Nordic Migraine Symposium 21

Summary Report

Paving the Way Towards Precision Medicine in Migraine

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Genetic aspects and latest findings

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The genetics of migraine is proving complicated with more and more variants associated with the disease being discovered. The challenge is to determine which are the most important for future management.

In the early days of genetic research in migraine, it was thought that it might be possible to identify a few genes related to pathology of the disease. However, that has not proved to be the case. The question now, is how can genetic studies be used to investigate brain disease as a whole, to generate a knowledge base for biological insight and therapeutic development? The strategy for the work aims to:

- establish associations between specific genes and variants
- interpret their specific phenotypic consequence
- glean insight into the cells and molecular pathways involved in order

Variants in the genome that contribute to disease either by increasing the risk or protecting people from it, are often divided into common (typically >5% of the population) and rare (<5%) variants. To be able to identify common variants, typically 20,000 cases or more are needed. This is partly because each variant has a very small effect on the phenotype.

Common variants in migraine are typically identified with genome-wide association studies (GWAS). The most recent GWAS was an analysis of 102,084 cases that identified 123 migraine risk loci and subtype-specific risk alleles. Analysis of the dataset revealed that there are genetic distinctions between migraine with aura and migraine without aura.[1]

From a drug development perspective, it might be possible to identify targets based on information generated by the genetic studies. For example, the locus containing *CALCA* and *CALCB* genes, which encodes *CGRP* that is the target of preventive and acute therapies via monoclonal antibodies and gepants, and the locus containing HTR1F gene, which encodes a serotonin 5-HT1F receptor that is the target of acute therapies via ditans.[1]

The important aspect in terms of therapeutics is being able to determine which genes are important, in other words which genes are implicated in pathology, and which is the relevant target tissue.[1]

In the Hautakangas study, the gene expression is in the cardiovascular and central nervous systems, fitting with the idea that migraine is a neurovascular disorder.[1]

To help understand the clinical relevance of the genetic risk associated with migraine, a polygenic risk score (PRS) that aggregates the effects from a large number of genes implicated in disease has been developed from the GWAS data. For example, people with earlier onset of headaches have a higher PRS.[2] In families with migraine, the PRS score is much higher than those in the general population in Finland with migraine; even those in migraine families who do not have migraine, have a PRS score similar to that seen in people in the general population with migraine. Similarly, the PRS score for people with migraine with aura is higher than among those with migraine without aura, and for people with hemiplegic migraine, the PRS score is higher again.[1] There is also evidence that people who attend outpatients for multiple prescriptions of triptans each month have a PRS similar to that seen in clinical, multiplex familial migraine.[2]

All these data indicate that there are hundreds, if not thousands of genes that contribute to migraine. The question is how those data can be used to inform the development of new therapeutic strategies to manage the disease.

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Clinical Implications

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Genomic research offers the possibility that personalised medicine for people with migraine will be a reality in the future. It may help determine who will respond to a specific drug and who may be at risk of side-effects.

Progress in the genetic study of migraine has been swift: in 2012 there were six known variants associated with migraine, in 2016 there were 38 and in 2021 there are 123.[1-3]

The PRS – a summary as it were of data from hundreds, thousands, and even millions of variants (single nucleotide polymorphisms [SNPs]) – is a number that clinicians can use because it gives an indication of an individual's genetic predisposition to specific diseases or traits.

Clinically, some key questions arise that GWAS data may be able to help answer, and thus inform management. Namely:

1. Is migraine with and without aura one or two disorders?
2. Where is the lesion in migraine?
3. Is hemiplegic migraine actually migraine?
4. Can treatment response be predicted based on the common variant burden?

In terms of migraine with or without aura, there are of course many patients who have both phenotypes – sometimes they have aura but most attacks occur without aura. Equally, there are those who never have aura, and then there are the rare cases who are often referred to a neurologist who have aura with every attack. Are these the same disease? Research suggests that there are common genes for migraine with and without aura. However, there are also genes associated with migraine with aura and others associated with genes without aura. Indeed, it could be argued that there are three types of migraine: migraine without aura (the most common phenotype), those with aura and without aura, and finally those with aura with every migraine attack.[3]

As far as identifying the lesion in migraine, it seems as though there are several lesions, not just one.[4]

The question of whether hemiplegic migraine can be considered as migraine per se from a genetic point of view, has been examined using data from the Finnish Migraine Genome Project 1993–20. Analysis of the data shows that hemiplegic migraine is associated with a higher risk score (PRS) than other types of migraine, probable migraine, headache or no headache. Indeed, hemiplegic migraine looks to be very much part of the migraine spectrum.[5]

Being able to predict how a person might react to a particular migraine treatment would be especially useful. The science has not achieved that goal yet, but there are preliminary studies that indicate it might be possible. For example, Kogelman et al. have shown that a twofold increase in migraine risk associates with positive response to migraine-specific acute treatment (odds ratio [OR] = 1.25 [95% confidence interval (CI) 1.05–1.49]).[6]

Perhaps even more promising in terms of precision medicine, is the discovery of drugs that are associated with specific genes. For example, mode of action of monoclonal antibodies and gepants are linked to *CGRP* genes (*CALCA* and *CALCB*) on chromosome 11 and ditans such as lasmiditan are 5HT1F agonists.[3,7]

TRPM8 (Transient receptor potential cation channel subfamily M member 8), the upstream variant rs10166942, shows extreme population differentiation, with frequencies that range from 5% in Nigeria to 88% in Finland. This may not be so surprising, as TRPM8 is a receptor for cold and menthol. However, it is also a migraine variant and may in part, explain some of the population differences in migraine.[8] Another example of the link between genetics and migraine, is that of a 45-year-old lady with a known *PRRT* gene mutation and migraine and cluster headache, who came forward to be part of the family migraine study in Finland. She had a history of epilepsy during the first years of life; she had migraine and cluster headache, and showed an excellent response to carbamazepine. It is a picture that fits well with what is known about *PRRT2* mutations that can cause hemiplegic migraine. People with the mutation have epilepsy at a young age. They then develop movement disorders and some develop hemiplegic migraine and ataxia.[9]

As the research with clinical and genomic big data develops, there is a real possibility that personalised medicine for people with migraine will be achievable. There is also the hope that not only the treatment responders can be identified, but also those who will not respond, as well as those at risk of rare side-effects, that are not identified in clinical trials.[10,11]

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PACAP and VIP

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Research into potential new targets for migraine treatment provides insights into a complex system that may hold the key to the development of the next generation of pharmacological treatments.

Pituitary adenylate cyclase-activating peptide (PACAP) and vasoactive intestinal polypeptide (VIP), both widely expressed in the nervous systems including the trigeminal ganglion, could have a role in migraine.[1,2] The strongest clinical evidence for this comes from migraine-like attacks in humans being triggered after infusion of PACAP-37, PACAP-38 and VIP.[3-7]

Pre-clinical evidence also links these peptides to migraine. For example, vasodilation, neuronal sensitisation and mast cell degranulation,[8-11] and recently some interesting data linking PACAP to photophobia in mice, which can be blocked with a PACAP antibody.[12]

Parallels with the CGRP story raise the question of whether either is a distinct pathway involving PACAP, or whether PACAP is somehow dependent on CGRP or vice versa.

PACAP-induced photophobia is not attenuated by CGRP blockade. Similarly, CGRP-induced photophobia is not attenuated by PACAP blockade,[12] suggesting that the pathways are indeed independent. Sometimes PACAP and CGRP are co-expressed and in other areas they are found in separate neurons in the trigeminal ganglia,[2,11,13] again suggesting that the PACAP pathway might be distinct from the CGRP pathway. Therefore, there could be added benefit from inhibiting both. However, there is some evidence of dependency. For example, PACAP-38 (but not -27 or VIP) causes CGRP release from the trigeminal nucleus caudalis but not the trigeminal ganglia.[2] It may be context dependent as to whether there is dependency between these pathways or not.

With evidence for a role of PACAP and possibly VIP in migraine, there are a number of strategies and approaches that might be made from a pharmacotherapeutic point of view. These include anti-peptide antibodies, anti-receptor antibodies, and receptor antagonists. To date, most of the research effort has focussed on PACAP with a number of drugs in development, including two antibodies that bind to the PACAP peptide and one designed to target one of the PACAP receptors – PAC1.

Evidence so far suggests that the PAC1 receptor blocker (AMG-301) does not prevent migraine.[14]

Although up until now, little has been known about the PACAP receptors, research is gradually revealing a complex system and shows that there are many possible variations of the PAC1 receptor, which in turn lead to different signalling effects.[15,16]

Recent research from New Zealand found that the receptors activate multiple signalling pathways. PACAP is a potent agonist of PAC and VPAC receptors; and PAC1s may be a dual receptor for PACAP and VIP.[17] Additionally, PACAP-38 is more difficult to antagonise than -27 and VIP, which has implications for the choice of agonist to screen for different antagonists of these receptors.

Therefore, PAC1 cannot be ruled out as a target because the receptors are clearly more complex than might have previously been appreciated. It is also important to remember that there are other splice variants, for example PAC1VS, that are expressed in relevant locations, and there are other receptors that have been proposed to be PACAP receptors such as MrgB3 and GPR55, which need more research to determine their role.[18-20]

In summary, the development of anti-PACAP/VIP agents for the treatment of migraine needs to consider multiple receptors, multiple ligands and their sites of expression.

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Targeting ion channels

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Ion channels, originally investigated as therapeutic targets in hypertension, may prove useful in the search for new treatments for migraine.

Migraine is unusual among neurological disease in that it can be studied in vivo in humans by provoking attacks using pharmacological triggers such as glyceryl trinitrate (GTN), VIP and PACAP.[1,2] Interestingly, GTN induces migraine attacks in 80% of patients who had migraine without aura[3] and in around 50% of patients with migraine aura but without inducing aura.[4]
A difference in response to migraine induced with CGRP and PACAP has also been recorded: CGRP-induced migraine without aura in around 72% of participants (very few developed attack with aura) and PACAP induced migraine without aura in 58–73% of patients with migraine without aura.[5-11] These findings again pose the question as to whether migraine with and without aura are two distinct disorders, reflected by different sensitivities to the various substances used to induce migraine attacks or different signalling pathways, for example.

Nitric oxide acts directly rather than via a receptor. Some substances that induce migraine attacks such as glyceryl trinitrate and sildenafil[12] act via cGMP, whilst others such as VIP, PACAP and CGRP act via cAMP.[13]

Two ion channels – K_{ATP} (ATP-sensitive potassium channel) and BK_{Ca} (large conductance calcium-activated potassium channel) – originally identified as targets for treating hypertension because opening them dilates blood vessels, are expressed in migraine-related structures such as the cranial arteries, trigeminal ganglion and trigeminal spinal nucleus. They are also activated by several key molecules in migraine pathogenesis, such as CGRP, PACAP38, cilostazol, sildenafil and nitric oxide. Synthetic K_{ATP} and BK_{Ca} channel openers provoke headache.[14,15] For example, 16 patients (100%) developed migraine attacks after infusion with K_{ATP} channel opener levcromakalim, compared with one patient (6%) after placebo ($p=0.0001$)[16], while 21 out of 22 (95%) patients with migraine without aura developed migraine attacks after infusion of the BK_{Ca} channel opener MaxiPost, compared with none after placebo ($p<0.0001$).[17]

These data suggest that stimulation of the K_{ATP} and BK_{Ca} channel leads to an increase in extracellular potassium, which sensitises and discharges perivascular trigeminal primary afferents. The nature of the neuronal vascular coupling and the mechanism of the interaction between them is still to be elucidated.

In terms of migraine with aura, it has proved difficult to induce this type of migraine experimentally. Levcromakalim has been shown to induce migraine attacks with and without aura in 14 out of 17 patients diagnosed with migraine with aura, compared with 1 out of 17 following placebo.[18] The finding was surprising and further work is being carried out to try to replicate the results.

Possible mechanisms for the effects include:

- Activation of K_{ATP} channel expressed on glial cells causes K^+ efflux and an increase in $[K^+]o$ leading to migraine aura
- Activation of K_{ATP} channel expressed on vascular smooth muscle cells causes K^+ efflux and a sensitisation of meningeal afferents resulting in migraine headache (i.e. without aura)

In summary[19,20]:

- Opening K_{ATP} channels causes migraine attacks with and without aura
- Opening BK_{Ca} channels causes migraine attack without aura
- Opening these channels is the strongest provocation of migraine ever studied
- Blocking these channels may offer a new therapeutic target downstream from signalling molecules

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Safety and tolerability, wearing-off

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Newer treatments for migraine, such as CGRP mAbs, may not only offer improved efficacy, but also better tolerability compared with established oral drugs.

In the past, migraine medication was associated with tolerability issues. For example, oral first-line prophylactic medication was linked with side-effects such as:

- Cognitive dysfunction
- Weight gain
- Fatigue, sleepiness
- Reduction of blood pressure
- Disturbances in heart rhythm

Tolerability issues are cited as one of the most common reasons for discontinuation of the medication.[1] In one study of 8688 patients diagnosed with chronic migraine, adherence to antidepressants, beta blockers, or anticonvulsants ranged between 26% and 29% at 6 months and 17% to 20% at 12 months.[2]

Newer treatments such as CGRP mAbs appear to be generally well tolerated. Injection site reactions and nasopharyngitis are among the most common adverse events (AEs). Few patients discontinued treatment as a result of AEs. There have been no meaningful changes in vital signs, physical examination findings or ECG results,[3,4] and low rates of anti-drug antibody development and adverse events related to anti-drug antibodies.[5]

In the HERMES study for example, which compared the tolerability of erenumab with topiramate, 10.6% of patients treated with erenumab (70 mg/140 mg sc monthly; n=388) took a treatment break because of adverse events, compared with 38.9% in the group who received topiramate (50–100 mg oral daily; n=388). The secondary endpoint of the study showed that erenumab was more efficacious than topiramate: 55.4% of the erenumab group (215/388) achieved a ≥50% reduction in monthly migraine days from baseline compared with 31.2% (121/388) in the topiramate group (odds ratio 2.76; 95% confidence interval 2.06–3.71; p<0.001).[6]

CGRP has vasodilatory properties and effects on the angiotensin-renin system, which needs to be taken into consideration when treating patients with hypertension, for example.

Preclinical data showed that supratherapeutic concentrations of erenumab did not affect the vascular tone of isolated human coronary arteries. A combination of sumatriptan and erenumab showed no vasoconstrictive effects. In cynomolgus monkeys, no biologically significant changes in systolic, diastolic or mean arterial pressures were observed with a single dose of erenumab 225 mg/kg (yielding a systemic exposure 150 times higher than that in humans at the 140 mg dose level).[7] Analysis of

	Placebo (*N*=1043)	Erenumab 70 mg (*N*=893)	Erenumab 140 mg (*N*=507)
Incidence of hypertension AEs, n (%)[7]	9 (0.9)	7 (0.8)	1 (0.2)
Serious hypertension AEs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Exposure-adjusted incidence rates of hypertension, per 100 patient-years	3.6	3.3	0.8
Patients without antihypertensive medication at baseline, *n*	972	859	485
Patients initiating antihypertensive medication [a]during 12-week DBTP, *n* (%)[b]	12 (1.2)	7 (0.8)	1 (0.2)

N = number of patients. [a]Antihypertensive medications with a reported indication of hypertension. [b]Percentage calculated based on number of patients without antihypertensive medication at baseline. Abbreviations: AEs, adverse events; DBTP, double-blind treatment phase.
From: Dodick et al. (2021).8

Table 1. Pooled analysis of hypertension AEs and antihypertensive medication use during the 12-week DBTP

data from phase 2 and phase 3 clinical trials for erenumab shows that there was no significant difference in the percentage of patients experiencing hypertension adverse events (AEs) or serious hypertension AEs associated with erenumab treatment or the percentage of patients starting antihypertensive medication compared with placebo (see Table 1). However, postmarketing data revealed a total of 362 AEs of hypertension of which 26.2% (95/362) were serious. There were 245,000 patient years of exposure and the exposure-adjusted incidence of hypertension was 0.144 per 100 patient-years.[8]

Trial data for fremanezumab show that no significant changes in systolic or diastolic blood pressure were observed during among participants with hypertension, and BP-related AEs were infrequent: one participant had increased diastolic BP and one had reduced systolic BP.[9]

In summary, clinical trials have not demonstrated an increased risk of hypertension in patients with migraine treated with erenumab or other CGRP mAbs compared with placebo. In the postmarketing setting, hypertension AEs have been reported following the use of erenumab, many of which occurred in patients who had pre-existing hypertension or risk factors for hypertension. Additional data are needed to fully characterise those at risk, as well as the nature, timing, and extent to which hypertension is a risk associated with erenumab and other CGRP-pathway antibodies. In the meantime, it is good practice to measure blood pressure before initiating CGRP antibody drugs and to monitor patients' blood pressure while they are being treated with these medicines.

Wearing off?

There are different types of wearing off: during the 4-week interval between doses of CGRP mAbs and wearing off over time.

Post hoc analysis of clinical trial data from episodic (EVOLVE-1; EVOLVE-2) and chronic (REGAIN) migraine on the efficacy of galcanezumab 120 mg compared with placebo showed no wearing off effect during the dosing interval.[10]

Real world data show that wearing off was self-reported by 34.7% (25/72), with 80% stating that it occurred 1 week before the next injection. There was a variable pattern in how often wearing off occurred, but 32.0% (8/25) reported that it occurred with all injections; 12% (3/25) of patients reported having no pattern; 20.0% (5/25) reporting it during months 1–2; 8.0% (2/25) during months 3–4; 20.0% (5/25) during months 5–6, and one person noted wearing-off in the middle and late months, but not during the first 2 months.[11]

Five-year open-label data for treatment with erenumab 140 mg show that the drug maintains efficacy over this time in patients with episodic migraine. Mean (standard error) change in MMDs from baseline of 8.7 (0.2) days was –5.3 (0.3) days; an average reduction of 62.3% at year 5. No wearing off effects were observed.[12]

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Combination therapy and switching

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Combination therapy for migraine is logical from a mechanistic viewpoint, and is supported by real-world evidence.

A lock and key analogy can be an effective way of explaining to patients how the CGRP mAbs work, helping them to understand why it may require more than one trial of drug treatment to find the optimal medicine for them. They target the CGRP pathway by binding to CGRP peptide (ligand) or its receptors: the CGRP peptide acts as the key and the receptor acts as the lock. For example, erenumab blocks the lock, so less of the CGRP peptide can bind to the receptors, preventing activation. In contrast, fremanezumab, galcanezumab and eptinezumab attach to the key, binding to it and preventing it from activating CGRP receptors. However, it is not possible to know which drug will work best in an individual patient – so trial and error is the only way to find out.

Evidence suggests that CGRP levels are higher in people with migraine than those who do not have the disease.[1] CGRP is among others found in the thinly myelinated (Aδ) and unmyelinated (C) fibres and it is suggested that the CGRP-targeted mAbs act primarily on the A fibres, and not the C fibres. Current theories suggest that onabotulinum toxinA also acts as an inhibitor of the CGRP pathways, probably mediated through the C fibres more than Aδ fibres.[2] Therefore, there could be synergistic effects by combining different drugs that target the CGRP system.[3]

It is important to be realistic about the prospects of treatment with migraine drugs, and to tell patients that whilst their migraine cannot be cured, the symptoms can be reduced. It is also important to stop treatment that is not working. Therefore, defining clinical effectiveness is a key aspect of managing migraine, to be able to determine whether a drug should be continued or not. The two most important factors that lead to the decision of continuing preventive drug treatment are the following[4]:

1. Objective – reduction in use of acute migraine treatment medication.
2. Subjective – positive patient perception of treatment effectiveness.

Intensity, duration, frequency and impact of migraine attacks are also considered when deciding whether to continue with treatment.

Real-world evidence supports the use of combination therapy for chronic migraine, with favourable outcomes: adding a CGRP-targeted mAb to botulinum toxin in patients with chronic migraine was associated with further reductions in monthly headache days and monthly migraine days as well as reduced headache severity. There were no major tolerability issues across a range of mAbs (erenumab, fremanezumab and galcanezumab).[5-8]

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Pathophysiological Aspects

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Research into the nature of episodic and chronic migraine reveals insights into their characteristics, as well as possible links between the two forms of the disease.

For a patient to have chronic migraine they must have had episodic migraine (see Box 1).

Around 92% of migraine patients have episodic migraine, of whom around 2.5% will go on to develop chronic migraine each year. There are several risk factors associated with the development of chronic migraine, including acute medication overuse and depression for which there is the strongest evidence.[2]

A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura
C. On ≥8 days/month for >3 months, fulfilling any of the following:
   1. Criteria C and D for 1.1 Migraine without aura
   2. Criteria B and C for 1.2 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.

Box 1. International Classification of Headache Disorders (ICHD-3) definition of chronic migraine[1]

Although the International Classification of Headache Disorders (ICHD) definition of episodic and chronic migraine suggests a dichotomy, they are actually on a continuum when considering the degree of disability, for example.[3]

Interestingly, some patients remit from chronic migraine back to episodic migraine. In some cases, it is a result of treatment, but there are also cases where it occurs through the natural course of the disease. Data from the Chronic Migraine Epidemiology and Outcomes (CaMEO) study, for example, shows that nearly 75% of people with chronic migraine will remit to episodic migraine at some point during a 12-month period.[4]

Pozo-Rosich et al. provide a detailed summary of the structural and functional imaging data as well as the data on neurophysiology and neurochemistry of chronic migraine.[5] Currently, what is known represents only some pieces of the jigsaw puzzle. Some of the observations made about chronic migraine may relate to chronic pain in general, similarly for episodic migraine, where some observations relate to acute pain in general.[6]

In episodic migraine, CGRP levels were found to be raised in the trigeminovascular system.[7] In chronic migraine, an interictal increase of CGRP level has been observed in peripheral blood, which may act as a biomarker for chronic migraine.[8]

From an electrophysiological point of view, chronic migraine looks like a never-ending migraine attack.[9-12]

There are a number of studies suggesting involvement of the cortex, limbic system, hypothalamus and the brainstem in chronic migraine[13-18] but further studies are needed to discover how these are linked.

The hope is that in the future, when more is known about the mechanisms underlying chronic migraine and the risk factors associated with chronification of migraine, biomarkers can be developed that will help in the detection and management of the disease.

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Epidemiological and clinical aspects

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Although episodic and chronic migraine appear to be aspects of the same disease, one is not simply more of the other.

The definition of episodic and chronic migraine can, at a simple level, be seen as a difference in frequency of attacks: episodic migraine involves headache that occurs <15 days a month and chronic migraine occurs ≥15 days a month. However, the descriptor chronic can be misleading for GPs and non-specialist neurologists who think migraine is chronic if it lasts for 10–20 weeks, for example. The reason to separate episodic migraine from chronic migraine is the individual burden, the burden on society, comorbidities and costs.

The ICHD definition of chronic migraine requires that the headaches have features of migraine headache on at least 8 days per month.[1]

The prevalence of migraine varies depending on the definition used at the time: using the definition of chronic daily headache, the prevalence is 2.9%; if the ICHD definition is used, the prevalence is 0.4%.[2]

Patients with chronic migraine tend to be older, have a higher body mass index and are less educated than people with fewer than 15 headache days per month.[2] Other researchers have found that people with chronic migraine have a significantly lower quality of life than people with acute migraine.[3] Also, comorbidities vary between people with episodic and chronic migraine: those with chronic migraine more frequently have depression, anxiety and chronic pain, for example.[4] Chronic pain also seems to be a feature in patients with chronic migraine. Yoon et al. found that the odds of having frequent low back pain (defined as self-reported low back pain on ≥15 days/month) were between 13.7 (95% CI 7.4–25.3) and 18.3 (95% CI 11.9–28.0) times higher in all chronic headache subtypes when compared with no headache.[5] The finding suggests that the entire pain matrix is more vulnerable in patients with chronic migraine, which means they may be more likely to have chronic pain generally. Chronic migraine patients also have higher costs associated with their medical care than do patients with episodic migraine.[6]

Development of chronic headache may not have a linear relationship with headache frequency, such that below 15 headache days a month, headache is episodic, and above that threshold, it is chronic. It is likely to be more complex. Indeed they may be different stages of the same disease, however, the transition between episodic and chronic migraine, if measured using parameters such as disability, health-related quality of life, wellbeing and depression and anxiety, does appear to happen at around 15 headache days per month.[7]

Risk factors for transition from episodic to chronic migraine include headache frequency at baseline (10–14 days per month versus 1–4 days per month), frequent drug intake (>10 days per month) and chronic back pain.[8] Additionally, several risk factors predict the persistence of chronic headache, particularly being female and medication overuse.[9]

Therefore, it would seem that episodic and chronic migraine are the same disorder, but chronic migraine is not simply more migraine, it is a qualitative change. Compared with episodic migraine, the burden of chronic migraine is much higher, and it is associated with more comorbidities and higher healthcare costs.

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Societal burden of migraine

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Migraine presents a significant burden, both for the individuals who suffer with the disease and for the society they live in.

Migraine starts early in life, in childhood and adolescence: new-onset cases are most common in young girls.[1] Eventually, this results in a high prevalence of migraine (excluding probable migraine) of around 14%. The greatest burden of disease is experienced among young women where more than 1 in 5 have migraine. The occurrence of migraine has also been slowly increasing. For example, in Norway over an 11-year period, there has been a 1% increase in migraine occurrence.[2]

Migraine severity varies, with around a quarter of people with migraine having two-thirds of the attacks.[3]

The burden of migraine includes the clinical symptoms,disability and the cost.

Headache is the cardinal feature of migraine and the symptom cited by most migraineurs as the worst symptom of the disease, but others cite aspects such as photo- and phonophobia, as well as vomiting, etc.[4]

Without treatment, pain associated with migraine fluctuates between severe and unbearable, and nausea fluctuates following almost the same pattern, probably driven by the underlying pathophysiology of the brain.[5]

There is disability between attacks as well. For example, when people are expecting an attack, there can be avoiding behaviour and feelings of guilt for not being as productive at work (Figure 1). When asked, only 43% of patients report complete recovery between attacks and the same percentage say they were more or less recovered. However, 9% say they did not recover at all; that group would include people with chronic migraine.[3]

The Global Burden of Disease study found that the most prevalent neurological disorders were tension-type headache (1505.9 [uncertainty interval {UI} 1337.3–1681.6] million cases), migraine (958.8 [872.1–1055.6] million) and medication overuse headache (58.5 [50.8–67.4] million). More than half of the disability caused by neurological disorders in mid-life is caused by headache, with migraine being ranked number 1 in Western Europe in terms of disability-adjusted life years.[6] That level of disability has an impact on everyday life for people with migraine, especially their ability to work, time with family and time for leisure activities – the same factors that people in the general population without migraine regard as most important in life.[3]

Quality of life is also adversely affected by migraine. A web-based survey of 630 people with migraine in Sweden found that the average loss in quality-adjusted life years (QALYs) increased with increasing migraine frequency.

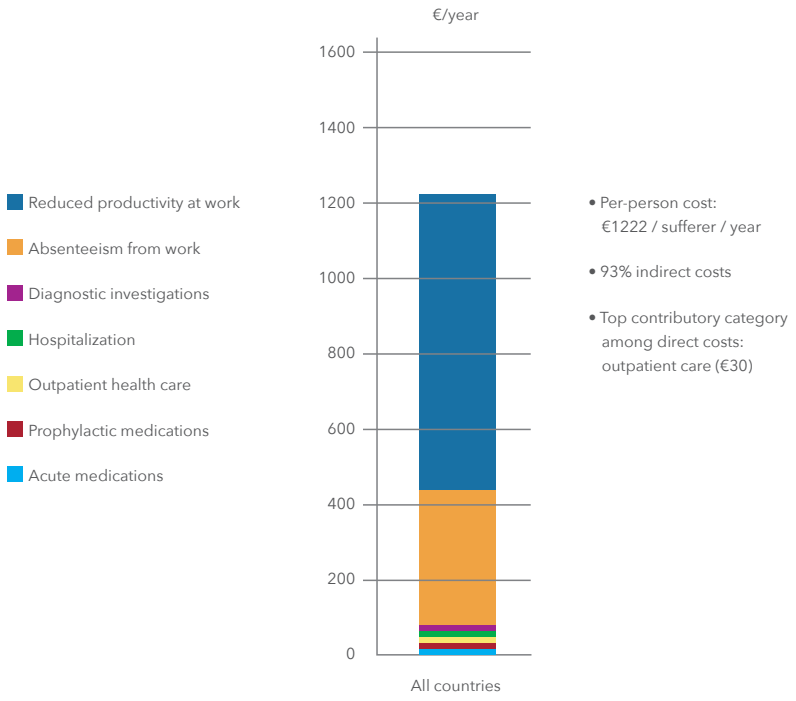

Figure 1 Mean cost of migraine per sufferer. Adapted from Figure 1 in Linde et al. (2021).[8]

The total average loss in QALYs per person and year was 0.10. The figure was significantly higher for respondents with chronic migraine compared with respondents with episodic migraine (0.25 vs 0.06, $p<0.001$).[7]

The mean cost of migraine per person in Europe is €1222 per year. Indirect costs, especially reduced productivity at work and absenteeism from work, account for 93% of the overall cost of migraine. Among direct costs, outpatient care amounts to €30 per person. Investment in migraine treatment, for example, would have an impact on other factors that account for a greater proportion of the overall cost. The annual cost of migraine increases with the frequency of attacks, with the cost of chronic migraine being around €20,000 per year.[8]

The total cost of migraine in Europe amounts to €112 billion annually. That breaks down to[8]:

- Migraine: €50 billion
- Medication overuse headache: €37 billion
- Tension-type headache: €21 billion
- Other: €3 billion

Indeed, the cost burden of headache is greater than the sum of the costs of multiple sclerosis, Parkinson's disease, and epilepsy.[9]

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Discrepancy between the recommendations and reimbursement regulations of the CGRP mAbs in the Nordics

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Differences in reimbursement rules in Nordic countries result in different levels of access to treatment, presenting challenges for clinicians trying to treat their patients, particularly in Denmark.

Reimbursement regulations have a significant impact on which patients clinicians can treat with CGRP-mAbs in the different Nordic countries (Table 1). In all countries but Finland, only patients with chronic migraine are eligible. In Finland, patients with ≥8 migraine days per month can receive the drugs. In Norway and Demark, medication overuse headache must be treated before a patient can receive a CGRP-mAb, but it is not a requirement in Finland and only a recommendation in Sweden (Table 2). Perhaps the biggest difference between the Nordic countries is who can give the treatment. In Denmark, only hospital-based neurologists can give CGRP-mAbs (clinicians in private practice are not allowed to administer the drugs), whereas in other countries, neurologists in private practice and pain specialists can give the medicines.

Requirements for continuing treatment also vary (Table 3). However, some criteria are not in the patients' best interests. For example, in Denmark the requirement for continuation of treatment is 30% reduction in moderate to severe migraine days or severe headache days. However, that omits mild migraine when a triptan would also be used to treat the symptoms, so the consumption of medicines overall is not reduced in the way it would be if a CGRP-mAb was used to treat mild migraine. In terms of quality of life for patients, the difference between a moderate migraine day and a mild migraine day is enormous but the current definition does not take that into account either. The solution may be either a reduction in moderate or severe headache days or monthly migraine days: that is something being explored in Denmark.

In Denmark, only the cheapest CGRP-mAb can be prescribed in most circumstances. In other countries, erenumab, fremanezumab and galcanezumab can be used. Switching is not allowed in Denmark if there is no response to the first drug prescribed as it is in Norway, Sweden and Finland, however switching is allowed in Denmark, if there are side effects.

Although in Denmark all healthcare is free at the point of use, it is not necessarily a better system than those that exist in other Nordic countries, where

	Norway	Sweden	Finland	Denmark
Who regulates?	The Norwegian Medicines Agency (Statens legemiddelverk)	TLV (national reimbursement authority) New Treatment (NT) council issues recommendations	Kela (Social Insurance Institution of Finland)	Danish Medicines Agency (Lagemiddelstyrelsen) and Medicinradet (recommendations)
Which patients can receive treatment?	Chronic migraine	0 (0.0)	8> migraine days per month	Chronic migraine
Are previous treatment failures required?	Failure* of preventive drugs from 3 different classes	Failure* of 2 preventive drugs	Failure* of 2 preventive drugs	Failure* of at least 1 anti-hypersensitive and 1 anti-epilectic drug
* Failure defined as lack of effect or intolerable side-effects				

Table 1. Pooled analysis of hypertension AEs and antihypertensive medication use during the 12-week DBTP

patients pay something towards the cost of their healthcare as they need it. If a similar system of part direct payment was adopted in Denmark, there may be fewer restrictions on what could be prescribed.

These rules also appear to have a direct impact on the number of patients treated: in Denmark around 1300 patients are treated compared with 7500 in Norway.

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Neurologists Marja-Liisa and Mikko Kallela (Finland), Neurologist Ingela Nilsson Remahl (Sweden), Neurologist, Lars Jacob Stovner (Norway), and Teva representatives

	Norway	Sweden	Finland	Denmark
Has MOH to be treated before starting CGRP-mAbs?	Yes	Not a requirement by TV for reimbursement, but a recommendation from NT council	No	Yes
Is failure to Botox required?	No	No	No	No
May both CGRP-mAbs and Botox be given?	Yes	This is not specified by neither TV nor NT	Yes	No
Who can treat?	Neurologists working at hospitals or in private practice. Physicians working at public hospitals	Neurologists working at hospitals or in private practice. Pain specialists trained to treat severe headache	Neurologists working at hospitals or in private practice. Physicians being migraine experts	Neurologists working at hospitals (not in private practice)*
* Treatment currently only given in 6 headache clinics in Denmark				

Table 2. Requirements for treatment

	Norway	Sweden	Finland	Denmark
Response needed to continue treatment?	Effect (not specified) after 12 weeks	No requirement for reimbursement (TLV). NT council recommends: At least 30% reduction in migraine days after first 3 months	At least 50% reduction in migraine days at weeks 9-12 after starting the treatment	At least 30% reduction moderate to severe migraine days or severe headache days
How often has response to be controlled?	After first 3 months. Then every year	Not specified by national authorities	According physicians preference	After first 3 and 6 months. Then every 6 months
Has treatment to be paused?	No, but new evaluation and prescription has to be made once a year	No requirement for reimbursement. NT councils recommends: Yes after 12-18 months	No	Yes for 1 month every 18 months

Table 3. Requirements for continuation of treatment

Impact on patients

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A survey of people with migraine in Norway and Finland provides some fascinating insights into how the disease affects their everyday lives.

The demographics of people with migraine and their treatment are revealed in a survey of 3397 patients with migraine from 41 countries, commissioned by the European Migraine and Headache Alliance (EMHA). Respondents from Norway and Finland totalled 364 (11%) (Denmark declined to take part): 5% of the sample in Norway and Finland were men compared with 10% of the survey population overall. In Finland, 48% of responders had chronic migraine compared with 70% in Norway. Seventy per cent of patients in Norway and Finland experienced migraine on 8 days or more per month and 82% had suffered migraine for 10 years or more.

Most patients received symptomatic over the counter medicine for their symptoms. CGRP mAbs were usually the last medicine be received. However, botulinum toxin and CGRP mAbs are used more frequently in Finland (47% of patients) and Norway (62%) than in EU countries overall (31%).

Even though two-thirds of patients reported that the treatment had an impact on their finances, only one-third asked for their treatment to be changed, perhaps indicating how much they valued their treatment and how important they deem it to be able to live something similar to a normal life.

Almost 100% of migraine patients received an effective treatment but access was difficult as evidenced by time since diagnosis, especially in Norway where 35% waited more than 5 years. Botulinum toxin and CGRP mAbs treatments were the most difficult treatments to obtain. The main issue, particularly in Finland, seems to be budget constraints and policy makers' stigma.

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The headache calculator – a diagnostic tool

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A new web-based tool is designed to help clinicians diagnose and manage migraine by giving them easy access to data generated by patients themselves, as well as the latest guideline information.

A digital tool is being developed to help non-specialist clinicians diagnose migraine for the benefit of patients.

Headache disorders are one of the main reasons for contact with a GP, and the majority of headache patients are treated in primary care. Unfortunately, the management and clinical knowledge of headache disorders among general practitioners is not optimal, so improved management in primary healthcare would benefit patients and society.

Answers from 367 Norwegian GPs responding to a survey found that[1]:

- More than 50% reported headache management to be clinically difficult.
- >96% rated their own knowledge of migraine and tension-type headache (TTH) as good or medium.
- Only 9% regarded their own insufficient knowledge to be the most important barrier.
- 70% believed that OTC (over the counter) drugs were the most commonly used medication by their chronic headache patients to treat headache.
- Only 4% thought that their headache patients used painkillers with addictive potential.
- One-third of the participants wrongly stated that the most commonly used headache prophylactics (antihypertensives, antiepileptics and antidepressant drugs) could lead to medication overuse headache (MOH).
- Almost 30% were unaware that triptans may induce MOH.
- Only 8% used diagnostic headache criteria (ICHD-3) regularly.

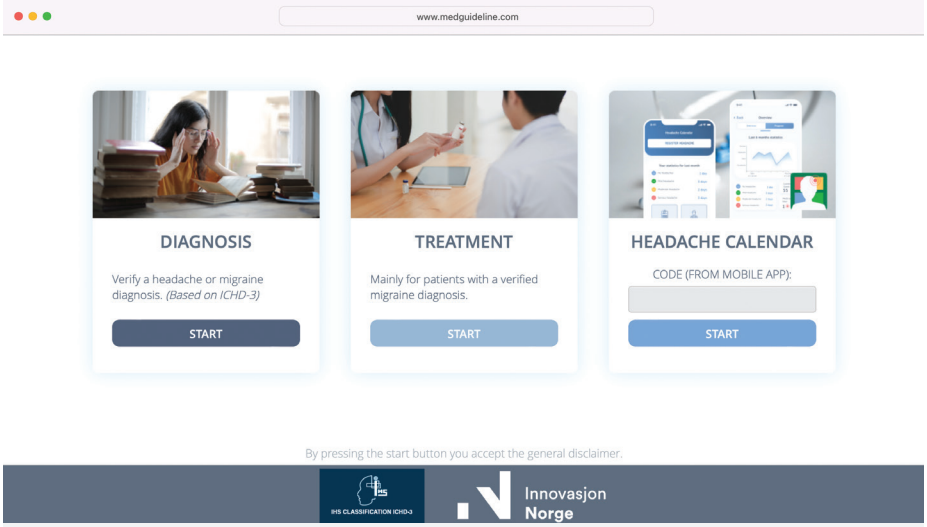

Figure 1 Screenshot from medguideline.com

Several factors point to the need for support in diagnosing migraine, including[2-4]:

- Pressure on time and cost in most healthcare systems.
- Treatment guidelines for chronic diseases becoming more complex.
- Migraine is underdiagnosed and patients are treated suboptimally.
- There are over 200 different diagnoses in headache (ICHD-3).
- Increased patient flow from GPs to headache specialists due to more advanced treatments.

A clinical support tool has been developed (Figure 1), comprised of three sections: diagnosis, based on International Headache Society classification ICHD-3; local guidelines, and a headache diary that generates data based on information patients input via an app on their phone. Data from the diary can be transferred directly from a patient's phone to their clinician's computer to help with diagnosis and treatment decisions. The tools are web-based and designed to be easy to use.[5] The app also provides patients with advice about their treatment.

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Intelligent digital technology in migraine management: examples from NTNU, Norway

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In future, biofeedback may be available at home to help people learn how to control aspects of their disease, while machine learning may ensure they receive effective medication more quickly than by just following traditional guidelines.

Biofeedback is a behavioural treatment that has been used for decades. It is based on self-regulation of physiological parameters, where patients are taught to recognise physiological and psychological activation and then learn exercises and techniques to engage with these changes in the body, assisted by physiological measurements. There is moderate-quality evidence for a medium-sized effect in adults[1] and low-quality evidence for a large effect in children and adolescents.[2]

The exact mechanisms of action for biofeedback have not been fully elucidated but it is thought that inducing physiological change results in beneficial biological adaptations, including:

- Long-term alterations in autonomic tone
- Reduction in cortical excitability
- Resilience to extrinsic stressors

Despite being effective, biofeedback is not widely available. In addition, the treatment is cost-and time-consuming and requires a trained therapist and specialised equipment, further restricting its use.

To address these challenges, a home-based system using smartphones and biofeedback sensors has been developed at NTNU. The aim was to produce a therapist-independent biofeedback treatment for people with migraine.

The first part of the project was to search for suitable sensors. In terms of surface electromyography (EMG), finger temperature and heart rate measurements, there was fair to excellent agreement between wearables such as smartwatches and stationary gold standard sensors (correlation coefficients ranging from 0.58 to 0.90).[3] A biofeedback algorithm was then created, combining feedback from trapezius surface EMG, peripheral skin temperature and heart rate.[4] A usability study of the set-up found high scores on functionality, lower scores on engagement and acceptable adherence among adults with 76% (SD 0.26) of daily biofeedback sessions completed in 1 month.[5]

A small pilot randomised controlled trial involved 23 adolescents, of whom 16 were randomised and used the app daily for 3 months. The biofeedback app was compared with a 'sham' version of the app. Unfortunately, there was poor adherence (40%) and a high drop-out rate (7/23). Therefore, the study failed primary efficacy outcome with no significant improvement in migraine frequency: the biofeedback group had a mean reduction of one migraine day/month (95% CI, -4.0–9.0) compared with the sham group.[6]

Another study using a heart rate variability app showed similar results with better outcomes among those with high adherence than those with low adherence.[7]

The data show that non-specific effects of treatment are lost when a biofeedback therapy is taken out of the clinic, and the treatment effect is lower. However, the researchers believe that the therapy may be useful for selected individuals who achieve high adherence.

Can machine learning predict treatment response?

Machine learning has been investigated as a prediction tool – to predict when a migraine attack might take place, and individual response to therapy, for example.

One study looked at forecasting attacks based on perceived stress. It involved 95 participants with episodic migraine with or without aura, who generated 4625 days of electronic data through completing a daily headache diary and scoring perceived stress levels. The performance on an unseen out-of-dataset sample was AUC 0.65 (95% CI, 0.6–0.67) which roughly translates to correct prediction of a headache or no headache the next day on approximately 2 out of 3 days.[8] In a smaller study with 18 participants and 295 days of data including diary data, premonitory

symptoms, and physiological data from biofeedback sessions, a similar result was seen with a performance of AUC 0.657 for predicting a migraine in the next 24 hours.

Machine learning is also being investigated to see whether it might be possible to predict an individual's response to a drug.

For example, one study looked at whether machine learning can predict individual treatment response and whether a machine prescription was superior to traditional heuristic evaluation. The study population comprised 1446 people with chronic migraine; 76 features or covariates were identified including aspects such as gender, age, frequency, intensity, symptoms, aura, headache triggers, comorbidities, family history, etc. Ten of the most commonly used migraine treatments were included and a clinically meaningful response was defined as a 50% reduction in headache frequency.

The machine learning model used was a causal multitask gaussian process model that infers individualised treatment effects (i.e. how likely a patient is to respond) from high-dimensional data to predict individualised treatment effects in unseen data.

The study found that a machine learning algorithm regularly arrived at a treatment with a 50% reduction in headache significantly sooner (-3.75 months; 95% CI, -3.993 to -3.507; $p<0.0001$) than the process following guideline and expert recommendations.

The data suggest that with relevant and sufficient data, machine learning can produce highly accurate forecasting models, and machine prescription can aid in choosing the correct migraine therapy at an individual level. The accuracy of these models is likely to increase with inclusion of more data.[9]

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