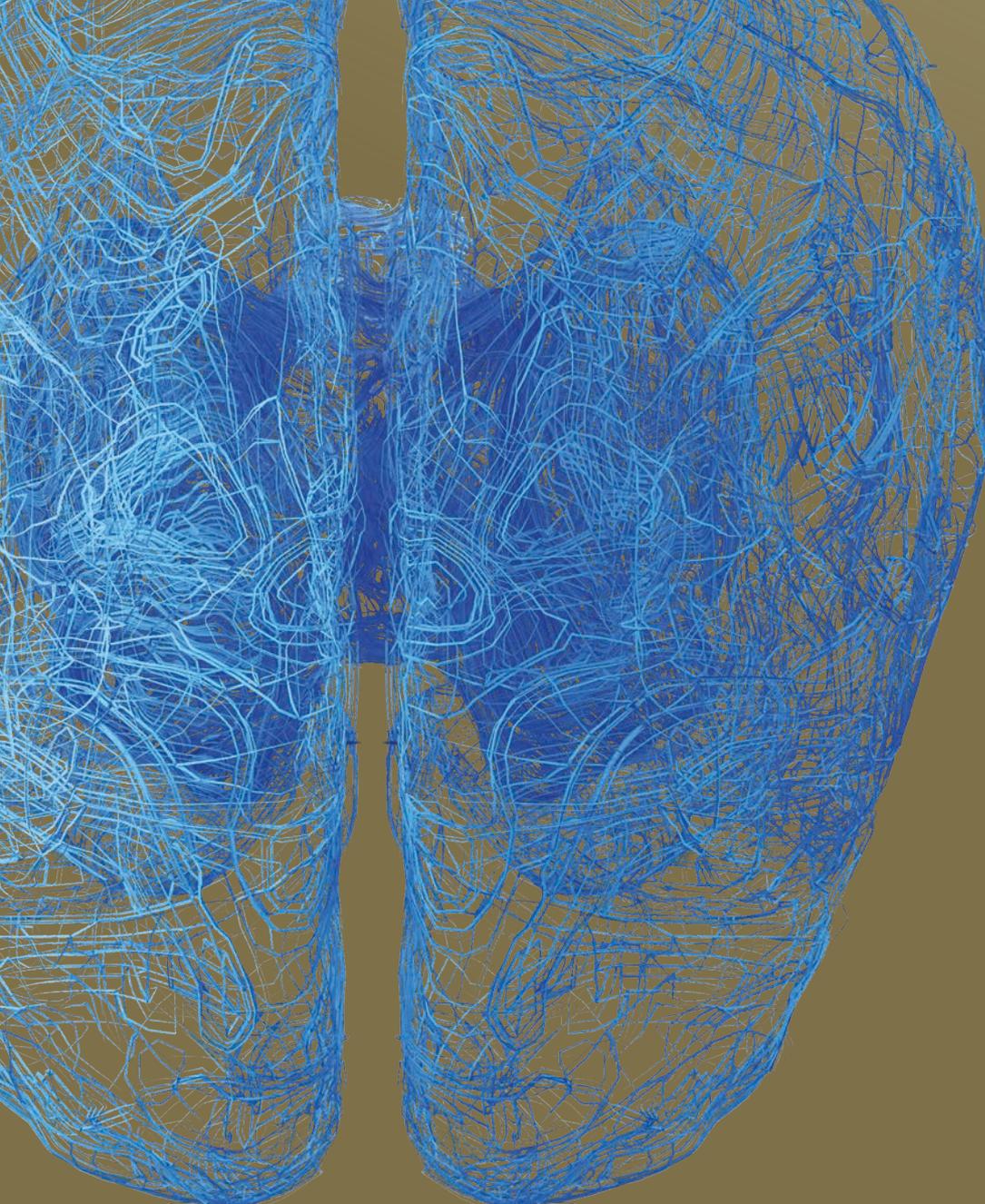
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MIGRAINE

Key drivers of migraine disease progression



“Migraine patients are more prone to be depressed, and this is not due to the fact that they have attacks, but it’s also genetically determined.”

“Patients get into a kind of vicious cycle with the intake of medication, medication overuse and the progression of migraine”



At EAN 2022, Gisela Terwindt, Professor of Neurology, Leiden University Medical Centre, discussed key drivers for migraine progression including genetically-determined comorbidities of depression and anxiety; allodynia, where the head and other parts of the body are painful to touch; and medication overuse headache, wherein a vicious cycle can develop when a patient strives to take enough medication to relieve their symptoms but chronic use of such medication causes headache.

What are the key drivers of migraine disease progression?

There are some key drivers for the progression of migraine, and one of the important ones is medication overuse. It seems very logical if you have a migraine attack, that you take acute medication. But some patients tend to take more and more medication and in the end this medication actually doesn't work. It works for a few hours or for a day, but the headache returns, and they have to take more acute medication. And with this, patients get into a kind of vicious cycle with the intake of medication, medication overuse and the progression of migraine. So that is one of the important factors for chronifying of migraine. But there are also others.

Another factor that has been shown to be important in the progression of migraine is the comorbidity of depression and anxiety. Migraine patients are more prone to be depressed, and this is not due to the fact that they have attacks, but it's also genetically determined. So, you can have a genetic preponderance to have both migraine and depression. We also know that people with depression and migraine are more likely to chronify during their life; that's the second important key factor.

The third important key factor is allodynia – the experience of touching your head during a migraine attack and it's very painful. Normally if you touch your head, it's not painful, but during the attack it might become very painful. We call that cephalic allodynia. It can even progress to other parts of the body so you could have painful arms and hands. People who experience allodynia during migraine attacks are more likely to chronify during their lifetime.

“People who experience allodynia during migraine attacks are more likely to chronify during their lifetime.”

So, there are three important factors in the progression of migraine: medication overuse, depression and anxiety, and allodynia.





“Migraine patients are different. They live different lives and they also respond differently to different kinds of symptomatic treatment”

How a patient-centric approach to migraine can aid in symptom management

At EAN 2022, Henrik Schytz, Associate Professor of Neurology, Denmark Headache Center, Denmark, discussed how there is a challenge for people with migraine due to the unpredictability of attacks. This can be a huge burden. A patient-centric approach necessitates a dialogue between the patient and healthcare professional to ascertain their needs so as to best treat the patient's symptoms and enhance their quality of life.

What are the challenges for people with migraine with regard to their symptoms and how would a patient-centric approach aid in symptom management?

Migraine patients have headaches that are unpredictable. So that means they cannot easily predict when they have migraines. And that's of course, a challenge in life because they might want to go to a party, they might have an important business meeting, something with the kids, and then they wake up and feel a migraine attack coming on. So, the unpredictable nature of migraines is a huge problem, and it can make patients restrict their life. They might not want to go out, go to the theater, go to social events because they know it might be a day when they have a migraine. And that's a huge burden on many migraine patients.

“The unpredictable nature of migraines is a huge problem, and it can make patients restrict their life”

I really believe that a patient-centric approach is needed in the treatment of migraine because migraine patients are different. They live different lives and they also respond differently to different kinds of symptomatic treatment. So, it's very important that we, as neurologists and those who treat headache patients, try to get into a dialogue with the patient and try to ask them about what their needs are and how they live their lives. And in that way try to find out the most optimal way of treating their migraine. So that's a very important task that we have to take on as those who treat headache patients.

MIGRAINE

Migraine burden is much more than pain

Headache is clearly key, but non-pain symptoms including cognitive dysfunction are a major contributor to the burden and disability of migraine. Functional brain imaging extends our understanding of the neural substrates and prolonged time-course of this complex condition.^{1,2} But the complexity and burden also have non-neurological aspects since stigma and self-blame are socially conditioned.



Cognitive dysfunction associated with the prodromal and postdromal phases of migraine was emphasized by Nazia Karsan (Clinical Fellow, King’s College Hospital, London, UK) in her Migraine World Summit 2023 interview focused on non-pain aspects of the condition.³

For many patients, inability to concentrate and even difficulties in reading, writing and speaking – along with somnolence – add greatly to the migraine burden, especially when they interfere with study or work, Dr Karsan said. Such non-pain symptoms are present in both prodromal and recovery phases⁴ which, taken together, mean a migraine episode may last for up to four days.

Disability outside the headache phase contributes greatly to morbidity. And these important elements of what is a heterogeneous disease can be difficult to communicate to friends, family and work colleagues, Dr Karsan commented.

Global cognitive dysfunction can be present before, during and after an attack

“Triggers” may reflect already evolving functional abnormalities

Migraine is a brain disorder, and the brain controls so much of the body that we should not be surprised that the range of associated symptoms reflects widespread dysfunction.

Other notable non-pain symptoms include irritability, mood swings, neck stiffness, sensory hypersensitivities such as photophobia, and abnormal eating behaviours like skipping meals and cravings for cheese or chocolate.

Phenomena like these have traditionally been considered as possible migraine triggers, but they may in fact be symptoms of a brain dysfunction that is already evolving,⁵ Dr Karsan suggested. If this is true, and such experiences actually reflect premonitory brain changes, avoidance of

bright lights or certain foods, for example, may not help in preventing a full-blown migraine episode.

Brain scans validate patient experience

Imaging studies in people with spontaneous migraine attacks and in those triggered by nitroglycerin infusion show good correlations between areas of abnormal brain function and patients’ experiences during the premonitory phase.

The cingulate cortex, involved in mood and cognition, shows up on MRI imaging during the prodrome as well as the acute phase, with regions of the pons and medulla implicated in the pain.

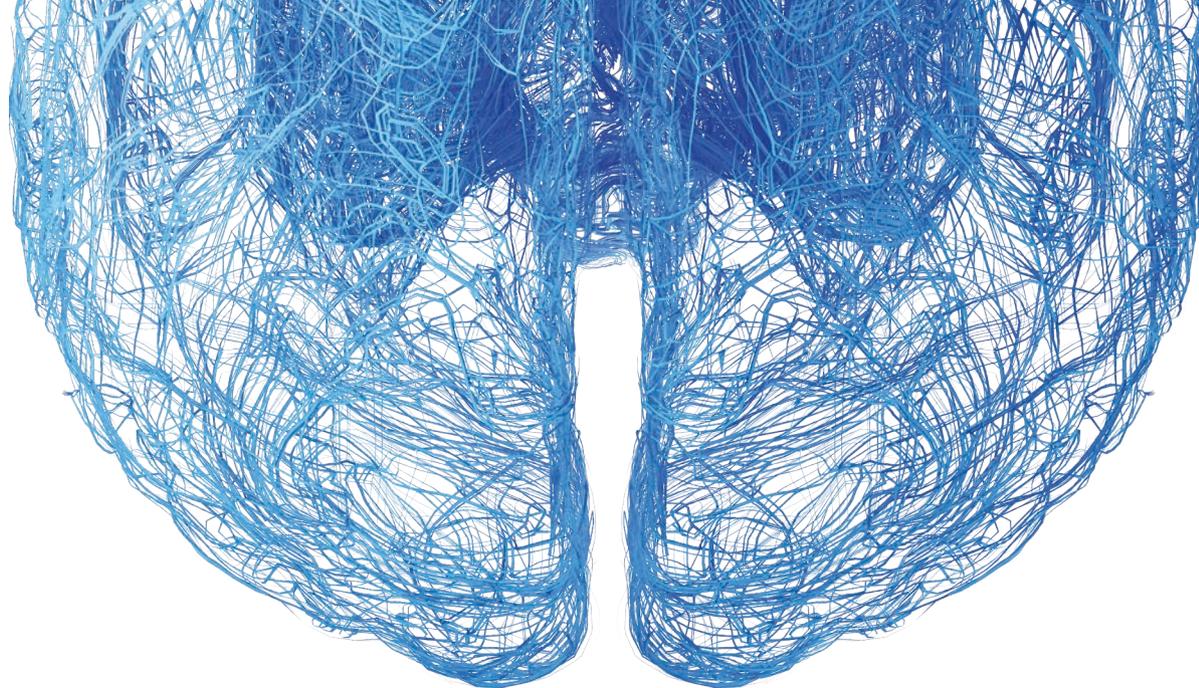
In the pre-headache phase, the brain is already functioning abnormally

Acute headache is the major symptom of migraine, but we also need research into non-pain aspects if we are more effectively to treat and abort an episode, Dr Karsan said. Clinical trials relating to CGRP inhibition have looked at effects on a range of disabling symptomatology and on return to functional ability, and have shown promising results.

We need to think about intervening before the process escalates to pain, and to recognize that patients are not necessarily “back to normal” once their headache has gone. This fact is massively under-recognized, Dr Karsan argued.

Stigma also contributes to burden

It is not just symptoms of migraine that impose burden. It is also stigma. The causes of migraine morbidity extend from the neurological to the sociological.



Partly because the symptoms of migraine cannot be seen, and there are no lab tests to define it, migraine is considered by some to be a condition that sufferers may exaggerate, possibly to obtain advantage, said Dr Robert Shapiro, of the University of Vermont College of Medicine, Burlington, USA.

Employers in particular may not regard migraine as a serious condition

The stigma associated with the disease may come from family and friends, work colleagues and employers, health professionals, and even patients themselves, Dr Shapiro commented during his Migraine World Summit interview. This unsupportive social environment can limit the ability of people with migraine to live full and productive lives.

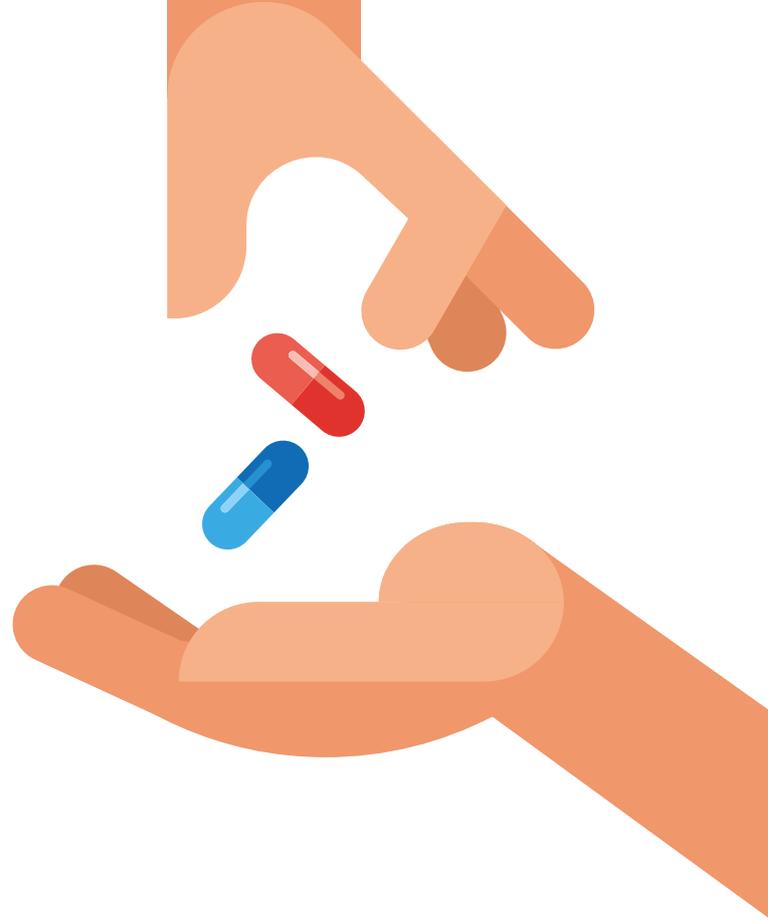
Importantly, it may lead those with the condition to conceal symptoms and avoid seeking effective treatment. Hence stigma has a direct effect on the physical morbidity associated with migraine as well as imposing an unnecessary psychological burden.

More positively, Dr Shapiro is hopeful that in the next decade or so we will have biomarkers – perhaps including imaging of the kind described above – which can provide a definitive objective diagnosis of migraine. Meanwhile it is important to continue efforts to educate the health community and the wider public about the realities faced by those with the condition.⁶

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2. Karsan N, et al. *Cephalalgia*. 2018; 38:36
3. Transcript of interview of Nazia Karsan by Lisa Horwitz, Migraine World Summit 2023.
4. Karsan N, et al. *Cephalalgia* 2021;41:721-30.
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MIGRAINE

Precision medicine for migraine



In a scientific session dedicated to precision medicine at the 16th European Headache Congress, December 7–10, 2022, Vienna, Austria, the speakers explored how research is helping to identify predictors of response to migraine medications. This will allow for targeted management decisions based upon patient characteristics in the future.

Diversity and response to antimigraine medication

As Professor Antoinette Maassen van den Brink, Rotterdam, Netherlands explained, despite numerous clinical trials and some real-world evidence (RWE), knowledge of the pharmacology and related clinical effects of new

treatments is low. Clinical trial data collected from mainly Caucasian, overweight females are not necessarily generalizable to all populations.¹ However, gender, body-mass index, age, ethnic background, ultrarapid metabolism, and other characteristics may affect the pharmacokinetics of therapies and contribute to low efficacy. Collection of RWE will expand knowledge on the effectiveness and safety of new migraine medications in a wider population.

Can we predict CGRP mAb super responders?

Uncovering differences between responders and non-responders to migraine medications will also help to improve migraine care. Defining patients who will derive greatest benefit from treatment with anti-calcitonin gene-related peptide (anti-CGRP) monoclonal antibodies (mAbs) may avoid unnecessary economic costs

and adverse effects, said Dr Ana Rita Pinheiro, Lisbon, Portugal. Some response predictors have already been identified, which include:^{2,3}

- Unilateral pain
- Allodynia in episodic migraine
- Response to triptans
- Lower number of failed preventives
- Lower frequency at baseline
- Shorter disease duration
- Lower analgesic intake.

Uncovering differences between responders and non-responders to migraine medications will help to improve migraine care

Dr Pinheiro presented results of a sub-analysis of a prospective study conducted in her clinic to determine predictors of super response to preventive therapies. Super responders were defined as those with $\geq 75\%$ reduction in migraine frequency for at least 6 months (n=29) and compared with super non responders ($< 25\%$ frequency reduction; n=13).

Factors predictive of super response to CGRP mAbs were found to be lower baseline frequency of migraine attacks, episodic migraine, and response to triptans. Conversely, disease duration, aura, absence of medication overuse and absence of psychiatric comorbidities were not found to be predictors of super response.

Predictors of super response to CGRP mAbs include lower baseline frequency of migraine, episodic migraine, and response to triptans

Scientific rationale

The overlap between response to triptans and anti-CGRP mAbs may be explained by convergence in their mechanisms of action. During a migraine attack, activation of the trigeminovascular system leads to CGRP release, vasodilation of the intracranial arteries, sensitization and activation of pain and inflammation. mAbs targeting CGRP lead to modulation of pain transmission and reduction in sensitization either by removing excess CGRP or by blocking receptor binding. Triptans constrict extracerebral blood vessels and reduce trigeminal sensory nerve activation, inhibiting vasoactive peptide release (including substance P and CGRP) thus indirectly affecting the CGRP pathway.⁴

Management decisions based upon patient characteristics could have a more prominent role in future migraine treatment

Future directions

Anti-CGRP mAbs are increasingly used as migraine preventives due to their proven benefits in clinical and real-life studies. As knowledge increases about the use of CGRP-targeted therapies from RWE, management decisions based upon patient characteristics could have a more prominent role in the treatment of migraine, concluded Professor Maassen van den Brink.

1. Al-Hassany L, et al. Lancet Neurol 2022;21(3):284-294.
2. Iannone LF, et al. CNS Drugs 2022;36(2):191-202.
3. Mascarella D, et al. Neurol Sci 2022;43(9):5673-85.
4. Frattale I, et al. J Headache Pain 2021;22:1.





MIGRAINE

Migraine: Your patient, your partner

Proactive prevention strategies that align research findings with patient needs and goals can prevent the cycle of worsening migraine and medication overuse. Experts at AAN 2023 provided practical tips on how to provide such proactive care for people with high frequency, worsening migraine and incorporate patient needs and goals into care plans.

1. Bigal ME, Lipton RB. Migraine chronification. *Curr Neurol Neurosci Rep.* 2011;11(2):139-148. doi:10.1007/s11910-010-0175-6

2. Buse DC, Greisman JD, Bajaj K, Lipton RB. Migraine progression: A systematic review. *Headache.* 2019;59(3):306-338. doi:10.1111/head.13459

3. Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. *Headache.* 2021;61(7):1021-1039. doi:10.1111/head.14153

4. Tepper SJ, Spears RC. Acute treatment of migraine. *Neurol Clin.* 2009;27(2):417-427. doi:10.1016/j.ncl.2008.11.008

Proactive prevention strategies are key to prevent the chronification of migraine

Episodic migraine that is not effectively managed can progress to new-onset chronic migraine,¹ said Professor Amaal Starling, Mayo Clinic College of Medicine, Phoenix, AZ. Many factors contribute to a cycle of worsening migraine and migraine chronification, including medication overuse.²

Factors leading to migraine chronification include medication overuse

Individualize migraine prevention goals for each patient, said Professor Starling, and aim to bridge the gap between intervention goals and patient goals.

- The intervention goals aim to improve migraine, reduce the need for acute treatment, and improve quality of life.³
- The patient goals include freedom from pain and associated symptoms, fast onset of prevention with limited side effects, and minimal need for rescue medication.⁴

Proactive prevention strategies that align research findings with the patient's needs and goals can prevent migraine chronification

Once an individual patient's needs and goals have been determined, proactive prevention strategies that align research findings with these needs and goals can be implemented to prevent the cycle of worsening disease and medication overuse.

Key questions to ask patients

Ask patients focused proactive questions and actively listen to their responses to assess patient-reported outcomes, disease burden, and the overall patient experience of migraine said Professor Robert Cowan, Stanford University School of Medicine, Stanford, CA.

The Patient Global Impression of Change (PGIC) is a straightforward and valuable migraine monitoring tool, he said. It is a one-question — “Since your last visit, how would you describe the change (if any) in your migraine and its impact?” —self-reported assessment of change.

The Patient Global Impression of Change is a valuable migraine monitoring tool

Professor Robert Cowan suggested that other useful patient-centered questions to consider asking to inform treatment are:

- Since your last visit, how would you describe the change (if any) in your migraine and its impact?
- How many headache-free days have you had over the past 3 months?
- Over the past 3 months, what has been the most bothersome symptom associated with your migraine?
- What would you most like to accomplish during your visit today?

Understand the patient's needs and incorporate them into a proactive, preventive care plan

Both experts emphasized that an effective partnership with a patient with migraine that supports the patient's treatment goals is key. This is achieved by understanding the patient's needs and incorporating them into a proactive, preventive care plan.

Educational financial support for this Industry Therapeutic Update was provided by Lundbeck.



MIGRAINE

Improvement in most bothersome symptom or monthly migraine days? Which contributes most to quality of life?



Improvement in the most bothersome symptom contributes more to improvement in health-related quality of life than a reduction in monthly migraine days for patients treated with an anti-calcitonin gene-related peptide monoclonal antibody after two to four prior preventive treatment failures. This is the finding of a study presented at AAN 2023.

Anti-calcitonin gene-related peptide monoclonal antibody efficacy mediators

Efficacy measures mediating the effect of an anti-calcitonin gene-related peptide monoclonal antibody (anti-CGRP mAb) on improvement in health-related quality of life (HRQoL) in patients with migraine were analysed using data from DELIVER (NCT04418765). DELIVER was a randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of an anti-CGRP mAb in patients with migraine and two to four prior preventive migraine treatment failures.¹

Efficacy mediators were canonical symptoms in Model 1 and patient-identified most bothersome symptom in Model 2

For the analysis it was assumed that the change from baseline in the three Migraine-Specific Quality of Life Questionnaire (MSQ) domain scores — Role-Function Restrictive, Role-Function Preventive, and Emotional Function² — could be used to estimate the change from baseline in HRQoL.

A reduction in monthly migraine days explained only one-third of the improvement in quality of life in Model 1

Two structural equation models identified potential effect mediators from treatment versus placebo on HRQoL.

- In Model 1, these mediators were canonical symptoms as defined by International Headache Society diagnostic criteria³ — monthly migraine days (MMD), severe migraine, nausea, light sensitivity, and pulsating headache — a backwards elimination method was used to identify mediators with p values less than 0.05 for the association with HRQoL.

A reduction in monthly migraine days explained only 17% of the improvement in quality of life in Model 2

- In Model 2, the mediator was patient-identified most bothersome symptom (PI-MBS). PI-MBS categories included nausea, vomiting, light sensitivity, sound sensitivity, mental cloudiness, fatigue, pain with activity, mood changes, and “other.” The most commonly reported categories were pain with activity (24.6%), fatigue (14.1%), and nausea (13.9%).

Improvement in the most bothersome symptom contributed most to improvement in health-related quality of life

The analysis revealed that a reduction in MMD explained only approximately one-third of HRQoL improvement in

Model 1. Reductions in MMDs, the percentage of severe migraine attacks, and canonical symptoms insufficiently explained how the anti-CGRP mAb treatment improved patients’ HRQoL.

An improvement in most bothersome symptom explained 69% of the improvement in quality of life in Model 2

In Model 2, 86% of the impact of anti-CGRP mAb treatment on HRQoL was explained by either an improvement in PI-MBS (69%) or a reduction in MMD (17%). The impact due to improvement in PI-MBS was therefore much greater than that of a reduction in MMD.

These results suggest that discussing improvements in a patient’s PI-MBS after starting a preventive migraine treatment provides a fuller picture of the impact of the treatment on the patient’s HRQoL than a discussion on the reduction in MMD.⁴

This study and poster were sponsored and supported by H. Lundbeck A/S (Copenhagen, Denmark).

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