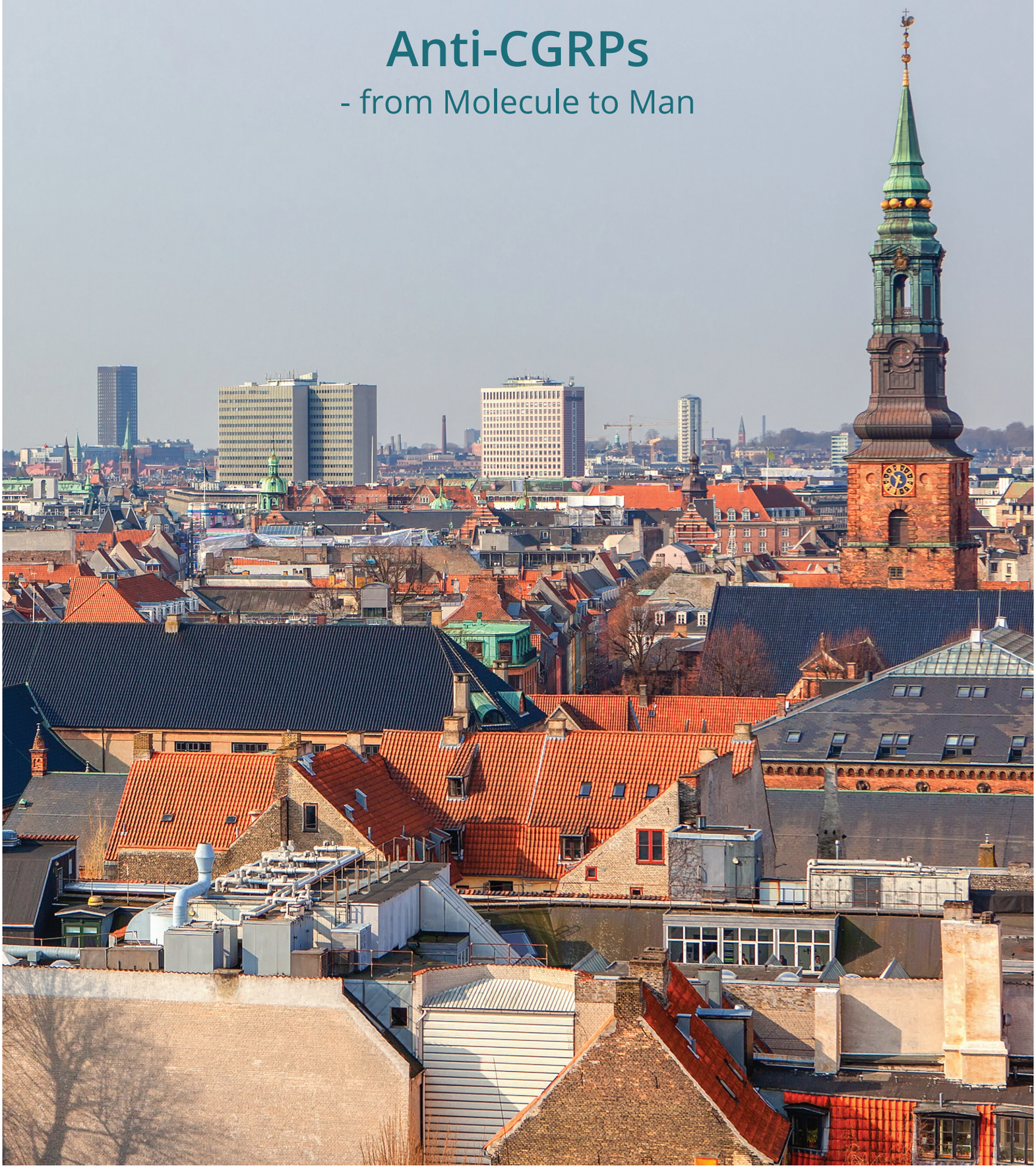
Nordic Migraine Symposium Report

Anti-CGRPs

- from Molecule to Man



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Burden of headache

Mattias Linde

Professor of Neurology in the Department of Neuroscience, Norwegian University of Science and Technology
Director of Tjörn Headache Clinic, Sweden

Prof. Mattias Linde presented an overview of the incidence and prevalence of migraine, the dynamics of a migraine attack, and the consequences of migraine for both patients and society.

Incidence and prevalence

The epidemiological burden of headache was assessed in a 30-year prospective Swiss cohort study, which showed that the incidence of migraine is highest in the first decades of life *(Figure 1)*.[1] Migraine still appears de novo in people 40 years and older, although it is not common.

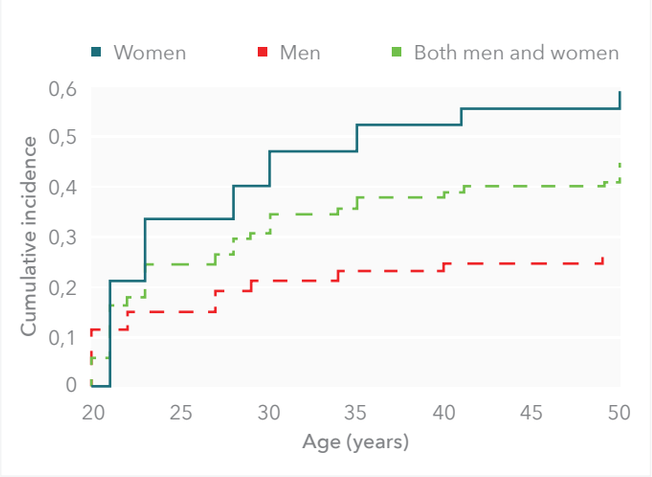

Figure 1 Cumulative incidence of women, men, and both men and women in Switzerland. Adapted from Merikangas KR et al. BMJ 2011;343:bmj.d5076.[1]

These incidence numbers lead to a high mean prevalence, which is estimated to be more than 10% globally.[2] A Norwegian study conducted in the Nord-Trøndelag region showed that migraine prevalence varies with age and sex and is highest in women between 20 and 50 years old, with more than 20% of them suffering from migraine *(Figure 2)*.[3]

The same study by Linde et al. looked at time trends in the prevalence of migraine and results showed a slow but significant ($P < 0.001$) increase from 12.1% to 13.2% over a period of approximately 11 years. The causes for this increase have not yet been clarified, but the authors of the paper think it might be due to environmental causes (most probably stress).

Severity, duration and dynamics of the migraine attack

Fortunately, most patients with migraine are not severely burdened by the disease. About 27% of patients suffering

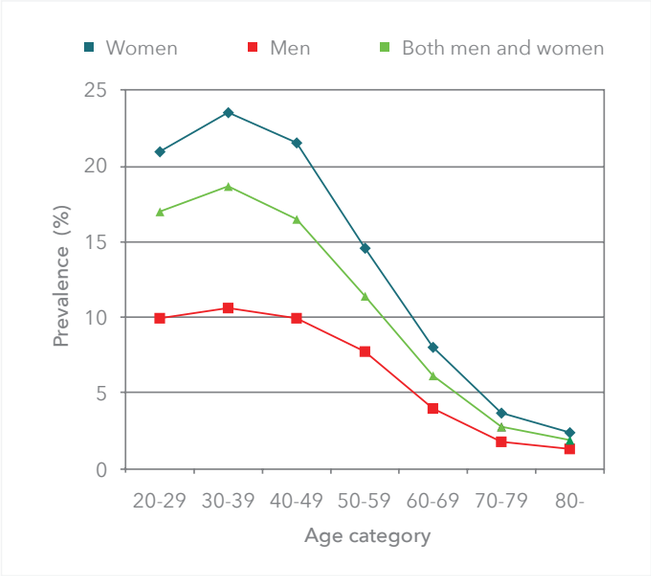

Figure 2 Prevalence of migraine in women, men, and both men and women in Nord-Trødelag, Norway. **Adapted from** Linde M et al. Cephalalgia 2011;31:585-96.[3]

from migraine account for 68% of all migraine attacks, as illustrated by a survey in Sweden.[4] This group of patients have frequent or even chronic migraine (CM).

The same study showed that the mean migraine attack duration in Sweden is 19 hours. In many cases, however, the attack lasts < 4 or > 72 hours, which is outside the timeframe (4-72 hours) defined in the international classification of headache disorders. Attacks that last longer than 72 hours, called 'status migrainosus', are not uncommon and were reported by 6.4% of patients suffering from migraine in the Swedish survey.

A migraine attack includes more than 'just' a headache *(Figure 3)*. Most patients experience a premonitory phase with neurophysiological dysfunction such as tiredness, yawning and memory difficulties and with hyperexcitability, meaning patients become hypersensitive to stimuli such as sound, light, smell, touch, and movement.[5] A subpopulation of approximately 1 in 5 patients with migraine have focal neurological symptoms, called aura, preceding the headache. Once the headache is over, many patients are left with

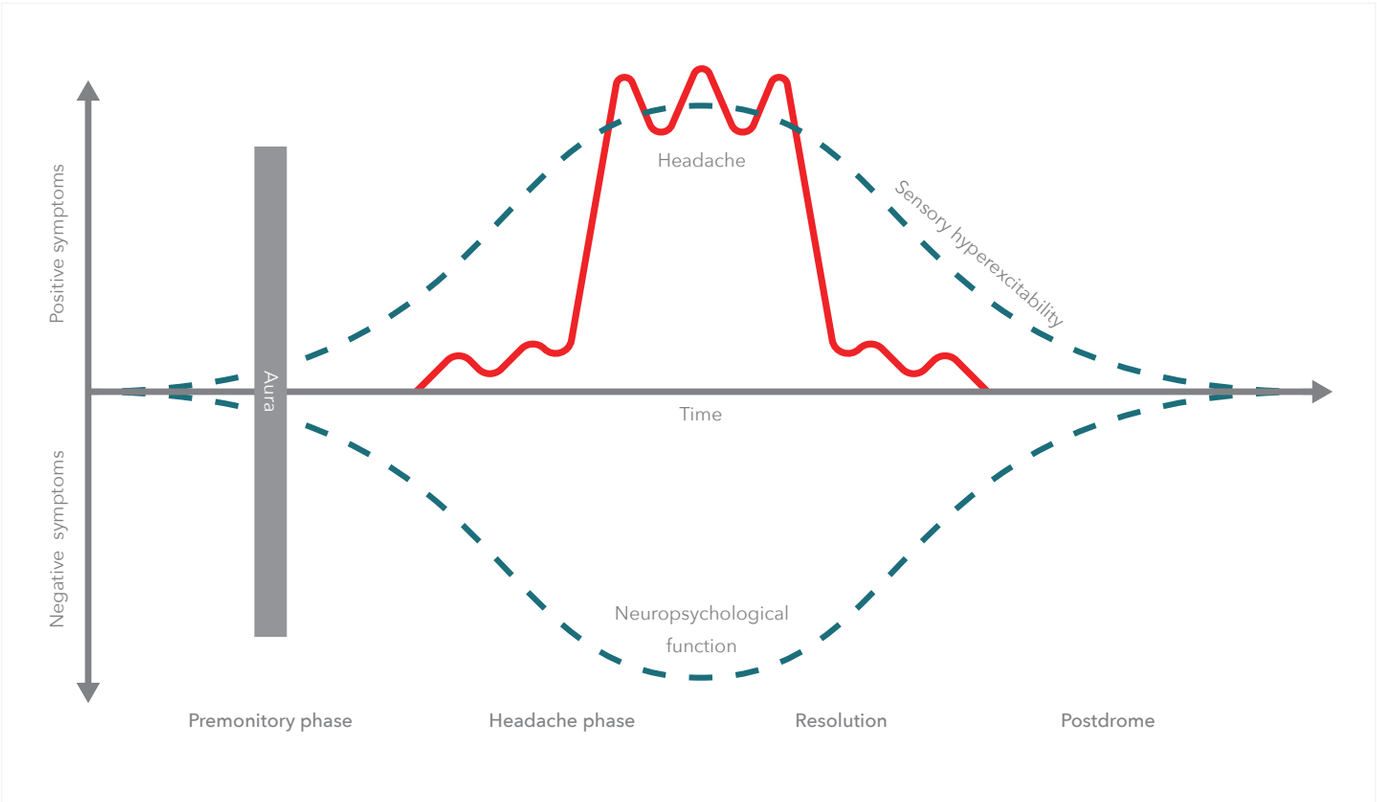

Figure 3 Dynamics of the migraine attack. Adapted from Linde M et al. Acta Neurol Scand 2006;114:71-83.[5]

allodynia. The hyperexcitability and neurophysiological dysfunction often continue in the so-called postdromal phase.

A study looking into the natural course of untreated attacks demonstrated that the pain intensity fluctuates from the highest (10/10) to middle intensity (5/10).[6] Interestingly, other symptoms such as nausea follow the same pattern. When the headache intensity is at the highest, patients often experience vomiting.

A subgroup of patients with migraine, approximately 1 in 10, have continuous symptoms.[3] In these patients the premonitory and postdrome phases overlap and they can even have a constant headache. Whether this is medication overuse headache (MOH) or CM is hard to say since they are very difficult to distinguish from each other in the clinic. The prevalence of chronic migraine without medication overuse was 0.5% in the above-mentioned Norwegian study.[3]

Personal and societal consequences of migraine

The Global Burden of Disease Study systematically analysed the burden of neurological disorders between 1990-2015.[7] They found that the 3 most common neurological disorders are tension-type headache (TTH), migraine and MOH. Moreover, migraine proved to be the most disabling neurological disorder in terms of Disability Adjusted Life Years (DALYs) during the most productive years of life *(Figure 4)*. Migraine ranked first as the most disabling neurological

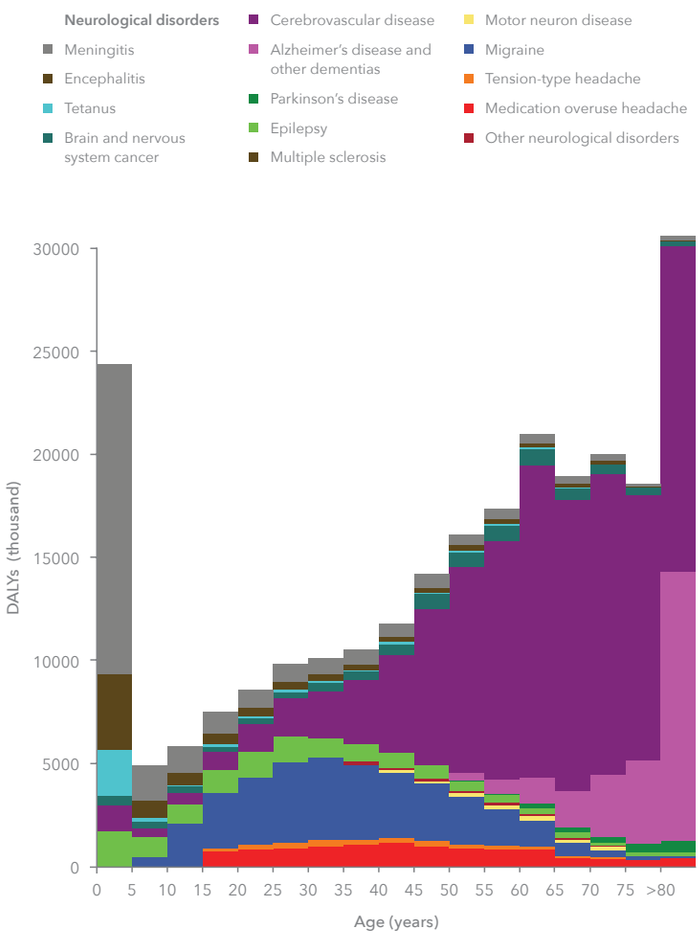

Figure 4 Global DALYs by age and neurological disorder in 2015. Adapted from GBD 2015 Neurological Disorders Collaborator Group. Lancet Neurol 2017;16:877-897.[7]

disease in Western Europe, before stroke, in this study. In Sweden, the total burden in terms of DALYs of Parkinson's disease, epilepsy and multiple sclerosis is lower than that of migraine alone (WHO 2018).

According to Swedish patients with migraine, the 3 most important elements in life are their family situation, ability to work and their free time.[4] The same 3 aspects of life were mostly impacted by migraine, demonstrating the burden of migraine on people's lives. Another study clearly demonstrated that this disability is related to the frequency of migraine attacks.[8]

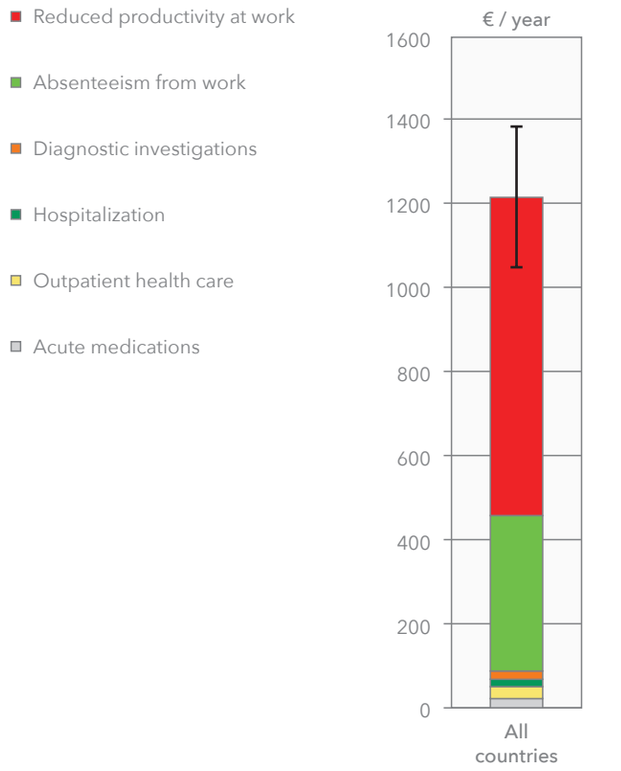

Figure 5 Mean per-person costs of migraine in Europe. Adapted from Linde M et al. Eur J Neurol 2012;19:703-e43. [9]

One of the most comprehensive health economics studies of the societal costs of migraine, performed in 9 European countries, showed that the mean cost of a person with migraine in Europe is more than EUR 1200 annually *(Figure 5)*.[9]

The total cost of headache disorders (migraine, MOH, TTH and other) in Europe adds up to about 112 billion euros a year. Most of the costs (93%) are indirect and due to loss of productivity, either because patients with migraine are not able to work at all or because they produce less than 50% of what they would have produced without migraine. Just like the loss in quality of life, societal costs increase with migraine frequency.[8] Considering these numbers, investment in the treatment of migraine, which currently accounts for only 7% of all costs, would therefore potentially be repaid several-fold.

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Challenges in clinical practice

Lars Bendtsen

Associate Professor at the Department of Neurology and Danish Headache Center, Rigshospitalet Glostrup, University of Copenhagen, Co-director of the Danish Headache Center

In his lecture, Dr Lars Bendtsen provided the audience with his strategies to tackle the major clinical challenge in headache management: provide headache management of high quality to a large number of sufferers. These strategies include increasing awareness, increasing interest, optimizing the organization of headache care, and improving treatment possibilities.

Increase awareness

In creating more awareness about migraine, 3 target groups can be distinguished: patients, decision makers, and healthcare providers. In patients, awareness could be increased through public campaigns. Pharmacies and the media can be used to provide information to the general public. Decision makers should preferably be targeted by patient organisations, with a focus on the burden and costs. Among healthcare providers, general practitioners, neurologists and junior colleagues should be better educated. Given their lack of time, general practitioners should be provided with easy-to-use materials covering the most important issues. Neurologists should try and get stage time at national and international neurology meetings to create more awareness, and, inspire junior colleagues.

Increase interest

Growing interest in migraine can be achieved through education and research. Getting young doctors interested in headache rather than e.g. multiple sclerosis and stroke takes investments. Employing medical students in specialised headache centers is a good way to introduce them to the topic. But also training neurologists to be headache specialists, e.g. in master programs, has a beneficial effect. Not only do they become headache specialists, they will also disseminate the interest and pave the way for new headache centers. Research is another way of fostering interest. When young doctors and/or neurologists get opportunities to do research, many will find out that headache and facial pain are interesting topics, and they will be more inclined to continue in the field.

Optimise the organisation of headache care

It is important to have a clear picture of how patients get treated at the first, second and third health care levels. Good and easy-to-use guidelines for primary and secondary treatment options can play a major role in this. Establishment of tertiary headache centers, working with multidisciplinary teams focusing on difficult to treat patient, further ensures optimal organisation of headache care and, ultimately, treatment. Also in these specialised centers, good guidelines and patient information are key to optimal treatment of patients.

Improve treatment possibilities

Both basic and clinical research have been instrumental for the development of headache treatment. It led to internationally accepted classifications and guidelines and gave doctors the tools to treat their patients. Medicines like triptans and botulinum toxin have had a great impact on the lives of patients. The new generation medicines, the monoclonal antibodies, also contribute notably. However, more research is needed to improve the treatment possibilities for migraine patients in the future.

Raising awareness in general practitioner and general neurology practice

Anne Christine Poole

General Practitioner and Headache Specialist at the Volvat Medical Center, Norway

Anne Christine Poole passionately made an argument for raising awareness in the general practitioner (GP) and general neurology practice, in order to deliver the comprehensive and effective care that migraine patients need.

For many patients that suffer from migraine, the disease is seriously disabling and can be extremely painful. As a consequence, a large number of patients with migraine don't have the same opportunities in life as others have. Every year, migraine causes millions of days lost from work and school.

Underdiagnosed

Migraine is underdiagnosed: only an estimated 30-50% of patients with migraine are diagnosed with the disease.[1] Moreover, many patients are misdiagnosed with e.g. tension-type headache.

Dr Faisal Amin from the Danish Headache Center investigated how many GPs and neurologists were able to correctly diagnose 2 cases of migraine without aura *(see Boxes)*. Out of 314 GPs and neurologists from 5 different countries, only 26 (<9%) were able to correctly diagnose these cases.[2]

It raises the question why migraine is so heavily underdiagnosed. Anne Christine Poole thinks this is on the one hand because patients don't discuss their headache with their doctor, thinking they are not interested. On the other hand, there is the problem that many GPs don't have enough time to properly diagnose and treat headache patients. And also, general neurologists are often not headache specialists.

Education

A study by Hirtz et al. showed that the prevalence of migraine (12.1%) alone is higher than the combined prevalence of Alzheimer's disease (6.7%), stroke (1%), Parkinson's and Huntington's disease (0.96%), epilepsy (0.71%) and multiple sclerosis (0.09%).[3] Given the relatively low number of patients who are correctly diagnosed with migraine, there is a big opportunity to improve treatment of the disease. Creating awareness among GPs and neurologists is key to fill this gap.

Increasing awareness is done through education. GPs and neurologists need to be better aware of what migraine is and how to treat it. All efforts should be taken to make sure that they have access to information and education.

Case 1 – Migraine without aura

28 year old woman

Right sided pulsating headache, pain intensity 4 (0-10). Aggravation by physical activity. Photo- and phonophobic. No nausea. Headache lasts for 24 hours. She has had this kind of headache once a month since she was 20.

Case 2 – Migraine without aura

21 year old woman

Bilateral pressure headache, pain intensity 7 (0-10). Aggravation by physical activity. A little nausea. Headache lasts for 4 hours. She had experienced this kind of headache many times in the past 4 years. No pulsation, no photophobia.

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CGRP - A key molecule in primary headaches

Lars Edvinsson

Director and Founder, Glostrup Research Institute, Copenhagen University Hospital Chairman, Department of Experimental Clinical Research, Glostrup Research Institute Professor MD, Lund University, Lund, Sweden and Copenhagen University, Denmark

Prof. Lars Edvinsson showed the audience how calcitonin gene-related peptide (CGRP) gradually became one of the most important molecules in primary headaches. From its discovery in the early 1980s to its role as an important target for novel specific anti-migraine drugs.

Innervation of intracranial vessels

Intracranial vessels are supplied by 3 types of nerves: sympathetic, parasympathetic and sensory fibres. Several signaling molecules are found in these nerves *(Figure 1)*.[1] In the sympathetic nerves, noradrenaline, ATP and neuropeptide Y are found. The parasympathetic nerves originating in the otic and sphenopalatine ganglia store vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), nitric oxide (NO) and acetylcholine. The sensory nerves, mostly derived from the trigeminal ganglion, contain substance P, neurokinin A, PACAP, nitric oxide, and CGRP.

Innervation of intracranial circulation

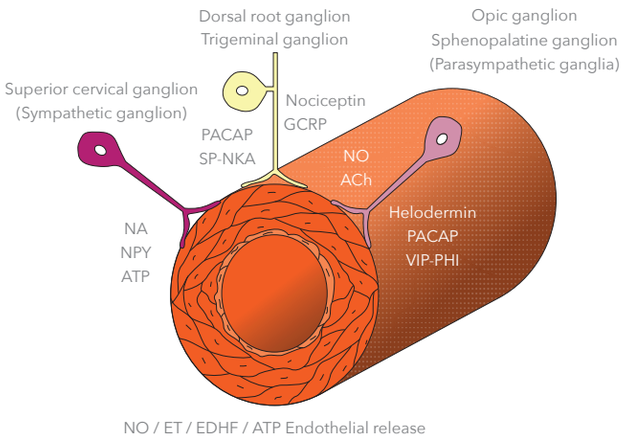

Figure 1 Schematic illustration of the perivascular nerves in intracranial vessels. Adapted from Edvinsson L et al. Brain Res Rev 2005;48:438-468. [1]

In the late 1970s, it was suggested that neurogenic inflammation in the dura mater was the underlying mechanism of migraine.[2] At this point in time, several pharmaceutical companies developed molecules to block substance P's endogenous receptor, the interleukin receptor. Neurogenic inflammation was indeed inhibited, but clinical studies did not show a significant effect in migraine.[3]

CGRP discovery

Meanwhile, CGRP was discovered. Researchers found that the gene normally producing calcitonin in the thyroid, produced an alternative peptide in neurons: CGRP.[4] CGRP turned out to be widely spread in the trigeminal system.[5]

Studies on the distribution and function of CGRP showed that CGRP was a very potent vasodilator[6] and abundantly stored in the perivascular nerves of the intracranial arteries.[7] From the beginning, it was hypothesized that CGRP plays a role in migraine.[6]

The trigeminovascular reflex

Subsequent experiments led to the discovery of the trigeminovascular reflex *(Figure 2)*. It was found that trigeminal nerves release CGRP in response to noradrenaline-induced vasoconstriction of cerebral arteries.[8,9] In case of a trigeminal lesion, noradrenaline induced the same amount of vasoconstriction but it took much longer to restore.[10,11] Because of the increased release of CGRP in migraine patients it is thought that the trigeminovascular reflex plays a role in the pathophysiology of the disorder.

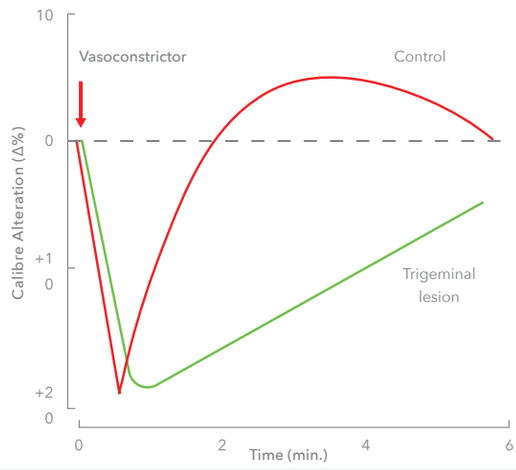

Figure 2 The trigeminovascular reflex. Adapted from Edvinsson L et al. Pharmacol Toxicol 2001;86:65-73. [9]

CGRP release during migraine attacks

The potential role of activation of the trigemino-vascular system in migraine was further investigated. A study by Goadsby and Edvinsson showed a significant increase of both CGRP and substance P in the cranial circulation following stimulation of the trigeminal ganglion.[12]

A subsequent study showed that CGRP levels increased in external jugular but not in cubital fossa blood during migraine attacks both with and without aura *(Figure 3)*.[12] Substance P levels, just like VIP and neuropeptide Y, were not elevated, however. Also, in cluster headache and paroxysmal headache CGRP levels turned out to be significantly increased.[13] While VIP was also shown to be released in the cluster headache patients, again no difference was seen for substance P and neuropeptide Y.

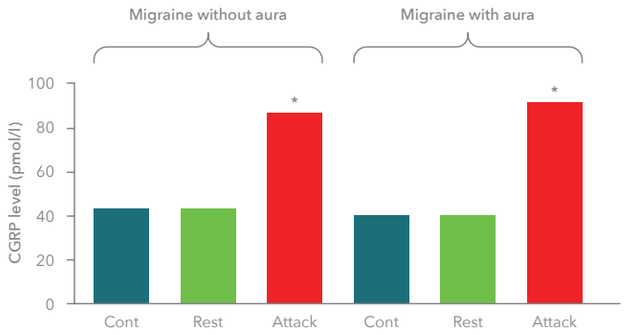

Figure 3 CGRP release during a migraine attack with or without aura. Adapted from Goadsby PJ et al. Ann Neurol 1988;23:193-196. [12]

From triptans to monoclonal antibodies

When sumatriptan was introduced in the early 1990s, another study was done to look at the role of CGRP in migraine. The study again showed elevated CGRP levels in the external jugular vein during a migraine attack, but also normalization of the CGRP level after treatment with sumatriptan.[14] This observation, together with other work, led to the suggested mechanism of triptans, which are thought to suppress the release of CGRP from trigeminal nerves via presynaptic 5-HT1B/1D receptors *(Figure 4)*.

These findings also led to the development of a new type of migraine medication, the gepants, which are CGRP receptor blockers. Although clinical trial results showed that gepants were effective in relieving pain in migraine patients, there were concerns about their hepatic safety and the development programs were stopped. Ten years later, the anti-CGRP monoclonal antibodies were marketed and demonstrated similar prophylactic effects but without serious safety concerns.[15]

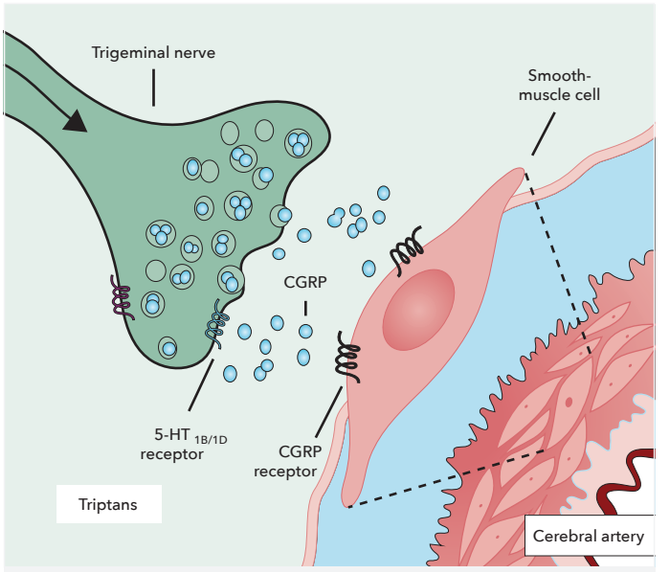

Figure 4 Suggested mechanism of action of triptans. Adapted from Goadsby PJ et al. Ann Neurol 1993;33:48-56. [14]

From the trigeminal ganglion, C- and Aδ-fibres link to the trigeminal nucleus caudalis of the brainstem. A tracing study showed that these fibres project to the intermediate grey layer of the superior colliculus in the midbrain, which is involved in photo- and phonophobia, but also to periaqueductal gray (PAG) and to the thalamus.[16] Almost all thalamus-related symptoms of migraine are endpoints of these fibres.

The central role of the trigeminal ganglion and CGRP in migraine was now widely accepted, but discussion remained as to where the drugs that target CGRP (receptors) act. Since migraine affects the brain, for many years it was thought that migraine medicines work in the brain too. However, both sumatriptan and CGRP blockers poorly cross the blood-brain barrier (BBB), with 2-3% passing it. Of the monoclonal anti-CGRP antibodies entering the body, even less (< 0.01%) passes the BBB. The discovery that the trigeminal ganglion is not protected by the BBB[17] was another important piece of the puzzle, leading to the proposal that the trigeminal ganglion is a key site of action for CGRP receptor antagonists and antibodies.[18]

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The clinical data of anti-CGRP antibodies

Mikko Kallela

Associate Professor, Neurology Specialist at Helsinki University Central Hospital and Helsinki Headache Center, Finland

Mikko Kallela presented an overview of the efficacy and safety of the currently available anti-CGRP antibodies erenumab, fremanezumab, galcanezumab and eptinezumab.

The data for efficacy and short-term safety of anti-CGRP monoclonal antibodies (mAbs) in episodic and chronic migraine presented here comes from two phase 2 and eight phase 3 clinical trials (summarized in *Table 1).* The results from these and other trials with anti-CGRP mAbs have been summarized by Dodick et al.[1]

Antibody	Trial	EM/CM
Erenumab	STRIVE (phase 3)[2]	EM
	ARISE (phase 3)[3]	EM
	Phase 2[4]	CM
Fremanezumab	HALO EM (phase 3)[5]	EM
	HALO CM (phase 3)[6]	CM
Galcanezumab	EVOLVE-1 (phase 3)[7]	EM
	EVOLVE-2 (phase 3)[8]	EM
	REGAIN (phase 3)[9]	CM
Eptinezumab	PROMISE-1 (phase 3)[10]	EM
	Phase 2[1]	CM

Table 1 Overview of trials with anti-CGRP mAbs in episodic (EM) and chronic (CM) migraine for which data is presented.

Efficacy in episodic migraine (EM)

In all trials, the primary endpoint was the reduction in the number of monthly migraine headache days. The reduction was evaluated between 3-6 months (erenumab), 1-3 months (fremanezumab), and 1-6 months (galcanezumab) after the first dose. The reduction in the number of migraine headache days ranged between 3.2 and 4.7 days in the groups that were treated with the anti-CGRP mAbs, compared to 1.8-3.2 days in the groups that received placebo *(Table 2).* In all these studies, the reduction in the number of migraine headache days was significantly higher after treatment compared to placebo.

Comparison of the number of migraine headache days at baseline with the number at the end of the studies also showed a significant reduction in all treatment groups. Again, the reduction was significantly higher compared to placebo in all cases.

Another way of looking at the effect of treatment is the 50% response rate; the proportion of patients have a reduction of at least half of their attacks. In the 6 trials evaluating anti-CGRP mAbs in episodic migraine, the 50% response rate ranged between 43% and 62% in the treatment groups, while in the placebo groups it was 27%-39%. Again, in all cases the difference between treatment and placebo was statistically significant.

Efficacy in chronic migraine (CM)

The primary endpoint in all clinical trials, except the phase 2 eptinezumab trial that evaluated the effect of antibody treatment in chronic migraine, was also the reduction in the number of migraine headache days. This was evaluated between 9-12 weeks (erenumab), between 1-12 weeks (fremanezumab), and between 1-3 months (galcanezumab) after the first dose. The reduction ranged between 4.3 and 6.6 days in the treatment groups, compared to 2.5-4.2 days in the placebo groups *(Table 3).* In all cases the difference between treatment and placebo was significant.

The number of migraine headache days at the end of the study was significantly reduced compared to baseline in all 3 studies and the reduction was significantly higher in all treatment groups compared to placebo.

The 50% response rate was assessed in all 3 clinical trials evaluating the effect of the anti-CGRP mAb treatment in chronic migraine. In the treatment groups, the rates ranged between 28%-57%, while in the placebo groups they were between 15% and 40%. Again, in all studies the

Monoclonal antibody in episodic migraine Study	Dose	Primary endpoint variable	Outcome - reduction in 4 weeks compared to baseline	Placebo
Subcutaneous injection				
Erenumab Strive	70 mg sc. monthly	Migraine headache days - weeks 13-24	3,2	1,8
	140 mg sc. monthly		3,7	1,8
Arise	70 mg sc. monthly	Migraine headache days - weeks 13-24	2,9	1,8
Fremanezumab HALO	225 mg sc. monthly	Migraine days baseline - week 12	4,3	3,2
	675 mg sc. quaterly		4,3	3,2
Galcanezumab Evolve-1	120 mg sc. monthly	Migraine headache days - months 1-6	4,7	2,8
	240 mg sc. monthly		4,6	2,8
Evolve-2	120 mg sc. monthly	Migraine headache days - months 1-6	4,3	2,3
	240 mg sc. monthly		4,2	2,3

Table 2 Overview of results for primary endpoints from trials with anti-CGRP mAbs given subcutaneously in episodic migraine. Adapted from Dodick DW et al. Cephalalgia 2019;39:1075-1085.[1]

difference between treatment and placebo groups was statistically significant.

Short-term safety in episodic and chronic migraine

Across studies (both episodic and chronic migraine), the number of adverse events was generally higher in the treatment groups compared to the placebo groups, driven by injection site reactions. The amount of serious adverse events was similar between treatment and placebo groups across all studies. Overall, few patients (0%-4%) discontinued the treatment.

Long-term safety in episodic and chronic migraine

A study by Ashina et al. investigated the long-term safety and tolerability of erenumab in episodic migraine.[11] After 3 years of treatment, relatively few patients had discontinued the study due to adverse events during both the 70 mg phase (first 2 years; 4.2%) and the 140 mg phase (third year; 0.4%).

Monoclonal antibody in chronic migraine Study	Dose	Primary endpoint variable	Outcome - reduction in 4 weeks compared to baseline	Placebo
Cutaneous injection				
Erenumab Phase 2	70 mg sc. monthly	Migraine headache days - weeks 9-12	6,6	4,2
	140 mg sc. monthly	Migraine headache days - weeks 9-12	6,6	4,2
Fremanezumab HALO	225 mg sc. monthly	Headache days of at least moderate severity baseline - week 12	4,6	2,5
	675 mg sc. monthly		4,3	2,5
Galcanezumab Regain	120 mg sc. monthly	Migraine headache days - months 1-3	4,8	2,7
	240 mg sc. monthly		4,6	2,7

Table 3 Overview of results for primary endpoints from trials with anti-CGRP mAbs given subcutaneously in chronic migraine. Adapted from Dodick DW et al. Cephalalgia 2019;39:1075-1085. [1]

The same was seen for discontinuation due to lack of efficacy (3.1% and 0%, respectively).

Another study evaluated the tolerability and safety of fremanezumab in episodic and chronic migraine after one year of treatment.[12] Again, the percentages of patients that discontinued the trial due to adverse events (4%) and lack of efficacy (4%) were low.

Potential safety concerns

A few potential safety issues are being monitored for the anti-CGRP mAbs.

Firstly, cardiovascular safety. Since CGRP has several functions in the vascular system, the lungs and the heart, cardiovascular safety is of particular concern. Fortunately, so far there have not been any warning signals regarding cardiovascular safety in clinical trials.[1]

Another potential safety concern is immunogenicity, antibodies against the anti-CGRP mAbs. This has also not been a problem so far. Low levels of binding and neutralising antibodies have been detected, but without any clinical implications.[1]

Difficult-to-treat patients

Fremanezumab was tested in both episodic and chronic migraine patients who failed 2 to 4 previous treatments. In all treatment groups, the reduction in the number of migraine headache days between 12 weeks after the first dose and baseline was significantly higher than in the placebo groups.[13] Interestingly, the placebo response in this study was relatively low. This could be explained by the study population, since it consisted of patients who already failed at least two previous treatments and therefore might expect less from the new treatment.

Patients with medication overuse are another difficult-to-treat patient group. In a study by Tepper et al. chronic migraine patients with or without medication overuse were treated with either 70 or 140 mg erenumab for 3 months. The reduction in migraine headache days was comparable between groups (6.6 vs 6.7), while the 50% response rates were higher in patients without medication overuse (42%-46%) than in patients with medication overuse (35%-36%).

Conclusion

In summary, anti-CGRP mAb treatment leads to 3-4 days reduction in monthly migraine headache days in episodic migraine and 4-5 days in chronic migraine. The 50% response rate is about 50% in episodic migraine and about 40% in chronic migraine. The treatments are generally very well tolerated and the safety data collected so far do not raise any concerns.

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Non-pharmacological treatments of migraine

Jakob M. Hansen

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Migraine is a multifactorial disease and many patients search for alternative, non-pharmacological treatments to get better. Jakob Hansen presented an overview of the currently available non-pharmacological treatments and the evidence that exists for their effectiveness.

Need for non-pharmacological treatment

Treatment of migraine includes different components. Apart from the acute and prophylactic pharmacological treatment, patient education and information is also part of this, as well as non-pharmacological treatment.

The reason why many patients look for non-pharmacological treatment is that there is a high unmet medical need among patients. Acute treatment with triptans has 2-hour pain-free rates of only 12%-40% and frequent use may lead to medication overuse headache.[1] Prophylactic treatments are, in turn, effective in only 40%-50% of patients, and are often discontinued because of side effects.[1]

Migraine is a biopsychosocial disorder and successful treatment needs to involve patients in their care, encouraging proactive behaviours, and using a patient-centered approach. In clinical practice, many patients are not well managed on classic drug treatments, so there is a need for low-risk and well-tolerated alternatives as supplements.

Evidence for effectiveness

Probyn et al. reviewed 16 randomized controlled trials (RCTs) testing 21 non-pharmacological self-management interventions compared with usual care.[2] There was some effect of these interventions on patients' mood, pain intensity, disability, quality of life and medication consumption. However, no statistically significant improvements with regards to headache frequency were seen.

Another systematic review looked at 7 RCTs assessing the effectiveness of manual therapies such as massage, physiotherapy and chiropractic interventions.[3] The effect size was about 25% when therapeutic gain was compared to placebo. However, these studies were very small and poorly powered, so there is a high risk of bias and a need for RCTs of better quality to really conclude on the impact of these interventions.

A third review article evaluated 3 RCTs assessing spinal manipulations for the treatment of migraine.[4] Again, the methodological quality of the studies was relatively poor. The most rigorous study showed no effect of spinal manipulation on migraine.

Acupuncture is a non-pharmacological treatment that many migraine patients try out. In a systematic review including 22 trials and almost 5000 patients, acupuncture was shown to reduce the headache frequency when added to standard treatment.[5] There seems to be a high placebo effect with acupuncture however, which was confirmed in a large trial by Diener et al. where treatment outcomes for migraine did not differ between patients treated with sham (placebo) acupuncture, verum acupuncture, or standard therapy.[6]

A second non-pharmacological treatment that demonstrated an effect on migraine frequency in clinical trials is magnesium. A systematic review by Von Luckner et al. showed that magnesium was significantly better than placebo in reducing migraine frequency.[7] The evidence however, is again thin, since there are only a few, small studies with methodological issues.

Summary

There are several good reasons for non-pharmacological treatment of migraine. It is a disease that has many causes and triggers, so it is very plausible that there is not just one intervention that fits all. Alternative treatment may complement other pharmacological treatment. On the other hand, non-pharmacological treatments lead to greater expenses and hard evidence for their effectiveness is scarce. There is a clear need for well-designed placebo-controlled trials assessing their real effectiveness.

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Acute and preventive treatments

Anna Sundholm

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Anna Sundholm presented an overview of all currently available acute and preventive treatments for the different migraine patients, and how to use them most effectively.

Right treatment for the right patient

The treatment goal for all migraine patients starts with a correct diagnosis. The next step is giving them the right treatment, either acute and/or preventive, based on the type of patient. Although it sounds simple, this is currently not happening optimally.

In order to reach the treatment goal, well-structured headache care is key. Roughly 90% of patients need to be taken care of in primary care, about 9% in secondary care and the remaining 1% in tertiary care.[1,2]

Since the majority of patients are treated in a primary care setting, staff working there needs to know the basics of migraine treatment. Therefore, in Sweden a hands-on document for primary care was developed, which is step-wise and simple, and helps to secure that patients get the correct diagnosis and the right treatment.[3,4] Moreover, it provides guidance on when to refer patients to specialized care.

Acute treatment

When choosing the appropriate treatment, several things should be considered. It is important to assess the headache intensity, the level of disability, the speed at which the headache pain escalates, and whether or not the patient experiences nausea or medication overuse.

There are 3 types of acute medications: non-specific drugs like acetylsalicylic acid, paracetamol and NSAIDs; migraine-specific medications such as triptans (primarily) and dihydroergotamine; and medications for relief of associated symptoms like antiemetics and corticosteroids.[5,6] Only in very severe cases, such as a longstanding migraine status and nothing else works, corticosteroids can be used. But in general they should be avoided.

Apart from the types of medications, there are different approaches to acute treatment of migraine.[7] With the stratified approach, the medication is based on the attack severity and disability of the patient. Following the step-care-across-attacks approach, a patient is started on the treatment that is most safe and tolerable. If this is ineffective, other options are considered for subsequent attacks. The third approach, the step-care-within-attacks approach, is essentially the same as the second but now the change of medication is tried during the attack. Looking at the evidence, the stratified approach proves to be most effective and associated with the lowest costs.[8,9]

Triptans

Triptans act both peripherally, leading to vasoconstriction and blocking release of vasoactive peptides, and centrally, interfering with the nociceptive signals to the trigeminal nucleus caudalis.

Many different triptans are available. Most are fast-acting but some are slow-acting. Moreover, formulations vary from subcutaneous injections to nasal sprays and tablets. Choices should be made based on the individual patient's needs.

A meta-analysis of 53 clinical trials with triptans showed subtle differences in the effectiveness and tolerability of triptans *(Table 1)*.[10] In clinical practice it is difficult to predict which triptan will work with which patient. So, if one doesn't work, maybe another will.

An important thing to consider when patients are given triptans, is to inform them to take their medications early on in the attack, since these medications will be more effective then.[11-13]

Other considerations for acute treatment

There is evidence that combining different types of acute medications makes them more effective. Sumatriptan and naproxen together, for example, are both more effective than when either drug is administered alone.[14] Adding metoclopramide to treat nausea may also enhance absorption of pain medications due to its prokinetic effect, and both caffeine and metoclopramide can enhance the effectiveness of analgesics.[7]

	Initial 2 h relief	Sustained pain-free	Consistency	Tolerability
Sumatriptan 50 mg	=	=	=/-	=
Sumatriptan 25 mg	-	=/-	-	+
Zolmitriptan 2.5 mg	=	=	=	=
Zolmitriptan 5 mg	=	=	=	=
Naratriptan 5 mg	-	-	-	++
Rizatriptan 5 mg	=	=	=	=
Rizatriptan 10 mg	+	+	++	=
Eletriptan 20 mg	-	-	-	=
Eletriptan 40 mg	=/+	=/+	=	=
Eletriptan 80 mg	+(+)	+	=	-
Almotriptan 12.5 mg	=	+	+	++

Table 1 Comparison of efficacy and tolerability of oral triptans versus 100 mg sumatriptan. Meta-analysis of 53 clinical trials. Adapted from Sculpher M et al. Pharmacoeconomics 2002;20:91-100. [9]

Medication overuse is relatively common when the migraine frequency is high. Therefore, it is important to inform patients not to take their medications too often and switch to preventive treatment to try to reduce that frequency. Keep in mind that simple analgesics can be taken up to 14 days a month and combinations of analgesics, opioids, ergotamines, or triptans up to 9 days a month.[15] A headache diary is a good way to keep track of both headache days and acute treatment usage.

Preventive treatment

Preventive treatment of migraine is indicated in case of (1) a high frequency of migraine attacks despite non-pharmacological treatments, (2) insufficient effect of acute treatment, (3) side effects to acute treatments, (4) severely bothersome aura, or (5) if the patients prefers it.[16]

Preventive treatment is given to reduce the attack frequency, improve the acute treatment response and the quality of life. It is advisable to start with a low dose and slowly increase until the treatment is effective or intolerable side effects appear. Given the variability in the monthly headache frequency, effectiveness can only be assessed adequately over a minimum period of 2 to 3 months.

There are several different classes of preventive medications used in migraine. Among them, the betablockers, antiepileptics, calcium antagonists and antidepressants are mostly used.[17] Different levels of evidence exist for these treatments *(Table 2).*[18] Betablockers and antiepileptics seem to be most effective. When it comes to chronic migraine, there is only evidence for topiramate, onabotulinumtoxin A and the new anti-CGRP antibodies to be effective.[19-23]

Level A: Effective	Level B: Probably effective	Level C: Possibly effective	Level U: Inadequate or conflicting data		Ineffective, probably or possibly effective
AEDs	**Antidepressants**	**ACE inhibitors**	**α-Agonists**	**B-Blockers**	**Ineffective**
Divalproex sodium	Amitriptyline	Lisinopril	Clonidine	Bisoprolol	Lamotrigine
Sodium valproate	Venlafaxine			Pindolol	
Topiramate		**Angiotensin blockers**	**Antidepressants**		**Probably ineffective**
	β-Blockers	Candesartan	Fluoxetine	**Ca + + blockers**	Clomipramine
β-Blockers	Atenolol		Fluvoxamine	Cyclandelate	
Metoprolol	Nadolol	**AEDs**	Protriptyline	Nicardipine	**Possibly ineffective**
Propanolol		Carbamazepine		Nifedipine	Acebutolol
Timolol			**AEDs**	Nimodipine	Clonazepam
		Antihistamines	Gabapentin	Verapamil	Nabumetone
		Cyproheptadine			Oxcarbazepine
					Telmisartan
		β-Blockers			
		Nebivolol			

Abbreviations: **ACE** = angiotensin-converting-enzyme; **AED** = antiepileptic drugs; **CA + + blockers** = calcium channel blockers. Adapted from Silberstein SD et al. CNS Spectr 2017;22(S1):1-13.[18]

Challenges

When treating migraine patients, either with acute or preventive treatments, there are a lot of challenges.[22] Many treatments, especially the oral ones, have bothersome side effects. Triptans cannot be used in patients with cardiovascular disorders and many patients have other comorbidities which makes that treatments are contraindicated. Finally, very often acute and preventive treatment lacks efficacy in severe migraine. It makes that there is still a lot work to do in order to meet the treatment goals for all migraine patients.

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EHF anti-CGRP treatment recommendations

Lars Bendtsen

Associate Professor at the Department of Neurology and Danish Headache Center, Rigshospitalet Glostrup, University of Copenhagen, Co-director of the Danish Headache Center

Co-author of the European Headache Federation (EHF) guideline on the use of anti-CGRP monoclonal antibodies (mAbs) for migraine prevention, Lars Bendtsen presented an overview of the scientific basis for the recommendations.

Scientific basis

The European guidelines were put together by a task force of 7 experts from 5 European countries.[1] The recommendations were developed to answer 7 clinically important questions on how to use the anti-CGRP mAbs.

For episodic migraine, the evidence included 4 phase 2 studies (one each for eptinezumab, erenumab, fremanezumab and galcanezumab) and 3 phase 3 studies (one each for erenumab, fremanezumab and galcanezumab). The evidence for chronic migraine came from two 2 phase 2 studies (one for erenumab and one for fremanezumab) and two 2 phase 3 studies (one for fremanezumab and one for galcanezumab).

Is treatment with CGRP mAbs effective?

It was found that the use of anti-CGRP mAbs reduced the number of migraine headache days with 1-2.5 days per month compared with placebo. Moreover, at least 50% reduction in migraine days was typically seen in 45%-50% of patients on active treatment and in 35%-30% of patients on placebo. Based on this evidence, the EHF guideline strongly recommends the use of erenumab, fremanezumab and galcanezumab.

When to offer treatment?

The guideline recommends using erenumab, fremanezumab or galcanezumab in episodic and chronic migraine patients that have failed at least 2 previous preventive medications.

How to manage other preventive treatments when patients are treated with anti-CGRP mAbs?

In patients with episodic migraine, oral preventives should be stopped before the use of anti-CGRP mAbs is started unless the patient has a history of chronic migraine. In patients with chronic migraine, oral preventives can be considered to be used in combination with anti-CGRP mAbs. In these patients, onabotulinumtoxin A should be stopped before use of anti-CGRP mAbs is started. This last recommendation is mainly driven by economic reasons.

When to stop treatment with anti-CGRP mAbs?

The EHF guideline recommends stopping the treatment with anti-CGRP mAbs in patients with episodic and chronic migraine after 6-12 months, like all other prophylactic medications. In case of worsening of migraine, treatment with anti-CGRP mAbs should be started again.

Should medication overuse headache be treated before chronic migraine patients are offered anti-GCRP mAbs?

In patients with chronic migraine and medication overuse, anti-CGRP mAbs can be used before or after withdrawal of acute medications.

When not to use anti-CGRP mAbs?

Anti-CGRP mAbs should not be used in pregnant or nursing women and in individuals with alcohol or drug abuse, cardiovascular and cerebrovascular disease and severe mental disorders.

Should neutralising antibodies be monitored?

There is no need to monitor binding and/or neutralising antibodies in clinical practice.

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US anti-CGRP guidelines and clinical experience with anti-CGRP antibodies

Andrew Blumenfeld

Director of the Headache Center of Southern California

The United States (US) perspective on the use of anti-CGRP monoclonal antibodies mAbs was presented by Andrew Blumenfeld. He discussed the US guidelines and the rationale for them.

US anti-CGRP mAbs guidelines

Anti-CGRP mAbs are approved for use in adults 18 years and older in the US. The conditions for recommending the use of anti-CGRP mAbs differ for 3 categories of patients:[1]

- Patients with 4-7 monthly headache days: unable to tolerate or insufficient response after 6 weeks to at least 2 medications AND at least moderate disability (Headache Impact Test (HIT)-6 > 50, Migraine Disability Assessment (MIDAS) > 11).
- Patients with 8-14 monthly headache days: unable to tolerate or insufficient response after 6 weeks of at least 2 medications.
- Patients with chronic migraine: unable to tolerate or insufficient response after 6 weeks to at least 2 medications OR unable to tolerate or insufficient response to at least 2 quarterly injections (6 months) of onabotulinumtoxin A.

The guideline recommends continuing the use of anti-CGRP mAbs in case of a reduction of 50% or more from baseline in the mean number of migraine headache days or if there is an improvement in disability, as assessed by the HIT-6, MIDAS or Migraine Physical Function Impact Diary (MPFID) questionnaires. Patients should be treated at least for 3 months when given monthly and for 6 months when administered quarterly to evaluate the effect.

Migraine freedom

With all the current options for treatment of migraine, the concept of migraine freedom is becoming more important. It is difficult to define a good response to medication because it differs from patient to patient what that means.

The barriers to achieving migraine freedom are various, since migraine is a multimodal disease driven by many variables. Good treatment means addressing all of them. If not, the disease is not controlled and the brain becomes increasingly sensitized.[2]

Allodynia is a manifestation of that central sensitization and predictive of chronification of migraine.[3] The likelihood of having allodynia increases when a patient has medication overuse.[4] Interictal allodynia may therefore be a marker for chronic migraine.

Interactions between factors

Figure 1 shows the many factors that play a role in migraine.[5-8] And there are many interactions between them that make it even more difficult to control the disease. It is important to understand all these factors and their interactions when treating (chronic) migraine.Treating only one factor may be insufficient for achieving migraine freedom. They need to be taken into account and an algorithm needs to be built that allows for an individual approach to management and treatment of migraine patients.

Receptor and ligand blocking

Migraine is a polygenetic disease; over 30 different genes have been identified to play a role in it. Patients have elevated CGRP levels and their allostatic load builds as they get exposed to risks. Eventually this is what triggers migraine. Treating patients with CGRP antagonists resets that allostatic load.

CGRP is part of a family of peptides that have known effects on gastric motility. Targeting the CGRP receptor may affect the ability of both CGRP and amylin to modulate gastric emptying[9], prevent CGRP but also adrenomedullin signalling[10], and contribute to gastrointestinal issues like diarrhea.[11] Blocking the ligand, CGRP still allows for these processes to take place. Prescription of erenumab, a receptor blocker, has stopped at the Headache Center of Southern California because of this. Several patients reported constipation, which was not seen with the ligand blockers.

Experience with anti-CGRP mAbs

Two studies with galcanezumab in episodic migraine demonstrated a sustained effect for up to 10 months in the

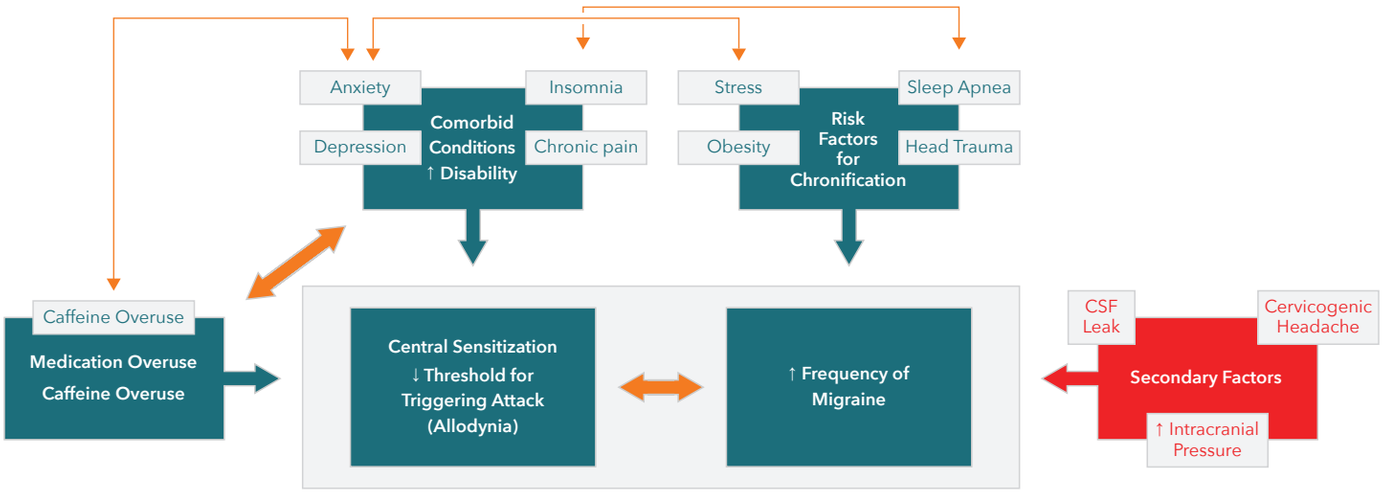

Figure 1 Overview of factors that influence central sensitisation and migraine frequency and their interactions.
Adapted from Lanteri-Minet M et al. Pain 2005;118:319-326, Rossi P et al. Headache 2005;45:561-570, Buse DC et al. Headache 2019;59:306-338, Spanou I et al. Headache 2019;59:1174-1186. [5-8]

reduction of the number of monthly migraine headache days.[12,13] Similar data was generated for fremanezumab in episodic migraine, showing long-term 50% response rates of > 60%.[14] Also in difficult-to-treat patients, fremanezumab has shown to be effective and safe.[15]

In the Headache Cener of Southern California, fremanezumab is the most frequently prescribed anti-CGRP mAb. The most important reason for this is that it is an IgG2Δa antibody. These antibodies cross the placenta the least, and mainly in the third trimester. Moreover, they don't activate the immune system.

Switching from one anti-CGRP mAb to another happens frequently. The data, however, show that there is little difference between the mAbs and that the minimum treatment time for establishing an effect is between 3 and 6 months. That is why in the Headache Center of Southern California, the recommendation is to only switch when there are side effect problems.

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Anti-CGRPs and onabotulinumtoxin A: why, when and how?

Andrew Blumenfeld

Director of the Headache Center of Southern California

In his second lecture, Andrew Blumenfeld presented the US treatment guidelines for onabotulinumtoxin A in migraine patients, its mechanism of action, and a summary of the most important US clinical data for this migraine treatment.

US guidelines for onabotulinumtoxin A

In the US, onabotulinumtoxin A is indicated in chronic migraine patients with 15 monthly headache days, with each headache day being more than 4 hours for at least the month before treatment. Patients must have failed 2 oral preventives from different classes. Failure includes side effects and lack of 50% improvement from baseline after 6 weeks of treatments. There is no stopping rule included in the guidelines.

Mechanism of action

Onabotulinumtoxin A works by inhibiting SNARE-mediated synaptic vesicle trafficking.[1] Injecting onabotulinumtoxin A around the nerve ending stops the vesicles from binding to the presynaptic membrane and prevents the release of neuropeptides and neurotransmitters from those vesicles, leading to muscle fibre paralysis and, thus, pain relief. In an early study, onabotulinumtoxin A was shown to reduce both intensity and duration of capsaicin-induced pain in humans.[2]

CGRP levels are elevated in most patients with chronic migraine. It is thought that onabotulinumtoxin A prevents excessive signals from the periphery to the spinal cord or into the trigeminal nucleus, potentially preventing central sensitisation *(Figure 1)*.[3-6]

Clinical trial results

In the PREEMPT study, onabotulinumtoxin A treatment resulted in a significant improvement in frequency of headache days compared with placebo at 24 weeks.[7] This improvement was sustained to the end of the 56-week open-label period. In another study, patients had statistically significant reductions in the number of headache days from baseline, ranging from 7.4 days at week 24 to 10.7 days at week 108.[8] The effect of onabotulinumtoxin A treatment was already seen after 3 weeks.[9]

Onabotulinumtoxin A and anti-CGRP mAbs

When considering the cascade of events of migraine, onabotulinumtoxin A and anti-CGRP monoclonal antibodies (mAbs) might very well work together to relief patients of their pain. During a migraine attack, blood vessels dilate and there is activation of the C- and Aδ-fibres. Activated C-fibres secrete CGRP, which leads to vasodilation and activation of the Aδ-fibres, which have CGRP receptors. Activation of the Aδ-fibres causes the cascade of messages that go back to the trigeminal nucleus. And that is where there might be synergism between onabotulinumtoxin A and anti-CGRP mAbs. Onabotulinumtoxin A could block the C-fiber from activating and the mAbs could mockup any residual CGRP that binds to receptors on the Aδ-fibres.

The first impressions of using onabotulinumtoxin A and fremanezumab are positive: onabotulinumtoxin A reduced the number of headache days by 7-12 days, addition of fremanezumab led to another reduction of 7-10 days, leaving patients with 22 headache days at baseline with only 3-5 monthly headache days at the end of the study.

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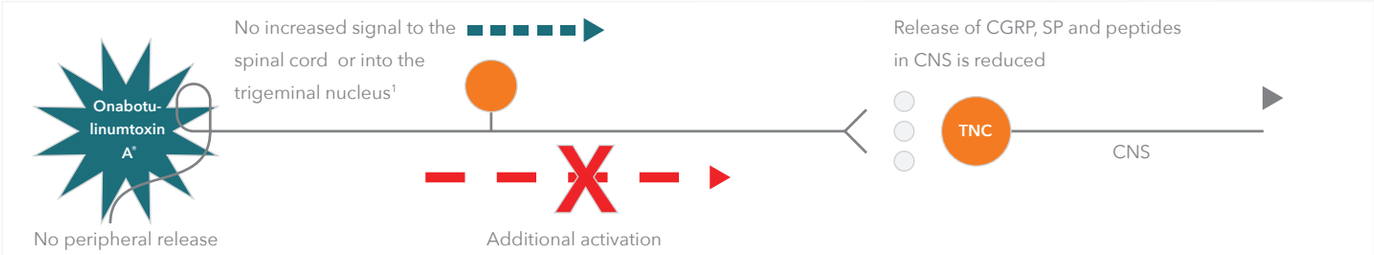

Figure 1 Proposed effect of onabotulinumtoxin A on peripheral and central sensitisation. **CGRP** = Calcitonin-gene related peptide, **CNS** = central nervous system, **SP** = substance P, **TNC** = trigeminal nucleus caudalis. Adapted from Aoki KR. Headache 2003;43:S9-15.[3]

Colophon

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