Nordic Migraine Symposium 22

Summary Report

The Many Faces and Phases of Migraine

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Treatment response as a biomarker

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Migraine is complex, encompassing a number of types, including with or without aura, retinal, with brainstem aura, hemiplegic, and so on,[1] so it may prove too complex for there to be just one biomarker. Work into migraine PRS (polygenic risk score), in other words an individual's predisposition to having migraine, shows some correlation with the ICHD-3 criteria for migraine without aura.[2,3] Further analysis of the genetic data reveals associations between certain genes and drug responses to CGRP antagonists and ditans, for example.[2,4]

The correlations between clinical trials for migraine treatments and GWAS suggests that there is a biological predisposition.[3]

However, treatment response may not be an ideal biomarker because it varies from person to person and depends on a multitude of factors, including: route of administration; absorption; metabolism; excretion; blood brain barrier (lipophilicity); volume of distribution; body fat; interactions with other medication; and patient age.

The old adage that if there is no response to a specific migraine drug such as a triptan it is not migraine is now known to be incorrect,[4,5] and some treatment response is not even specific for migraine. For example, some secondary headaches can respond to sumatriptan, e.g. subarachnoid haemorrhage.[6] Treatment response is therefore not a good biomarker because of low specificity.

In terms of efficacy data, in the case of an effective sc triptan, such as sumatriptan, 4 out of 10 patients do not respond, and among oral treatments, such as a combination of sumatriptan and naproxen, 7 out of 10 patients do not respond. For ditans the non-response rate is 60% and for gepants the figure is 80%, so these specific treatments are specific for a subpopulation and not all migraine. Similarly for monoclonal antibodies (mAbs), in episodic migraine about 50% of patients do not show a great response. The same is the case in chronic migraine,[7] therefore these treatments are biomarkers for some migraine but that is not the whole story. However, these migraine-specific treatments have improved understanding of the pathophysiology of migraine.[8]

The consensus seems to be that mAbs are approximately equally effective in migraine with and without aura.[9] However, when patients are selected for clinical trials there is a bias towards headache: the inclusion criteria are usually ≥4 headache days per month, so the pure migraine with aura patients might be excluded if they have no significant headache. Indeed there are two treatments that are more efficacious for migraine with aura than they are for headache, tonabersat and lamotrigine.[10,11]

In future we will see the identification of endophenotypes of migraine, which might be defined by treatment response, but it might prove difficult to find large numbers of a particular type of endophenotype to study (Fig. 1).[8,12] That is where data from the large registries that already exist for a number of conditions, including migraine [e.g. www.finregistry.fi] may help. Once sufficient numbers of patients who respond to one type of drug have been identified then the biomarkers will be easier to define.

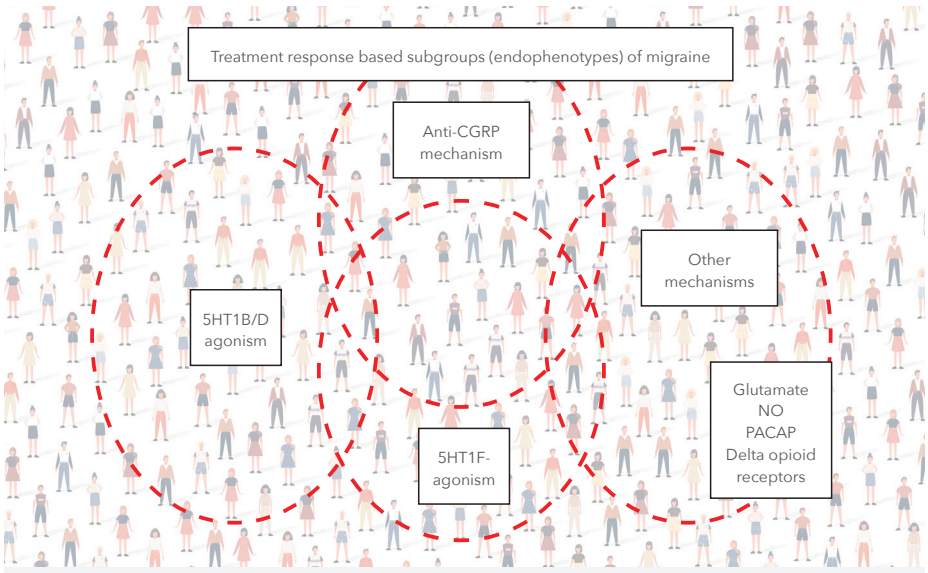

Figure 1 Identifying the endophenotypes of migraine.

References

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38(1):1–21.
2. Hautakangas H, Winsvold BS, Ruotsalainen SE, et al. Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. medRxiv 2021.01.20.21249647.
3. Happola P, Gormley P, Nuottamo ME, et al. Polygenic risk provides biological validity for the ICHD-3 criteria among Finnish migraine families. Cephalalgia 2022;42(4-5):345–56.
4. Chan C, Goadsby PJ. Recent advances in pharmacotherapy for episodic migraine. CNS Drugs 2019; 33(11):1053--71.
5. Tfelt-Hansen PC, Koehler PJ. One hundred years of migraine research: major clinical and scientific observations from 1910 to 2010. Headache 2011;51:752–78.
6. Pope JV, Edlow JA. Favorable response to analgesics does not predict a benign etiology of headache. Headache 2008;48(6):944–50.
7. Ashina M. Migraine. N Engl J Med 2020;383(19):1866–76.
8. Ong JJY, Wei DY, Goadsby PJ. Recent advances in pharmacotherapy for migraine prevention: from pathophysiology to new drugs. Drugs 2018;78(4):411–37.
9. Ashina M, Goadsby J, Dodick DW, et al. Assessment of Erenumab safety and efficacy in patients with migraine with and without aura: a secondary analysis of randomized clinical trials. JAMA Neurol 2022;79(2):159–68.
10. Hauge AW, Asghar MS, Schytz HW, et al. Effects of tonabersat on migraine with aura: a randomised, double-blind, placebo-controlled crossover study. Lancet Neurol 2009;8(8):718–23.
11. Buch D, Chabriat H. Lamotrigine in the prevention of migraine with aura: a narrative review. Headache 2019;59(8):1187–97.
12. Ashina M. Targeting enkephalins and pituitary adenylate cyclase-activating polypeptide (PACAP) in migraine. Brain 2022;145(8):2619–20.

Biomarkers with a focus on genetics

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A biomarker is a measurable indicator of a biological state, condition or disease. It can be measured and evaluated using biological tissue such as blood, urine or soft tissues. Biomarkers are used to examine normal biological processes. Pathogenic processes, and pharmacological responses to a therapeutic intervention, with a role that can be:

- Pharmacodynamic/response
- Predictive
- Safety
- Susceptibility/risk
- Diagnostic
- Monitoring

Biomarkers take decades or more to develop. However, in heterogeneous disorders such as migraine biomarkers they could help to:

- Simplify diagnosis by enabling improved, faster and more accurate diagnosis and prognosis.
- Develop new drug therapies by identifying novel drug targets or even a cure.
- Choose treatment by streamlining choice and thus move towards better outcomes and fewer side-effects, e.g. precision medicine.

It is known that there are strong genetic links in migraine.[1-3] And there has been a lot of progress in the last decade in the development of genetic biomarkers for migraine. Three main types of study have been used: linkage studies; candidate gene studies and GWAS (Genome Wide Association study). Linkage and candidate gene studies have helped identify a gene for familial hemiplegic migraine that maps to chromosome 19,[4] mutations in CACNA1A gene for the calcium channel for hemiplegic migraine[5] and migraine with or without aura.[6]

However, migraine is heterogenous and there have been conflicting results when trying to identify genetic markers among candidate genes.[7]

The first GWAS study in migraine as done 10 years ago with 2731 patients and 10,747 controls. Locus rs1835740 associated with migraine was found on chromosome 8q22.1. The association was replicated in 3202 patients and 40,062 controls. rs1835740 was found between two genes – MTDH (astrocyte elevated gene 1, also known as AEG-1) and PGCP (encoding plasma glutamate carboxypeptidase involved in glutamate homeostasis).[8]

A meta GWAS combining several studies including 59,674 patients and 316 078 controls was done in 2016. It identified 38 loci, 28 of which were new and the first one on chromosome X.[9]

A new meta GWAS involving 102,084 cases and 771,257 controls identified subspecific risk alleles associated with migraine for the first time, including:

- Migraine with and without aura – 29,679 cases with subtype information.
- Three risk alleles for migraine with aura – HMOX2, CACNA1A and MPPED2.
- Two risk alleles for migraine without aura – close to SPINK2 and close to FECH.
- Nine risk alleles for migraine regardless of subtype.

Two new risk loci include genes encoding recent migraine-specific drug targets – calcitonin gene-related peptide (CALCA/CALCB) and serotonin 1F-receptor (HTR1F) – were found. Migraine-associated variants were enriched in vascular and central nervous system tissue, which supports the hypothesis of neurovascular involvement in migraine.[10]

The next step in the research will be to see if there are connections with aspects such as treatment response, age of onset, trigger factors, chronic disease and sex differences, for example.

If a genetic variant is associated with treatment response it may help predict which patients are likely to respond and therefore streamline treatment choice. Some genetic markers for treatment response are already known for the triptans:

- Additive effects of the intergenic variants rs1024905 and rs6724624 are associated with triptan response in migraine without aura;[11]
- Previously been linked to migraine without aura;[9]
- Another GWAS migraine SNP, rs2651899, located in the PRDM16 gene, was associated with triptan response;[9]
- Serotonin transporter gene polymorphism (STin2 VNTR) confers an increased risk of inconsistent triptan response.[12]

However, more work is needed to confirm the findings.

Epigenetic biomarkers relate to phenotypic changes that do not involve alterations in the DNA sequence. For example, a small epigenome-wide association study of 67 migraine cases and 67 controls quantified patterns of DNA methylation in migraine. It found:[13]

- 62 independent differentially methylated regions (DMRs);
- 45 hypomethylated regions;
- 17 hypermethylated regions.

Migraine-associated DMRs were enriched in regulatory elements and in close proximity to genes involved in solute transportation (SLC2A9, SLC6A5, and SLC2A9) and haemostasis (DGKG, KIF26A, DOCK6, CFD). But so far this is the only study in this area.[13]

Provocation biomarkers involve various trigger factors that produce migraine attacks. Signalling pathways that cause migraine are identified through human provocation models. Only individuals with migraine develop provoked attacks. Examples include nitric oxide donor, glyceryl trinitrate,[14] pituitary adenylate cyclase-activating polypeptide (PACAP)[15] and calcitonin gene-related peptide (CGRP).[16]

Blood biomarkers might be useful to monitor treatment and predict response. For example, during the ictal phase, CGRP plasma concentrations are elevated in people with migraine compared with controls[17] and PACAP is elevated during spontaneous migraine attacks.[18] During the interictal phase CGRP plasma levels are elevated in episodic and chronic migraine.[19] Higher CGRP levels have been found in individuals who benefited from onabotulinumtoxinA, which may act as a predictor of response.[20]

Neuroimaging biomarkers may help identify structural and functional changes caused by migraine and / or its treatment. Electro- and magneto-physiological brain activity (M/EEG), neurovascular and metabolic recordings from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) all show characteristic patterns that differentiate between chronic and episodic migraine.[21]

In conclusion, there are several biomarkers proposed for migraine and research needs to continue to validate their role in clinical practice.

References

1. Russell MB, Rasmussen BK, Fenger K, Olesen J. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. Cephalalgia 1996;16(4):239–45.
2. Honkasalo M-L, Kaprio J, Winter T, et al. Migraine and concomitant symptoms among 8167 adult twin pairs. Headache 1995;35:70–8.
3. Whitty CW. Familial hemiplegic migraine. J Neurol Neurosurg Psychiatry 1953;16(3):172–7.
4. Joutel A, Bousser MG, Biousse V, et al. A gene for familial hemiplegic migraine maps to chromosome 19. Nat Genet 1993;5(1):40–5.
5. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell 1996;87(3):543–52.
6. Terwindt GM, Ophoff RA, van Eijk R, et al; Dutch Migraine Genetics Research Group. Involvement of the CACNA1A gene containing region on 19p13 in migraine with and without aura. Neurology 2001;56(8):1028–32.
7. Colson NJ, Fernandez F, Lea RA, Griffiths LR. The search for migraine genes: an overview of current knowledge. Cell Mol Life Sci 2007;64(3):331–44.
8. Anttila V, Stefansson H, Kallela M, et al; International Headache Genetics Consortium. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. Nat Genet 2010;42(10):869–73.
9. Gormley P, Anttila V, Winsvold B, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet 2016;48;856–66.
10. Hautakangas H, Winsvold BS, Ruotsalainen SE, et al. Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. Nat Genet 2022;54:152–60.
11. Cargnin S, Viana M, Sances G, et al. Using a Genetic Risk Score approach to predict headache response to triptans in migraine without aura. J Clin Pharmacol 2019;59(2):288–94.
12. Terrazzino S, Viana M, Floriddia E, et al. The serotonin transporter gene polymorphism STin2 VNTR confers an increased risk of inconsistent response to triptans in migraine patients. Eur J Pharmacol 2010;641(2-3):82–7.
13. Gerring ZF, McRae AF, Montgomery GW, et al. Genome-wide DNA methylation profiling in whole blood reveals epigenetic signatures associated with migraine. BMC Genomics 2018;19:69.
14. Olesen J, Iversen HK, Thomsen LL. Nitric oxide supersensitivity: a possible molecular mechanism of migraine pain. Neuroreport 1993;4(8):1027–30.
15. Schytz HW, Birk S, Wienecke T, et al. PACAP38 induces migraine-like attacks in patients with migraine without aura. Brain 2009;132(Pt 1):16–25.
16. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia 2010;30(10):1179–86.
17. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 1990;28(2):183–7.
18. Tuka B, Helyes Z, Markovics A, et al. Alterations in PACAP-38-like immunoreactivity in the plasma during ictal and interictal periods of migraine patients. Cephalalgia 2013;33(13):1085–95.
19. Ashina M, Bendtsen L, Jensen R, et al. Possible mechanisms of glyceryl-trinitrate-induced immediate headache in patients with chronic tension-type headache. Cephalalgia 2000;20(10):919–24.
20. Cernuda-Morollón E, Ramón C, Larrosa D, et al. Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: What happens after one year? Cephalalgia 2015;35(10):864–8.
21. Gomez-Pilar J, Martínez-Cagigal V, García-Azorín D, et al. Headache-related circuits and high frequencies evaluated by EEG, MRI, PET as potential biomarkers to differentiate chronic and episodic migraine: Evidence from a systematic review. J Headache Pain 2022;23:95.

Epidemiology

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Migraine is one the major health burdens during mid-life[1] and in terms of number of years lived with disability.[2]

Mid-life is the major focus for treatment of migraine when the disease prevalence peaks but younger and older age groups must not be forgotten as they also suffer with migraine, albeit at a lower level. However, chronic headache (more than 15 headache days/month) is not reduced as much at older age. In addition and unlike migraine, the prevalence of tension-type headache increases with age and may be a source of misdiagnosis (Fig. 1).[3]

The gender ratio of migraine varies with age: in children the female to male ratio is 1:1; in adults it is 3:1 and in elderly people it is 2:1.[4]

Unlike headache, migraine prevalence seems to vary by country; the reason is not clear but it may partly reflect differences in culture and diagnostic tradition. The trend, however, is an increase in all headache in all regions, whereas the prevalence of migraine and tension-type headache has remained quite steady overall.[3] One limitation of the analysis is the large inter-study variability. However, most studies have been done in high income countries, which are more homogenous in their study populations.[3] Disability adjusted life years (DALYs) rates per 100,000 population for headaches have stayed fairly level from 1990–2017 in the US, whereas the DALY burden for other neurological disease such as stroke, encephalitis, meningitis and traumatic brain injury has fallen.[5]

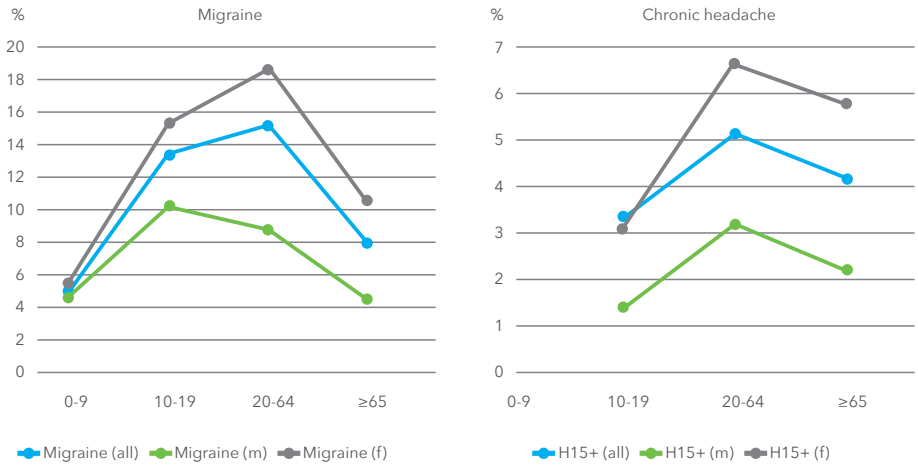

Figure 1 The prevalence of headache and migraine by age. Adapted from Stovner et al. (2022).

Factors influencing prevalence include year of publication – the later the study the higher the prevalence – and the number of participants – with a lower prevalence in studies with larger numbers of participants compared with smaller studies. Random sampling was associated with lower prevalence, compared with selected populations, as were studies conducted by interview compared with questionnaire. A higher prevalence was seen in studies including probable migraine compared with those including definite migraine only. Screening questions also influenced prevalence. For example, a higher prevalence was seen in studies where the screening question was 'have headache' compared with those with the screening question worded 'suffering from'.[3]

There are diagnostic challenges with children and elderly people with migraine that may affect prevalence. In children, for example communication can be an issue and there is the question of who should collect the data – should it be parents, for example, although that may introduce reporter bias. Parents who are not aware of their children's headache are likely to under-report whereas parents of children with migraine are more aware. There is a gender difference with parents more aware of daughters' headache, and parents who have headache themselves are more aware of their children's headaches.[6] Parents under report headache in their youngest children and fathers under report most, especially for daughters.[7,8]

A headache diary could be employed but there are questions about what age a diary can be used from and how it should be adapted for children.

Population studies in children show a fairly similar prevalence of migraine of about 28% with the higher prevalence

among adolescents,[9–11] whereas clinical studies show large variation.[12]

Elderly people with migraine have a different symptomatic picture compared with other ages with more tension-type headache like characteristics, lower severity and frequency but more aura. The aura is sometimes difficult to differentiate from a stroke or transient ischaemic event. We must not forget that there are more secondary headaches among older patients and a lower threshold for imaging is necessary.[4]

It has been suggested that elderly people with migraine have a different symptomatic picture compared with other ages and migraine can look like a stroke or transient ischaemic event (TIA). Migraine in elderly patients can be differentiated from TIA by:[13,14]

- Duration of aura;
- Visual, paraesthesias, focal numbness (very short);
- Gradually spreading/changing;
- Often some headache;
- Good prognosis/no vascular risk factors.

Prevalence of migraine in elderly studies is similar to that in children at around 10% but shows less variation in clinical studies. So it is important not to neglect the disease in these age groups.[15,16]

Healthcare use

Norwegian population health data show that 10–15 per 1000 population had at least 3 contacts with the health service for migraine in 2021, mostly in primary care. Thus only around 12% of the estimated total number of people with migraine use the health service in relation to their migraine. There are few regional differences in the number of days of sick leave but there are large variations in the availability and use of specialist health services for migraine.[17]

References

1. GBD 2015. Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol 2017;16:877–97.
2. Steiner TJ, Stovner LJ, Jensen R, et al. Lifting The Burden: the Global Campaign against Headache. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain 2020;21(1):137.
3. Stovner LJ, Hagen K, Linde M, et al. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. J Headache Pain 2022;23:34.
4. Straube A, Andreou A. Primary headaches during lifespan. J Headache Pain 2019;20(1):35.
5. GBD 2017 US Neurological Disorders Collaborators, Feigin VL, Vos T, et al. Burden of Neurological Disorders Across the US From 1990-2017: A Global Burden of Disease Study. JAMA Neurol 2021;78(2):165–76.
6. Şaşmaz T, Öner S, Öner Kurt A, et al. Prevalence and risk factors of Internet addiction in high school students. Eur J Public Health 2014;24:15–20.
7. Lundqvist C, Clench-Aas J, Hofoss D, Bartonova A. Self-reported headache in schoolchildren: Parents underestimate their children's headaches. Acta Paed 2006;95:940–6.
8. Lundqvist C, Rugland E, Clench-Aas J, et al. Children are reliable reporters of common symptoms: results from a self-reported symptom diary for primary school children. Acta Paed 2010;99:1054–9.
9. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol 2010;52(12):1088–97.
10. Sillanpää M, Lastunen S, Helenius H, Schmidt D. Regional differences and secular trends in the incidence of epilepsy in Finland: A nationwide 23-year registry study. Epilepsia 2011;52:1857–67.
11. Metsähonkala L, Sillanpää M. Migraine in children – an evaluation of the IHS criteria. Cephalalgia 1994;14:285–90.
12. Hershey AD, Powers SW, Vockell AL, et al. PedMIDAS: development of a questionnaire to assess disability of migraines in children. Neurology 2001;57(11):2034–9.
13. Fisher CM. Late-life migraine accompaniments as a cause of unexplained transient ischemic attacks. Can J Neurol Sci 1980;7(1):9–17.
14. Fisher CM. Late-life migraine accompaniments – further experience. Stroke 1986;17:1033–42.
15. Hagen K, Åsberg AN, Uhlig BL, et al. The epidemiology of headache disorders: a face-to-face interview of participants in HUNT4. J Headache Pain 2018;19(1):25.
16. Wijeratne T, Tang HM, Crewther D, Crewther S. Prevalence of migraine in the elderly: a narrated review. Neuroepidemiology 2019;52(1–2):104–10.
17. Helseatlas. Equitable health services – regardless of where you live? (www.skde.no/helseatlas; accessed 20 December 2022).

Migraine in the elderly

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Late-onset migraine, after the age of 50 years is considered a red flag symptom. Diagnosis of migraine in older adults is more complex because of the higher rates of atypical clinical features and comorbidities. Older adults are often excluded from randomised controlled trials of migraine therapies. As a consequence there is limited evidence of effectiveness, tolerability and safety of migraine therapies in older adults.[1,2]

Rates of vascular events (e.g. myocardial infarction and stroke), conditions (e.g. angina, claudication, cerebral small vessel disease) and procedures (e.g. coronary bypass surgery, carotid endarterectomy) increase with age in people with or without migraine, and there is an increase in the prevalence of cardiovascular risk factors (e.g. hypertension and hyperlipidaemia).[3,4] These factors can make diagnosis and treatment of migraine more complicated in older people.

Clinical features of migraine in older people are less stereotypical, often with bilateral headache and a higher frequency of autonomic symptoms (e.g. tachycardia, facial flushing). There is an increase in the frequency of attacks but a decrease in intensity. Aura without headache becomes more common in older people.[2,5–9]

Treatment

The primary management goals are identical in younger and older adults:

- Minimisation of migraine-attributed disability – best achieved by reduction in attack frequency – along with avoidance of acute medication overuse.
- Careful review of acute headache medication usage is mandatory.

A stepped care approach to acute medication for migraine is recommended, starting with NSAIDs. If they are contraindicated then paracetamol can be offered. If there is insufficient response to the treatment of three migraine attacks triptans can be tried after careful screening for cardiovascular factors. If the response is inadequate triptans can be combined with naproxen. If after three consecutive attacks there is still insufficient response to treatment or side-effects are intolerable a gepant or ditan can be used.[10]

Contraindications and cautions associated with migraine treatments and drugs for prevention of migraine in older adults need to be taken into account when making treatment decisions.[11]

Some data for the efficacy of monoclonal antibodies in the treatment of migraine in older patients show a similar response rate in people with migraine aged over 60 years to that of people with migraine aged under 60 years[12] and similar levels of cardiovascular adverse events (hypertensive crisis, tachycardia, ventricular extrasystoles) across age groups.[13]

In conclusion, migraine is a chronic, evolving and, for some individuals, a lifelong disorder. There are crucial gaps in the fundamental understanding of the effect of aging on migraine, which is largely built on epidemiological observation. Little is known about the mechanism of age-related remission. Long-term longitudinal studies of individuals with migraine are needed, and older people with migraine need to be included in trials if better treatment decisions are to be made for them.

References

1. Do TP, Remmers A, Schytz HW, Schankin C, et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology 2019;92(3):134–44.
2. de Rijk P, Resseguier N, Donnet A. Headache characteristics and clinical features of elderly migraine patients. Headache 2018;58:525–33.
3. Lipton RB, Reed ML, Kurth T, et al. Framingham-based cardiovascular risk estimates among people with episodic migraine in the US population: results from the American Migraine Prevalence and Prevention (AMPP) Study. Headache 2017;57(10):1507–21.
4. Buse DC, Reed ML, Fanning KM, et al. Cardiovascular events, conditions, and procedures among people with episodic migraine in the US population: results from the American Migraine Prevalence and Prevention (AMPP) Study. Headache 2017;57(1):31–44.
5. Martins KM Bordini CA, Bigal ME, Speciali JG. Migraine in the elderly: a comparison with migraine in young adults. Headache 2006; 46: 312–6.
6. Bigal ME, Liberman JN, Lipton RB. Age-dependent prevalence and clinical features of migraine. Neurology 2006;67:246–51.
7. Mazzotta G, Gallai V, Alberti A, et al. Characteristics of migraine in an out-patient population over 60 years of age. Cephalalgia 2003;23:953–60.
8. Fisher CM. Late-life migraine accompaniments – further experience. Stroke 1986;17:1033–42.
9. Wijman CAC, Wolf PA, Kase CS, et al. Migrainous visual accompaniments are not rare in late life. Stroke 1998;29:1539–43.
10. Ashina M. Migraine. N Engl J Med 2020;383(19):1866–76.
11. Ashina M, Buse DC, Ashina H, et al. Migraine: integrated approaches to clinical management and emerging treatments. Lancet 2021;397(10283):1505–18.
12. Nahas SJ, Naegel S, Cohen JM, et al. Efficacy and safety of fremanezumab in clinical trial participants aged ≥60 years with episodic or chronic migraine: pooled results from 3 randomized, double-blind, placebo-controlled phase 3 studies. J Headache Pain 2021;22(1):141.
13. Lampl C, Kraus V, Lehner K, et al. Safety and tolerability of erenumab in individuals with episodic or chronic migraine across age groups: a pooled analysis of placebo-controlled trials. J Headache Pain 2022;23:104.w

Migraine in paediatric patients

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Children's vocabulary differs from adults and so their description of migraine symptoms will differ – describing nausea as a sore throat, for example, because they are not familiar with the term 'nausea'. That may lead to misunderstanding and misdiagnosis.

Left untreated, or misdiagnosed, migraine leads to school absenteeism and presenteeism. It can result in problems with social life, taking too little exercise, psychiatric comorbidity and long-term consequences for work and income.

There are a number of challenges to managing paediatric migraine. Neurologists rarely see patients under the age of 18 years and not all neurologists are headache specialists. Paediatricians are very conservative about giving medications for migraine, and again not all paediatricians are headache specialists. Primary care doctors may have too little knowledge and interest in migraine and not all doctors in primary care are headache specialists. Another challenge is that there are few clinical studies on migraine medications under the age of 18 years, although that situation is changing.

Treatment should involve a combination of non-pharmacological and pharmacological approaches.

Sleep duration appropriate to age is important; regular meals, including breakfast, are important, as is hydration. Physical activity can be beneficial. Rest and relaxation is also helpful following an attack.

Cognitive therapy combined with prophylactic medication is more effective than medication alone.[1]

One of the most important goals in managing migraine is to prevent episodic migraine from transforming into chronic migraine. Yet we hesitate to start preventive treatment in children with migraine. Sometimes that may involve using off-label medication because of the dearth of clinical studies.

Acute medication

Patients have usually tried over the counter medications such as NSAIDs or paracetamol before they see their doctor, so the likely starting point for treatment when people with migraine come to clinic is triptans. It is good to offer a choice of triptans as well as different formulations – a nasal spray and a tablet, for example.

For female patients it is important to ask about menstrual migraine and menstrual-related migraine. NSAIDs may be effective, but if there is insufficient response after three cycles naratriptan or frovatriptan can be offered as 'mini prophylactive treatment'. Magnesium during the luteal phase can be beneficial. The combination contraceptive pill taken continuously with pauses only every 3-6 months is another option, but oestrogen should not be used for migraine with aura especially if the patient smokes as well.[2,3]

It is important to show young people with migraine respect and to take time over the first consultation to get to know them, to make them feel comfortable. Ask plenty of questions. Discuss the treatment options, and involve the child in the decisions. Offer non-pharmacological approaches and talk about triggers but do not stress them too much. Cognitive therapy in groups can be beneficial especially as it introduces patients to others with similar problems and they can learn from each other. Acute and prophylactic pharmacological treatments need to be tailored to the individual who must be followed closely. So it is good to encourage them to keep a diary, which also helps them feel more in control.

References

1. Powers SW, Kashikar-Zuck SM, Allen JR, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. JAMA 2013;310(24):2622-30.
2. SLK okt. 1999. Nytt om Legemidler Vol. 22 suppl. 6/ Infomed Årgang 10, no. 6, September 2002.
3. Dahløf CGH, Linde M, Linton-Dahlof P. Migrän, Kliniska Aspekter. 2003

Misconceptions about migraine and treatments – social media, Google, etc.

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Data from a survey of around 4000 people with at least one headache day in the past year found that around 44% have never consulted a doctor. Of those who have a weekly headache and are burdened by it 28% have never been to their doctor.[1] In the general population the figure may be higher and in countries where migraine is not recognised as an illness it will be higher still.[2] So these individuals are most likely obtaining information about migraine from other sources such as social media.

People are influenced by what others are saying online and they do search for information about pathophysiology and treatment of migraine, for example.[3] The most popular videos on migraine on YouTube have 163 million views. So the impact of social media cannot be ignored. In terms of the sources of information of online information healthcare providers form the minority (<20%). The majority are from people who do not deal with migraine professionally. Around 44% of the treatments recommended fall into the category of complementary and alternative medicine, which comprise mostly homemade solutions such as a couple of lemon slices in drinks.[4] People who follow these recommendations are most likely to still have a headache afterwards.

The most common searches for migraine topics on Google relate to pathophysiology or treatment.[5] Some of the commonest non-pharmacological treatments that come up are relaxation, ice pack on the head or neck, which are not supported by evidence. Perhaps worryingly NSAIDs are recommended in less than two-thirds of the Google search results. Opioids are also recommended online. In terms of preventive measures avoiding triggers is the most common Google search result. While avoiding triggers can be part of migraine management it should not be the main approach. Herbs and acupuncture are also mentioned for which there is little evidence of efficacy. Botox comes out as the number one recommended pharmacological preventive. First-line pharmacological approaches do not appear on all the pages.[6] So there is a discrepancy between internet search results and what clinicians would recommend.

Many of the websites that are found as a result of a Google search for migraine are owned by commercial organisations.[6] Health professionals and professional organisations such as IHF should have a greater representation.

Among people with migraine eligible for treatment with monoclonal antibodies, i.e. those with the highest burden of disease, 33% had actively used non-pharmacological interventions within the previous 3 months. However, on a scale of 1 to 6 they rate efficacy as 2, so it is below acceptable. Nevertheless they spend more than DKK1000 per month on these therapies.[7] So even the most educated patients are still paying for products that may not work, based on recommendations they may find

from sources other than their medical provider. Another survey of people with migraine in Denmark found that more than half had used complementary or alternative medicine for their illness – similar to the proportion who had used a healthcare provider.[8]

Perhaps effort should be put into disseminating information from healthcare professionals and promoting it so that it ranks higher in online searches than information from commercial and non-professional sources.

References

1. Do TP, Stefansen S, Dømgaard M, et al. One-quarter of individuals with weekly headache have never consulted a medical doctor: a Danish nationwide cross-sectional survey. J Headache Pain 2022;23(1):84.
2. Ashina M, Katsarava Z, Do TP, et al. Migraine: epidemiology and systems of care. Lancet 2021;397(10283):1485–95.
3. Liu M, Caputi TL, Dredze M, et al. Internet Searches for Unproven COVID-19 Therapies in the United States. JAMA Intern Med 2020;180(8):1116–8.
4. Saffi H, Do TP, Hansen JM, Dodick DW, Ashina M. The migraine landscape on YouTube: A review of YouTube as a source of information on migraine. Cephalalgia 2020;40(12):1363–9.
5. Google trends. Explore what the world is searching (https://trends.google.com; accessed 20 December 2022).
6. Bojazar R, Do TP, Hansen JM, et al. Googling migraine: a study of Google as an information resource of migraine management. Cephalalgia 2020;40(14):1633–44.
7. Rundblad L, Cullum CK, Sacco S, et al. Use of non-pharmacological therapies in Individuals with migraine eligible for treatment with monoclonal antibodies targeting calcitonin gene-related peptide (CGRP)-signaling: a single-center cross-sectional observational study. Front Pain Res (Lausanne) 2022;3:935183.
8. Characterizing healthcare utilization patterns in a Danish population with headache: Results from the nationwide Headache in Denmark (HINDER) panel.

Patients' frequently asked questions and demands and how to address them

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Patients' questions regarding acute or prophylactic medication are mostly about:

- Timing and dosage, for example:
  - When should I take acute treatment?
  - I was prescribed medication to take once a day. Should I take it in the evening or morning?
  - I did not understand the instructions for increasing the dose, can we go over them again?

- Side-effects, for example:
  - The doctor prescribed me medicine x. Now I read that it can cause y. I do not want to start the medicine.

- Medication overuse headache, for example:
  - I have been told not to use acute treatment too much. How often can I use acute medication?
  - How do I choose which attacks to treat?

Patients are confused by medication that has to be titrated over time: they forget whether they were supposed to take it once a day or once a week or every five days, and when and by how much they should increase the dose.

There are a lot of questions about side-effects, even before patients start their medication. When patients collect their medicine and read the patient leaflet they may decide to not take the treatment because they are concerned about side-effects such as weight gain, confusion or dizziness. As a result when they return to the clinic a couple of months later it is only then the doctor discovers they have not even started their treatment, so they have effectively wasted one appointment. That is why it is important to explain side-effects carefully to patients at the outset.

Patients usually know they should not take too much acute medication but may not know what the limits are because nobody has told them. This is an opportunity for healthcare professionals to educate them about the risk of medication over use headache. Patients with chronic migraine also want to know how to choose which attacks to treat, because the total number of days each month their treatment is limited to is usually less than the number of days they will experience headache. It is a question for which there is no clear answer because the advice is usually to take medication early rather than wait but there is no way of knowing whether an attack is going to be mild or severe.

Most questions from patients relate to their expectations for their treatment: they want treatment that has no side-effects, works immediately and that can be taken for every episode. Obviously such a treatment does not exist, so a lot of time is spent in educating patients about what can be realistically expected from treatment.

Patients also want to know about treatment response: when can I expect prophylactic medication to work; why am I being asked to take a triptan again when it did not work the last time?

Questions about non-pharmacological treatments focus on supplements, lifestyle, environment and other alternative methods. Topics raised in the popular media can also propagate questions. Recently in Finland there were questions about ferritin values following a magazine interview with a woman who claimed that taking iron supplements cleared her migraine. Similarly with daith piercing.

As for migraine itself, patients want to know whether it can be cured, how they can tell if they are having an attack and what days they should record in their headache diary. Again it is important to explain to patients how to use their headache diary, particularly what to report and how.

Many questions about migraine stem from fears that something much more serious is wrong, and there is a lot of debate about imaging. Clinicians are aware that they should not order scans unnecessarily but patients may be angry if they do not receive a scan. That is why it is important to involve patients in decision making about their treatment, so that they understand the process and are in agreement. Providing written instructions is also

very important because it allows patients to go through everything they have been told during an appointment in their own time and to digest the information. Information should be written in non-technical language using as few medical abbreviations as possible, making sure everything is clear, including information such as when to take a medicine that is prescribed as 'twice a day', for example.

Perhaps the most important aspect of the whole process is to gain patients' trust by building a good relationship from the beginning.

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Patients who might be viewed as self-educated or internet-educated have a lot of questions when they visit their physician, who they expect to know almost everything. Clinicians have to be aware of that and they have to address it. Sometimes patients will source good information and advice but they are often not aware that a lot of information on the internet, for example, is not evidence-based or peer reviewed and yet they may trust it. Steven Hawking once said that the greatest enemy of knowledge is not ignorance, it is the illusion of knowledge.

The most frequently asked questions seem to be similar across settings – those asked of clinicians, nurses, on social media, etc.

Demanding patients expect a cure; no side-effects; a complete explanation of symptoms, reactions and prognosis; to be understood, and that clinicians have an up-to-date knowledge of everything regarding medication and treatment. The most important aspect in interacting with these patients for clinicians is communication in a way that is not condescending, and that patients can understand.

When communicating with patients, healthcare professionals must:

- Be open and honest;
- Show respect and acknowledge patients' personal experience;
- Always be aware of individual differences in symptoms and responses to medication;
- Remember that statistics and clinical experience are not the same.

Living with a chronic disorder requires a lifetime of continuous education, not only for patients but also for the healthcare professionals looking after them. Interactions with patients provide valuable knowledge and learning for those responsible for their care. No-one is ever too old to learn, because no-one can know everything.

New EHF guideline on the use of mAbs for migraine prevention

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Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.

Guidelines can play an important role in health policy formation and have evolved to cover topics across the healthcare continuum (e.g. health promotion, screening, diagnosis)

Guideline development needs to be based on a rigorous process and based on evidence, not solely on expert opinion.

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology is one example of a framework for developing guidelines. It is structured, transparent framework for developing and presenting evidence summaries.[1] As part of the process the quality of evidence used to develop guidelines is rated from high to low. If the quality of evidence is high it means that further research is unlikely to change confidence in the estimate of effect. Very low quality evidence is very uncertain. Strong recommendations in guidelines usually reflect high-quality evidence but occasionally a strong recommendation can be based on weak evidence, where there is a clear advantage to the intervention (i.e. benefits far outweigh disadvantages). Similarly, a weak recommendation may be based on high quality evidence where the balance of benefits and harms are similar.

In the absence of evidence, expert consensus statements are useful but they should be clearly signalled as such.

Updated guidelines on the use of monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway for migraine prevention were published in June 2022.[2] The guideline is in two parts – the first is based on GRADE methodology and the second is based on expert opinion.

Trials supporting the use of mAbs are all of high quality (Fig. 1). Efficacy was judged on three criteria – change in monthly migraine days, at least 50% responder rate, and change in monthly days of medication use for acute attacks. All of the mAbs were beneficial in episodic and chronic migraine prevention, and as a result the guidelines make a strong recommendation for the use of mAbs as a preventive treatment in episodic and chronic migraine. The evidence also supports the use of erenumab rather than topiramate for prevention for people with episodic or chronic migraine based on tolerability. The evidence is from one study only so is of low quality, nevertheless it was considered that there were greater benefits from erenumab than topiramate.[2]

In the expert consensus statement section of the guideline there is a recommendation that: 'In individuals with migraine who require preventive treatment, we suggest monoclonal antibodies targeting the CGRP pathway to be included as a first line treatment.' In other words, mAbs targeting the CRGP pathway should be considered alongside other drugs. Of course, local reimbursement rules will have a bearing on this, so in some countries mAbs will not be available as first-line treatment. However, the guideline may provide some basis on which to change current rules.[2]

Contraindications and comorbidities also help to guide treatment selection. For example CGRP-mAbs could be considered in:

- patients with medication overuse,
- obese individuals who have depression,
- and in those with other psychiatric illness.

They should be avoided in people with cardiovascular disease and in women who may become pregnant.[3-x5]
Other consensus statement recommendations include a suggestion that individuals with episodic or chronic migraine who start a new treatment with one mAb targeting the CGRP pathway should have the mAb's efficacy evaluated after a minimum of 3 consecutive months of treatment.[2]
mAbs are challenging the conventional temporal paradigm for migraine

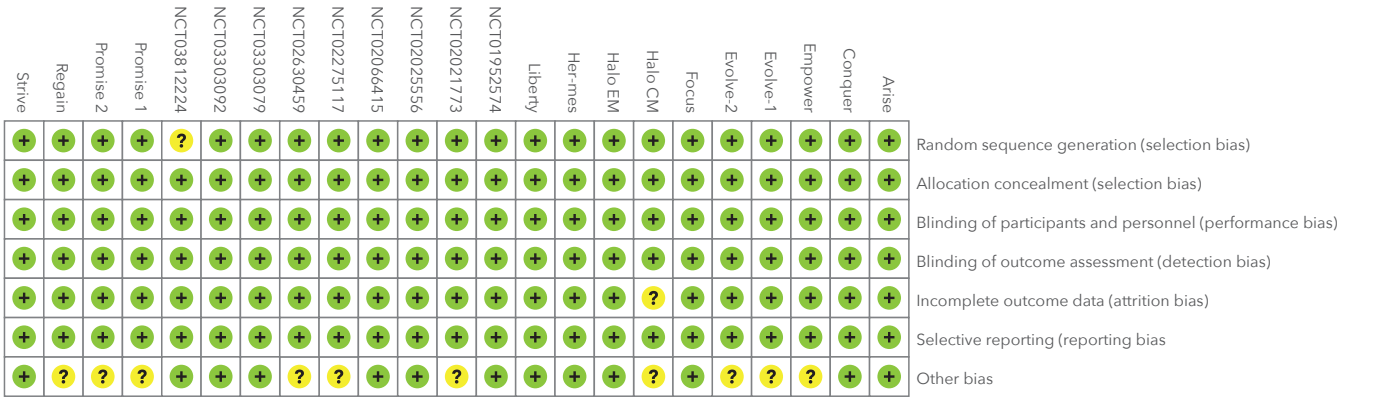

Figure 1 Risk of bias summary for each included study. Reproduced from Sacco et al. (2022).

treatment. It used to be thought that treatment should last for as short a time as possible partly because patients became non-adherent to therapy over time, to some extent due to side-effects. However, for well tolerated therapies such as mAbs expert consensus suggests considering a pause in the treatment with mAbs targeting the CGRP pathway after 12–18 months of continuous treatment. If deemed necessary, treatment should be continued as long as needed. In individuals with migraine who pause treatment, the suggestion is to restart treatment if migraine worsens after treatment withdrawal.[2]

For patients who do not respond to one CGRP-mAb, switching may be a possible strategy even though there is insufficient evidence on the benefits of switching.[2]

References

1. GRADE (www.gradeworkinggroup.org; accessed 20 December 2022).
2. Sacco S, Amin FM, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update. J Headache Pain 2022;23:67.
3. Sacco S, Braschinsky M, Ducros A, et al. European headache federation consensus on the definition of resistant and refractory migraine. J Headache Pain 2020;21:76.
4. D'Amico D, Tepper SJ. Prophylaxis of migraine: general principles and patient acceptance. Neuropsychiatr Dis Treat 2008;4(6):1155–67.
5. Silberstein SD. Preventive Migraine Treatment. Continuum (Minneap Minn) 2015;21(4 Headache):973–89.

Comorbidities and management

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The term comorbidity is used for an entity that occurs before the onset, during the course, or after the treatment of a disease. Although there are different mechanisms of migraine comorbidity, the most plausible one is bidirectional causality due to common risk factors.

It is known that people with migraine are at increased risk of vascular disease, including ischaemic stroke, transient ischaemic attack, haemorrhagic stroke, cardiac events, possibly with vascular death and brain lesions.[1] It is therefore important to check these risk factors in people with migraine.

Management involves lifestyle modification such as stopping smoking where appropriate, regular exercise, healthy diet, etc.[2]

Non-vascular comorbidities of migraine include:[3]

- Psychiatric disorders (depression, anxiety, bipolar disorder, panic disorder, PTSD);
- Sleep disorders (RLS, narcolepsy, insomnia, daytime sleepiness, OSA);
- Pain disorders (low back pain, fibromyalgia, abdominal pain);
- Gynaecological disorders (pre-eclampsia, endometriosis, PMS);
- Movement disorders (Parkinson's disease, essential tremor, Tourette's syndrome, dystonia);
- Other disorders (syncope, obesity, asthma, allergies, diabetes, multiple sclerosis, cancer).

Migraine is associated with epilepsy: 1–17% of people with migraine have epilepsy compared with 0.5–1% of the general population, and the prevalence of migraine is increased in epilepsy patients, especially among children and adolescents with migraine. EEG abnormalities may be seen in people with migraine but they do seem

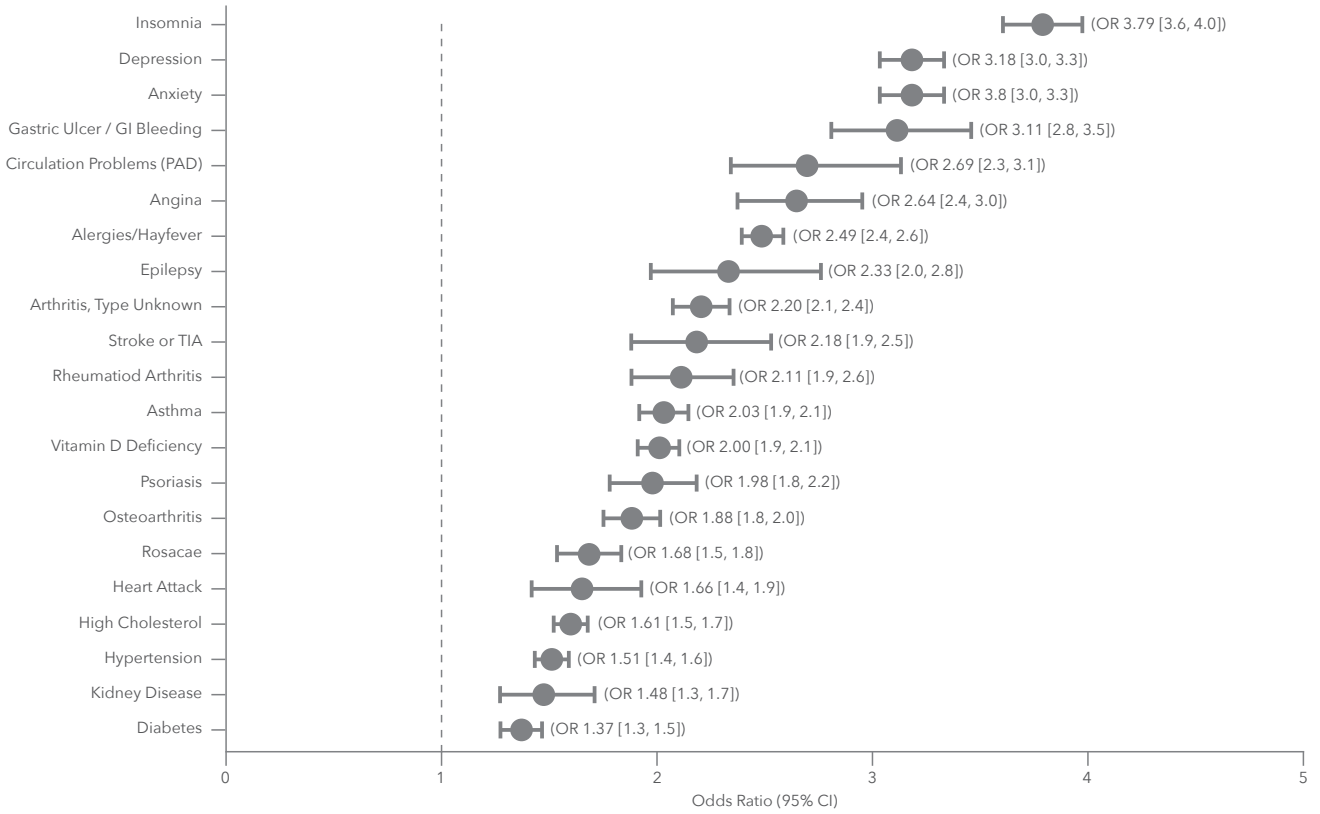

Figure 1 Relative odds of migraine (and 95% CI) vs. migraine-free controls for each comorbid condition*. *Adjusted for sociodemographic characteristics (age, gender, Hispanic origin, race, marital status, employment, household income). Reference group is the non-migraine cohort. GI, gastrointestinal; OR, odds ratio; TIA, transient ischemic attack. Reproduced from Buse et al. (2022).

to be related to cortical spreading depolarisation. Antiseizure drugs such as topiramate and lamotrigine are effective in migraine.[4,5]

A prospective, web-based survey of 15,133 people with migraine and 77,453 controls found that the most commonly reported comorbidities with migraine were insomnia, depression and anxiety. Other common comorbidities included gastric ulcer/GI bleeding, circulation problems, angina, allergy/hay fever, epilepsy, etc. (Fig. 1).[6]

Some conditions were associated with headache intensity [e.g. inflammation (psoriasis, allergy), psychiatric disorders (depression, anxiety) and sleep conditions (insomnia)] and others were associated with headache frequency (e.g. gastric ulcers/GI bleeding, diabetes, anxiety, depression, insomnia, asthma and allergies/hay fever).

In the CaMEO study there was an attempt to classify migraine into different natural subgroups based on 'profiles of comorbidities and concomitant conditions'. The analysis included 11,837 people with migraine who responded to a web-based survey and reported ≥1 comorbidity. Researchers identified eight subgroups (classes 1-8). Individuals in class 1 had most of the comorbidities, while individuals in class 8 had the fewest comorbidities. They found that those in class 1 had the highest MIDAS (Migraine Disability Assessment) grade score and those in class 8 had the lowest MIDAS grade. Those with pain syndromes alone (class 7) or combinations of respiratory/psychiatric (class 2) and respiratory/pain (class 3) disorders had a moderately severe clinical phenotype. Those with a low prevalence of comorbidities (class 8) or cardiovascular comorbidities alone (class 6) had a milder clinical phenotype.[7]

The comorbidities in patients with migraine provide some indication of how disabling their migraine might be. Further research into the common pathways of these comorbidities in patients with migraine may lead to insights into pathophysiology of the disease and better treatment in the future.

References

1. Sacco S, Ripa P, Grassi D, et al. Peripheral vascular dysfunction in migraine: a review. J Headache Pain 2013;14:80.
2. Stroke112 (stroke112.org; accessed 8 December 2022)
3. Ferrari MD, Haan J, Charles A, et al. (eds). Oxford Textbook of Headache Syndromes. Oxford: Oxford University Press, 2020.
4. Davassi C, Pulitano P, Mecarelli O. Migraine. In: Mecarelli O. (ed.) Clinical Electroencephalography. Cham, Switzerland: Springer, 2019.
5. Jancic J, Djuric V, Samardzic J, et al. Comorbidity of migraine and epilepsy in pediatrics: a review. J Child Neurol 2018;33:801–8.
6. Buse DC, Reed ML, Fanning KM, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study. J Headache Pain 2020;21(1):23.
7. Lipton RB, Fanning KM, Buse DC, et al. Identifying Natural Subgroups of Migraine Based on Comorbidity and Concomitant Condition Profiles: Results of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. Headache 2018l;58(7):933–47.

Combining preventative therapies

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There are European guidelines for management of headache for primary care from the European Headache Foundation[1] as well as guidelines for Denmark,[2] Finland, Norway and Sweden. Combining therapies is not mentioned in the EHF Guidelines, nor in the Finnish or Norwegian guidelines. The Danish guidelines say that there is no evidence for combining prophylactic therapies. According to the Swedish Headache Association guidelines oral prophylactics, but not botulinum toxin, may be combined with CGRP monoclonal antibodies.

A literature search of PubMed using the MeSH (medical subject headings) terms 'migraine' AND 'prophylaxis' AND 'combination' resulted in 191 publications since January 2012.

In practice, monotherapy is the most common approach to preventive therapy. For example, the majority (90%) of patients with episodic migraine were controlled on single preventative medicines in a tertiary centre in India.[3] The proportion (89%) was similar among patients with oral migraine prophylaxis in a Swiss healthcare insurance database.[4] For chronic migraine, it was more common to use more than one medication. For example, in a tertiary centre in Italy, two-thirds of patients with chronic migraine were prescribed ≥2 prophylactics simultaneously.[5]

In other specialities it is common practice to combine several drugs for prophylaxis, for example in cardiology where an average of four drugs is used.

Barriers to using polypharmacy for migraine prevention include drug interactions, cost and adherence. However, in reality there is little risk from drug interactions with drugs used to prevent migraine. Direct costs will be lower than the saving of indirect costs if frequent or chronic migraine is effectively treated, and one-third of patients are non-adherent on monotherapy; that is not made worse by using more than one drug.[6–9]

Some people favour non-pharmacological approaches, and there is some evidence to support them. For example, physical activity, which is regarded as a trigger for migraine, may actually be beneficial between attacks, in episodic migraine at least.[10] There is also some evidence that aerobic exercise can be as effective as pharmacotherapy in people with frequent migraine.[11–13] Aerobic exercise is recommended in European, Swedish

and Norwegian guidelines. It is mentioned in the Danish guidelines, but not mentioned in Finnish guidelines.

According to the Swedish FYSS guidelines, prophylactics may be combined with physical exercise.[14] For example, the combination with amitriptyline is more effective than amitriptyline alone.[15] Similarly, progressive muscle relaxation and biofeedback lead to an additive effect when combined with pharmacological prophylaxis.[16] Amitriptyline combined with cognitive behavioural therapy was found to be more effective in reducing days with headache and migraine-related disability than amitriptyline plus education in young people with chronic migraine.[17] Adding acupuncture to patients already on pharmacological prophylaxis resulted in significant improvement.[18]

In terms of oral drug preventive treatments, no trials were found on combinations of first-line drugs in primary care (beta blockers, candesartan, amitriptyline). Adding propranolol is not useful if chronic migraine is not adequately controlled by topiramate.[19]

Combining drugs so that lower dosages can be used is a helpful strategy to reduce side-effects. For example, two-thirds of patients responding to high dosages of topiramate or valproate but experiencing intolerable side-effects reported benefit and improved tolerability on their combination in low dosage. The combination of flunarizine and topiramate is more effective with less body weight change than flunarizine or topiramate in monotherapy.[20,21]

Oral treatments can be combined with injectables. For example, in patients with chronic migraine who are being treated with a partially effective oral drug, anti-CGRP mAbs can be added, and the oral drug can be withdrawn later, and vice versa for patients with chronic migraine who are being treated with partially effective anti-CGRP mAbs.[22]

There may be a case for combining botulinum toxin with anti-CGRP mAbs as they have different modes of action and there could be a synergistic effect.[23] Indeed, real world evidence reviews indicate the combination is well tolerated and has additional clinical benefits over monotherapy.[24–27]
In conclusion, single-drug prophylaxis is the preferred first-line approach for both new and old generation drugs. Combining this with non-pharmacological prophylaxis as needed is uncontroversial. Polypharmacy prophylaxis should be tried in cases of refractory migraine (resistance to single drug + non-pharmacology) and low-dose drug combinations may also be tried in cases intolerant to full-dose monotherapy.

References

1. Steiner TJ, Jensen R, Katsarava Z, et al. Aids to management of headache disorders in primary care (2nd edition). J Headache Pain 2019;20:57.
2. Schytz HW, Amin FM, Jensen RH, et al. Reference programme: diagnosis and treatment of headache disorders and facial pain. Danish Headache Society, 3rd edition, 2020. J Headache Pain 2021;22:22.
3. Angra M, Bhardwaj A, Sharma A, et al. Is single-drug prophylaxis in migraine prevention a better option than combination therapy? An observational study in a rural tertiary care center in north west India. J Neurosci Rural Pract 2019;10(3):479–82.
4. Huber CA, Agosti R, Näpflin M, Blozik E. Treatment patterns in patients using triptan and prophylactic medication: an analysis of clinical practice prior to the introduction of CGRP antagonists. J Pain Res 2019;12:2211–21.
5. D'Amico D, Curone M, Tullo V, et al. Polytherapy for the prophylaxis of chronic migraine: an Italian survey. Neurol Sci 2011;32 Suppl 1:S185–8.
6. Dozza AL, Krymchantowski AV. Adherence to migraine treatment does not depend on the number of prescribed medications. Arq Neuropsiquiatr 2013;71(3):171–3.
7. Linde M, Jonsson P, Hedenrud T. Influence of disease features on adherence to prophylactic migraine medication. Acta Neurol Scand 2008;118(6):367–72.
8. Linde M, Gustavsson A, Stovner LJ, et al. The cost of headache disorders in Europe: the Eurolight project. Eur J Neurol 2012;19(5):703–11.
9. Martelletti P. Combination therapy in migraine: asset or issue? Expert Rev Neurother 2020;20(10):995–6.
10. Varkey E, Hagen K, Zwart JA, Linde M. Physical activity and headache: results from the Nord-Trøndelag Health Study (HUNT). Cephalalgia 2008;28(12):1292–7.
11. Hagen K, Wisløff U, Ellingsen Ø, et al. Headache and peak oxygen uptake: The HUNT3 study. Cephalalgia 2016;36(5):437–44.
12. Varkey E, Cider A, Carlsson J, Linde M. A study to evaluate the feasibility of an aerobic exercise program in patients with migraine. Headache 2009;49(4):563–70.
13. Varkey E, Cider A, Carlsson J, Linde M. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. Cephalalgia 2011;31(14):1428–38.
14. Swedish National Institute of Public Health. Physical activity in the prevention and treatment of disease (www.fyss.se/in-english/introduction; accessed 8 December 2022).
15. Santiago MD, Carvalho Dde S, Gabbai AA, et al. Amitriptyline and aerobic exercise or amitriptyline alone in the treatment of chronic migraine: a randomized comparative study. Arq Neuropsiquiatr 2014;72(11):851–5.
16. Kropp P, Meyer B, Meyer W, Dresler T. An update on behavioral treatments in migraine – current knowledge and future options. Expert Rev Neurother 2017;17(11):1059–68.
17. Powers SW, Kashikar-Zuck SM, Allen JR, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. JAMA 2013;310(24):2622–30.
18. Foroughipour M, Golchian AR, Kalhor M, et al. A sham-controlled trial of acupuncture as an adjunct in migraine prophylaxis. Acupunct Med 2014;32(1):12–6.
19. Silberstein SD, Dodick DW, Lindblad AS, et al. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. Neurology 2012;78(13):976–84.
20. Krymchantowski AV, Jevoux Cda C. Low-dose topiramate plus sodium divalproate for positive responders intolerant to full-dose monotherapy. Headache 2012;52(1):129–32.
21. Luo N, Di W, Zhang A, et al. A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis. Pain Med 2012;13(1):80–6.
22. Sacco S, Bendtsen L, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain 2019;20(1):6.
23. Pellesi L, Do TP, Ashina H, et al. Dual therapy with anti-CGRP monoclonal antibodies and botulinum toxin for migraine prevention: is there a rationale? Headache 2020;60:1056–65.
24. Armanious M, Khalil N, Lu Y, Jimenez-Sanders R. Erenumab and OnabotulinumtoxinA combination therapy for the prevention of intractable chronic migraine without aura: a retrospective analysis. J Pain Palliat Care Pharmacother 2021;35(1):1–6.
25. Blumenfeld AM, Frishberg BM, Schim JD, et al. Real-world evidence for control of chronic migraine patients receiving CGRP monoclonal antibody therapy added to OnabotulinumtoxinA: a retrospective chart review. Pain Ther 2021;10(2):809–26.
26. Mechtler L, Saikali N, McVige J, et al. Real-world evidence for the safety and efficacy of CGRP monoclonal antibody therapy added to OnabotulinumtoxinA treatment for migraine prevention in adult patients with chronic migraine. Front Neurol 2022;12:788159.
27. Silvestro M, Tessitore A, Scotto di Clemente F, et al. Additive interaction between Onabotulinumtoxin-A and Erenumab in patients with refractory migraine. Front Neurol 2021;12:656294.

Multidisciplinary management

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Although there are a number of studies into multidisciplinary care of people with headache more are needed. However, the evidence so far seems to show improvement in symptom control and patient satisfaction.[1-6]

Multidisciplinary treatment should aim to inform and educate patients better in handling headache and to improve therapy, reduce headache frequency and enhance quality of life.[1] A team of healthcare professionals is central to the multidisciplinary approach, including neurologists, physiotherapists, headache nurses and psychologists (Fig. 1).

Situations where a multidisciplinary approach should be considered include:

- Patients with chronic and refractory headaches of any type
- Headaches with severe physical and/or psychological comorbidities
- Medication overuse headache (where withdrawal attempts have failed)
- Requests from patients are increasing
- Possibly new patients?

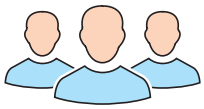
Patient education is an important part of the process to help them understand their illness and learn about aspects they may not be aware of, such as what aura is.

The Danish Headache Centre has a large team, including nine neurologists, five headache nurses, four physiotherapists and two psychologists (Fig. 1). There is also access to a dentist and psychiatrist.

Headache Nurse:

Headache School (4 weeks, 2.5 hours)

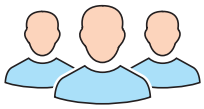
Ear acupuncture (NADA) 45 minutes, 12 times



Psychologist:

Pain and stress management (8 weeks, 2.5 hours)

Relatives — (1 evening, 2 hours)



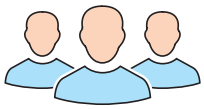
Physiotherapist:

Relaxation therapy (6 weeks)

Gym strength (8 weeks)

Cardio (12 weeks)

IIH physical activity

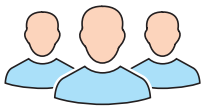


In-patients:

MOH — 6 bed, 12 days

Neurologists, Headache nurse,

Physiotherapist, Psychologist

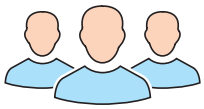


PTH:

10 persons, 1 year

Headache specialist, Headache nurse,

Physiotherapist, Psychologist



Managing waiting lists?

Secretaries

Delegated responsibility

Remember to move patients from list, when not relevent

Figure 1 The teams involved in patient management at the Danish Headache Centre.

The Centre offers patients six main group meetings where therapeutic courses for patients are available to complement drug therapy. These include pain and stress management with a psychologist, relaxation therapy with a physiotherapist and ear acupuncture.

Nurses who are members of the multidisciplinary team provide a:

- 'bridge' and middleman who provides connection between other healthcare personnel,
- common link in the treatment,
- contact that is easy to reach.

Their role includes:

- individual consultations,
- medication (side-effects, titration, change in medication),
- patient education/group sessions,
- telephone consultations/ follow-ups/open phone hours (advice and support),
- withdrawal from medication overuse headache,
- supervise/educate new staff and stay updated,
- specific treatments (GON-blocks, Botox, CGRP-mAbs, oxygen, Imigran injections),
- administration (handling journals and documentation according to guidelines),
- evaluate and improve written information,
- team meetings,
- reflection/development/decide whether there is a need for improvement / make changes?

For this type of organisation to work efficiently and effectively there needs to be:

- a good plan,
- close contact with headache specialists,
- allocated time for supervision,
- guidelines,
- ongoing education (meetings, courses, forums, congresses, etc.),
- opportunities to learn from others,
- room for innovation.

References

1. Gaul C, Visscher CM, Bhola R, et al. Team players against headache: multidisciplinary treatment of primary headaches and medication overuse headache. J Headache Pain 2011;12(5):511–9.
2. Wallasch T-M, Angeli A, Kropp P. Outcomes of a Headache-Specific Cross-Sectional Multidisciplinary Treatment Program. Headache 2012;52:1094–1105.
3. Gaul C, Liesering-Latta E, Schäfer B, et al. Integrated multidisciplinary care of headache disorders: A narrative review. Cephalalgia 2016;36(12):1181–91.
4. Gaul C, van Doorn C, Webering N, et al. Clinical outcome of a headache-specific multidisciplinary treatment program and adherence to treatment recommendations in a tertiary headache center: an observational study. J Headache Pain 2011;12(4):475–83.
5. Jensen R, Zeeberg P, Dehlendorff C, Olesen J. Predictors of outcome of the treatment programme in a multidisciplinary headache centre. Cephalalgia 2010;30(10):1214–24.
6. Zeeberg P, Olesen J, Jensen R. Efficacy of multidisciplinary treatment in a tertiary referral headache centre. Cephalalgia 2005;25(12):1159–67.

Safety, tolerability and possible interactions of the mAbs

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Monoclonal antibodies (mAbs) have a reputation for being well tolerated (apart from the well-known side-effects of constipation and injection site reactions) and have few if any interactions. A Google search also suggests that there are no interactions with the drugs.[1]

Randomised controlled studies support the notion that general tolerability of mAbs is good, with similar levels of side-effects in people with migraine being treated with mAbs and those receiving placebo, including constipation.[2]

Tolerability of mAbs also seems to be favourable compared with other drugs used to treat migraine. For example, there were fewer treatment-related adverse events and fewer treatment withdrawals with erenumab compared with topiramate.[3]

However, caution is advisable because mAbs are relatively new, so there are fewer years of experience with them compared with more established therapies. On average it takes around 4.2 years before the first postmarketing safety events are reported. During that time there have been three withdrawals of mAbs, two due to cardiovascular adverse events and one because of progressive multifocal leukoencephalopathy.[4]

Constipation is seen at similar levels in patients treated with mAbs as those exposed to placebo in randomised controlled studies. However, real world evidence reveals a range of rates of, for example, erenumab-associated constipation, from 7.6% in Spanish patients to 32.6–65% among Dutch patients. This may not be so surprising given CGRPs physiological role in stimulating intestinal propulsion, secretion and transit in humans.[5]

CGRP also causes vasodilation so there is a question as to whether CGRP antibodies might cause vasoconstriction or prevent vasodilatation.[6] A study of 88 patients randomised to receive 140 mg erenumab i.v. or placebo found that erenumab did not adversely affect exercise time in a high cardiovascular risk population of patients. However, these were not patients with migraine.[7]

There have been reports of erenumab-associated raised blood pressure. For example, in a retrospective analysis of postmarketing case reports submitted to the FDA Adverse Event Reporting System from 17 May 2018 to 30 April 2020 there were 61 cases of elevated blood pressure. Of those 86% (49/57) were women; 41 cases were associated with a serious outcome as defined by regulatory criteria and seven cases require hospitalisation.[8]

A more recent Dutch study found that among patients treated with erenumab (n=109) systolic and diastolic pressure were raised compared with baseline for 12 months of follow-up ($p<0.001$). In patients who received fremanezumab (n=87) systolic but not diastolic pressure was raised compared with baseline at 3 months ($p=0.006$) and 6 months ($p=0.004$) follow-up. Four patients with normal blood pressure at baseline required antihypertensive treatment after starting treatment with erenumab.[9]

There are a few case reports of people treated with mAbs who experience a worsening of their Raynaud's symptoms.[10] For example, two cases of people with migraine who reported Raynaud's phenomenon exacerbated while taking fremanezumab and galcanezumab) and one case of new-onset Raynaud's phenomenon while taking erenumab.[11]

In another study of 169 patients with history of migraine, past or current treatment with CGRP antagonists (mAbs or gepants), and diagnosis of primary or secondary Raynaud's phenomenon 9 (5.3%) exhibited microvascular complications after initiation of CGRP antagonist therapy for migraine. Complications ranged from worsening Raynaud's phenomenon (characterised by more frequent episodes of pain and discoloration elicited by cold temperature exposure) to worsening facial telangiectasias to digital gangrene and autonecrosis that required distal digit amputation.

Five of the nine patients (55.6%) had previously diagnosed Raynaud's phenomenon. The other four patients (44.4%) were newly diagnosed with Raynaud's phenomenon after administration of CGRP antagonists. The CGRP antagonist agents temporally associated with the microvascular complications included: galcanezumab (three patients); erenumab (five patients), and fremanezumab (one patient). The mean time from

CGRP antagonist induction to microvascular complication was 163 days (range 26–365 days).[12]

Other case studies include a report of thunderclap headache after starting treatment with erenumab, which resolved after treatment with verapamil 40 mg three times a day.[13]

One of Dr Artto's patients who had chronic migraine and chronic cluster headache had treatment-related adverse effects following treatment with mAbs. She was treated initially with erenumab. That was followed by fremanezumab when erenumab was no longer effective, however, there was no response so the patient was treated with galcanezumab. A few days after the first dose the patient developed a skin infection that required treatment with antibiotics. After the second dose she developed abscesses to her breasts and gluteal region. She needed treatment with several antibiotics and took several months to recover.

Drug interactions

mAbs are broken down into smaller peptides and amino acids by proteolytic pathways and are not metabolised by either CYP450 or mono-amine oxidase type A (MAO-A) enzymes.

Drug interactions due to pharmacokinetics with other migraine medications are unlikely to occur because of different routes of administration (oral versus parenteral). The kidneys and the liver are not involved in the elimination and metabolism of mAbs.[14]

No interaction between erenumab and oral contraceptives or sumatriptan was observed in studies with healthy volunteers, and the mAb has no relevant food–drug interactions. Concomitant use of acute migraine treatments (analgesics, ergots and triptans) and migraine preventive medicinal products during clinical studies did not affect pharmacokinetics of fremanezumab. Moreover, mAbs do not show any pharmacokinetic interactions with other drugs.[14] Also, in reducing migraine symptoms mAbs reduce the need for other migraine medications and therefore reduce the risk of drug-drug interactions.

References

1. Ferri N, Bellosta S, Baldessin L, et al. Pharmacokinetics interactions of monoclonal antibodies. Pharmacol Res 2016;111:592–9.
2. Alasad YW, Asha MZ. Monoclonal antibodies as a preventive therapy for migraine: a meta-analysis. Clin Neurol Neurosurg 2020;195:105900.
3. Reuter U, Ehrlich M, Gendolla A, et al. Erenumab versus topiramate for the prevention of migraine – a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia 2022;42(2):108–18.
4. Downing NS, Shah ND, Aminawung JA, et al. Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. JAMA 2017;317(18):1854–63.
5. Holzer P, Holzer-Petsche U. Constipation caused by anti-calcitonin gene-related peptide migraine therapeutics explained by antagonism of calcitonin gene-related peptide's motor-stimulating and prosecretory function in the intestine. Front Physiol 2022;12:820006.
6. McCulloch J, Uddman R, Kingman TA, Edvinsson L. Calcitonin gene-related peptide: functional role in cerebrovascular regulation. Proc Natl Acad Sci USA 1986;83(15):5731–5.
7. Depre C, Antalik L, Starling A, et al. A randomized, double-blind, placebo-controlled study to evaluate the effect of Erenumab on exercise time during a treadmill test in patients with stable angina. Headache 2018;58(5):715–23.
8. Saely S, Croteau D, Jawidzik L, et al. Hypertension: a new safety risk for patients treated with erenumab. Headache 2021;61:202–8.
9. de Vries Lentsch S, van der Arend BWH, Maassen VanDenBrink A, Terwindt GM. Blood pressure in patients with migraine treated with monoclonal anti-CGRP (Receptor) antibodies: a prospective follow-up study. Neurology 2022;99(17):e1897–e1904.
10. Wigley FM, Flavahan NA. Raynaud's Phenomenon. N Engl J Med 2016;375(6):556–65.
11. Evans RW. Raynaud's Phenomenon associated with calcitonin gene-related peptide monoclonal antibody antagonists. Headache 2019;59(8):1360–4.
12. Breen ID, Brumfiel CM, Patel MH, et al. Evaluation of the safety of calcitonin gene-related peptide antagonists for migraine treatment among adults with Raynaud phenomenon. JAMA Netw Open 2021;4(4):e217934.
13. Rozen TD, Bhatt AA. Reversible cerebral vasoconstriction syndrome developing after an erenumab injection for migraine prevention. Cephalalgia 2022;42(3):250–6.
14. Szkutnik-Fiedler D. Pharmacokinetics, Pharmacodynamics and drug-drug interactions of new anti-migraine drugs-Lasmiditan, gepants, and calcitonin-gene-related peptide (CGRP) Receptor Monoclonal Antibodies. Pharmaceutics 2020;12(12):1180.

Rationale for switching of preventative treatments

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Answering the question about whether switching is a good strategy for preventing migraine when using anti-CGRP mAbs is difficult because there are no head-to-head studies comparing the different mAbs. Placebo-controlled trials suggest there is not a great difference in efficacy between different anti-CGRP mAbs.[1]

In Denmark at least, the Danish Medicines Agency (Lægemiddelstyrelsen) and Medicinrådet (the national council that provides guidelines for the use of drugs at Danish hospitals), have decided that switching between CGRP mAbs is not permitted due to lack of evidence of efficacy.

Prophylactic treatments are effective (as determined by 50% reduction in migraine frequency) in only 40–50% of patients and are often discontinued because of side-effects, e.g. topiramate by 25%.[2,3] There is therefore a need for switching preventive drugs in people with migraine. Indeed a consensus statement in 2021 said it is generally agreed that efficacy and tolerability of migraine preventive treatments vary considerably among patients – therefore it is often necessary to switch to another option.[4]

It should also be remembered that no two individuals are alike so there can be significant variation in efficacy of a drug between individual patients despite efficacy of different drugs appearing similar in clinical trials when comparing population effects.[5]

With the triptans, for example, it is known that if one is not effective for an individual patient they may respond when switched to another.[4]

So why should the same not be true of anti-CGRP mAbs?

mAbs are also known to differ in terms of tolerability and safety. The tolerability and safety of anti-CGRP mAbs have been demonstrated in RCTs and corroborated by long-term clinical studies: adverse events leading to study discontinuation were uncommon (≤6%). The most frequently reported AEs (≥10%, any dose) were:

- Fremanezumab (CM + EM): Injection-site induration, pain and erythema, upper respiratory tract infection and nasopharyngitis.
- Erenumab (EM): Constipation and upper respiratory tract infection.
- Galcanezumab (EM + CM): Injection-site pain and reaction, nasopharyngitis, upper respiratory tract infection, back pain, sinusitis.
- Eptinezumab (EM): Upper respiratory tract infection.

There have been no new safety signals in long-term studies. Cardiovascular adverse events have not been reported in short-term trials; however, these were detected with long-term use, including hypertension, but in most cases severity was mild or moderate.[6–12]

The Danish authorities recognise there are differences in tolerability between the mAbs and allow switching on that basis. That position is also in some way supported by the European guideline, which says that in individuals with inadequate response to one CGRP mAb, there is insufficient evidence on the potential benefits of antibody switch but switching may be an option.[13]

More trial data are needed to support switching. We need to optimise treatment for people with migraine so that their attacks are reduced as far as possible for each individual. If that involves switching therapies or combining therapies then those strategies should be allowed and should be tried – clinical experience shows that efficacy can be improved with switching and combination therapy. With more data to support those strategies the clinical case becomes stronger.

References

1. Ashina M. Migraine. N Engl J Med 2020;383(19):1866–76.
2. Tfelt-Hansen P, Olesen J. Taking the negative view of current migraine treatments: the unmet needs. CNS Drugs 2012;26(5):375–82.
3. Bussone G, Diener HC, Pfeil J, Schwalen S. Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomised controlled trials. Int J Clin Pract 2005;59(8):961–8.
4. Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol 2021;17(8):501–14.
5. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001;358(9294):1668–75.
6. Goadsby PJ, Silberstein SD, Yeung PP, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: a randomized study. Neurology 2020;95(18):e2487–e2499.
7. Ashina M, Goadsby PJ, Reuter U, et al. Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. Cephalalgia 2019;39(11):1455–64.
8. Camporeale A, Kudrow D, Sides R, et al. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. BMC Neurol 2018;18(1):188.
9. Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: A randomized, double-blind,

placebo-controlled study (PROMISE-1). Cephalalgia 2020;40(3):241–54.

10. Mavridis T, Deligianni CI, Karagiorgis G, et al. Monoclonal antibodies targeting CGRP: from clinical studies to real-world evidence - what do we know so far? Pharmaceuticals (Basel) 2021;14(7):700.
11. Goadsby PJ, Reuter U, Hallström Y, et al. One-year sustained efficacy of erenumab in episodic migraine: results of the STRIVE study. Neurology 2020;95(5):e469–e479.
12. Ashina M, Goadsby PJ, Reuter U, et al. Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial. Eur J Neurol 2021;28(5):1716–25.
13. Sacco S, Amin FM, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update. J Headache Pain 2022;23:67.

The outlook of a tertiary treatment and research centre

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There are many aspects of migraine that are beyond the control or influence of clinicians, such as genetics, sex and some lifestyle factors like sleep. However, suboptimal healthcare services are an area where improvements can be made, including clinical skills, consistency of approach to management and integration of systems.

What is really needed in Norway, for example, is a structure whereby most patients with migraine are treated in primary care. There also needs to be a secondary care neurology service that can cope with a large number of patients, and good collaborative approach with private neurologists. Then there needs to be a tertiary service at selected at perhaps two or three university hospitals.

A group has been formed to address some of these challenges.

A new research organisation – the Norwegian Headache Research Centre or NorHEAD – has been established 50% funded by the Norwegian Research Council with a grant of NOK128 million over 8 years. The other 50% of the funding will come from partner institutions. Patient organisations and an innovation network will also be involved.

The main work of the centre will be clinical trials (Fig. 1). Data will also be collected from national registries.

A headache diary – BrainTwin – is being developed that can be used as a clinical headache diary, for real-world data collection, and as a research tool, study recruitment platform and a PROMS platform. A portal for doctors is also planned so they can input into research. There are also plans to do machine learning, for example to try to predict which order of migraine medications has the greatest efficacy.[1]

The group also plans to work on developing different MRI techniques to give insights into brain biology.
A clinical registry is being set up as well as a registry for interventional/surgical headache treatment, and there are plans for a biobank.

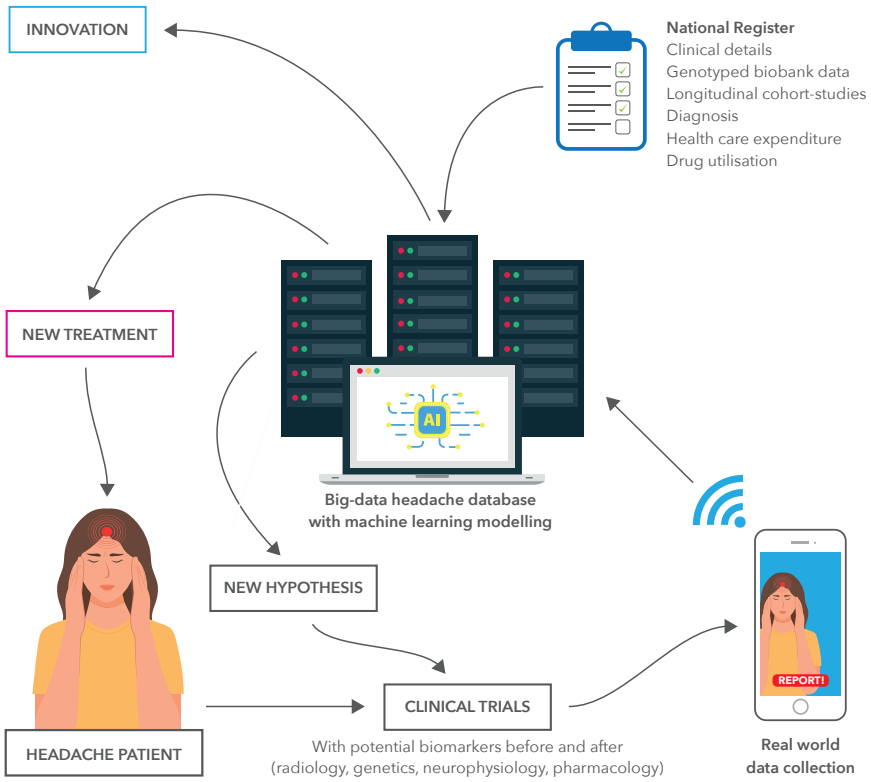

Figure 1 Data collection and processing by NorHEAD will ultimately lead to patient benefits.

E-health tools to support treatment are also being developed like the aura app that is being tested, along with innovation biofeedback tools.

As a result of some of the work NorHEAD is doing it is hoped that there will be greater integration between different institutions and groups involved in headache research and management in Norway, to improve the overall care people with migraine receive.

Reference

1. Stubberud A, Gray R, Tronvik E, et al. Machine prescription for chronic migraine. Brain Communications 2022;4:fcac059.

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