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- Guidelines for diagnostics and therapy in neurology

# Treatment of migraine attacks and preventive treatment of migraine

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## Gender neutrality

This guideline refers to male, female and non-binary individuals equally.

The form of speech used in specific cases only has editorial reasons and is without prejudice. Respective terms apply to all genders in terms of equal treatment and non-discrimination.

## What's new?

- Lasmiditan, a serotonin 1F receptor agonist in dosages of 50 mg, 100 mg and 200 mg is more effective in the treatment of acute migraine attacks than placebo. No comparative trials with triptans are available as yet.
- Lasmiditan has no vasoconstrictive properties and can be used with patients exhibiting contraindications to triptans.
- Lasmiditan can cause adverse effects on the central nervous system including fatigue and dizziness. Patients are not permitted to drive a vehicle or operate machinery for up to eight hours after the administration of lasmiditan.
- Rimegepant, a CGRP receptor antagonist, is more effective in the treatment of acute migraine attacks than placebo. No comparative trials with triptans are available as yet.
- Rimegepant demonstrates good tolerability in the treatment of acute migraine attacks.
- Monoclonal antibodies against CGRP or the CGRP receptor are effective in preventing episodic and chronic migraines. Very good tolerability is observed.
- A randomised comparative study between a monoclonal antibody against the CGRP receptor (erenumab) and a traditional migraine prophylactic (topiramate) has been published. That study demonstrated that erenumab was more effective and better tolerated than topiramate.
- Patients at increased risk of vascular disease should not yet be treated with the monoclonal antibodies against CGRP or the CGRP receptor or gepants due to pathophysiological considerations.
- Rimegepant is effective in preventing episodic migraines.
- Propranolol is effective in preventing chronic migraine to an extent comparable with topiramate.
- Prophylactic medication with topiramate, onabotulinumtoxinA or a monoclonal antibody against CGRP or the CGRP receptor can also be initiated in the event of existing medication overuse.
- External transcutaneous stimulation of the trigeminal nerve in the supraorbital region (Cefaly®) is effective in treating acute migraine attacks and preventing migraines.
- Endurance sports are effective in preventing migraines.

# The most important recommendations at a glance

### Treatment of migraine attacks

*Triptans and ergot alkaloids*

- The triptans (in alphabetical order) almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan are the substances with the highest degree of effectiveness in treating acute migraine attacks. They should be used for severe headaches and for migraine attacks that do not respond to analgesics, combinations of analgesics with caffeine or to NSAIDs.
- Triptans are superior to analgesics for the freedom-from-pain endpoint after two hours. There are no differences as regards the headache-relief endpoint after two hours.
- Sumatriptan 3 mg or 6 mg administered subcutaneously is the most effective and fastest-acting treatment for acute attacks of migraine.
- Eletriptan 40 mg and rizatriptan 10 mg are the fastest-acting oral triptans according to the results of meta-analyses.
- Naratriptan and frovatriptan have the longest half-life and are therefore the longest-acting.
- If a patient does not respond to one triptan, another triptan may be tried.
- Combining triptans with naproxen is more effective than monotherapy.
- Ergotamine is effective in the treatment of acute migraine. However, its effectiveness is poorly documented in prospective studies.
- Ergot alkaloids must not be combined with triptans.

*Antiemetics and analgetic agents*

- Antiemetics taken during a migraine attack are effective in treating nausea and vomiting.
- Analgesics such as acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs) and the combination of acetylsalicylic acid, paracetamol and caffeine are effective in treating migraine. Mild and moderate migraine attacks should be treated with these substances first. They also work for some patients with severe migraine attacks.
- The efficacy of medications for treating acute migraine attacks, including triptans, is higher if they are taken early in the headache phase.
- Opioid analgesics should not be taken in the treatment of acute attacks of migraine.
- The threshold for the development of headache due to overuse of analgesics or migraine medications is ≥ 10 days/month for triptans and combination analgesics and ≥ 15 days/month for monoanalgesics.

*Substances approved in Germany but not yet available in December 2022*

- Rimegepant can be used in patients for whom analgesics or triptans are not effective or are not tolerated.
- Lasmiditan can be used if the use of triptans is contraindicated.
- Lasmiditan can cause adverse effects on the central nervous system including fatigue and dizziness. Patients are not permitted to drive a vehicle or operate machinery for up to eight hours after the administration of lasmiditan.

*Emergency treatment*

- Patients who call a doctor to treat their migraine attacks or go to A&E have usually used oral medication before without success. As a result, studies available in connection with emergency treatment tend to focus on parenterally administered substances.
- The following treatments can be applied: ASA i.v., triptans s.c., metoclopramide i.v. (as well as other dopamine antagonists), metamizole i.v. and, in the case of status migraenosus, steroids orally or i.v.

*Non-medication treatment of migraine attacks*

- There is evidence of an effect of acupuncture in the treatment of acute migraine attacks, but the quality of the available studies does not allow any clear recommendations.
- External transcutaneous stimulation of the trigeminal nerve in the supraorbital region (Cefaly®) is effective in treating acute migraine attacks.
- Vasoconstriction training (blood volume pulse biofeedback) is recommended as a psychological procedure for the treatment of an acute attack.
- A distinction must be made between non-medicated acute treatment and psychological prevention.

**Preventive treatment of migraine**

- In the case of frequent migraine attacks or migraine attacks with pronounced symptoms or persistent aura, migraine prevention with medication should be offered in addition to prevention through information and behavioural adjustments.
- The choice of a migraine prevention treatment should be based on attack frequency (episodic versus chronic), concomitant diseases and the individual needs of the patient.
- The beta-blockers propranolol and metoprolol, the calcium antagonist flunarizine as well as the anticonvulsants valproic acid and topiramate and the antidepressant amitriptyline are effective in migraine prevention treatment.
- Valproic acid must not be administered to women of childbearing age. The use of valproic acid for migraine prevention treatment is off-label.

*Monoclonal antibodies against CGRP or the CGRP receptor*

- The monoclonal antibodies against CGRP (eptinezumab, fremanezumab and galcanezumab) or against the CGRP receptor (erenumab) are superior to treatment with placebo in the prevention of episodic migraine.
- The at least 50% responder rate for the monoclonal antibodies ranges from 30% to 62% after 3-6 months. The at least 50% responder rate for placebo ranges from 17% to 38%.
- The efficacy of monoclonal antibodies can be evaluated within 4–12 weeks. In chronic migraine, a delayed response may occur, so that a response can still be observed after 5-6 months. According to the approval, treatment success is to be reviewed after 3 months (for eptinezumab after six months).
- A direct comparison of the monoclonal antibodies with each other is not possible due to the data currently available.
- Erenumab is discontinued less frequently due to adverse reactions compared to topiramate. Erenumab is more effective and better tolerated than topiramate in a direct comparison.
- Comparative studies with other migraine prevention treatments to date are not available.
- The efficacy of the monoclonal antibodies has also been demonstrated for patients with headaches associated with overuse of analgesics or migraine medications (MOH).
- All monoclonal antibodies are approved for migraine prevention treatment in adults experiencing at least four migraine days per month.
- For episodic migraine, treatment success is defined as a reduction in average monthly migraine days of 50% or more compared to pre-treatment over a period of at least three months. In chronic migraine, a reduction in migraine days of 30% or more is considered a therapeutic success. Documentation using an analogue or digital headache calendar is recommended.
- Alternative clinically acceptable criteria include significant improvements in validated, migraine-specific, patient-reported outcome measurements such as a 30% reduction in MIDAS score for those with baseline scores above 20 or a reduction in the score on the 6-item Headache Impact Test (HIT-6) of at least 5 points.
- If there is no response to one monoclonal antibody, a switch to another monoclonal antibody may be considered. Here, the differences in the amounts reimbursed with regard to previous treatments must be taken into account.
- Monoclonal antibodies against CGRP or the CGRP receptor should not be administered to pregnant women and during lactation. They should not be used in women who are not using contraception or not using adequate contraception.
- Furthermore, monoclonal antibodies should be used with caution in patients with coronary heart disease, ischaemic insult, subarachnoid haemorrhage or peripheral arterial occlusive disease as well as inflammatory bowel disease, COPD, pulmonary hypertension, Raynaud's disease, wound healing disorders and after organ transplants until appropriate safety data are available.

For children and adolescents, there is as yet insufficient information on tolerability and safety.

*Duration of the migraine prevention treatment*

- The duration of effective migraine prevention treatment depends on the severity of the migraine, comorbidities (e.g. MOH) and the substance administered. Flunarizine should not be taken for longer than six months, according to the product information. All other substance classes are usually administered for at least nine months. The indication for each prevention treatment must be reviewed throughout the treatment, at the latest after a treatment duration of 24 months.
- With prophylactic drug treatments, a withdrawal trial may be attempted, the timing of which should depend on the frequency of headaches, impairment and comorbidities.

*Miscellaneous*

- Rimegepant administered orally is probably suitable for the prevention of episodic migraine.
- For chronic migraine with or without analgesic or migraine medication overuse, topiramate, onabotulinumtoxinA and the monoclonal antibodies against CGRP or the CGRP receptor were effective, according to the results of placebo-controlled trials.
- OnabotulinumtoxinA is only effective in the treatment of chronic migraine with and without overuse of analgesics and migraine medications. OnabotulinumtoxinA should be used in this indication by neurologists experienced in the diagnosis and treatment of chronic headaches.

*Interventional procedures*

- The use of occipital nerve block has shown moderate effects in short-term (<3 months) treatment of chronic migraine in a few trials. In view of the minor adverse effects, its use can be considered in individual cases, although it was unclear whether local anaesthetics, steroids or both were most effective. Acute effects on migraine attacks have not been sufficiently studied.
- Invasive neurostimulation procedures such as bilateral stimulation of the greater occipital nerve may be considered in refractory patients with chronic migraine after evaluation in a headache centre on a case-by-case basis.
- Implanting an electrode into the sphenopalatine ganglion is not recommended for migraine prevention.
- Given their good tolerability, non-invasive stimulation procedures can be used in patients who refuse migraine prevention treatment with medication.

At this point in time, only electrical stimulation of the supraorbital nerve is of practical importance in migraine treatment.

- Surgical transection of the corrugator muscle and other pericranial muscles is not recommended.
- Closure of a patent foramen ovale is not recommended.

*Psychotherapeutic methods and lifestyle changes for migraine prevention*

- Prevention treatment using medication should generally be accompanied by psychological procedures such as education, self-observation, self-management, cognitive behavioural treatment, social skills training, relaxation procedures, mindfulness, biofeedback and others.
- In patients with pronounced migraine-related impairment and/or psychological comorbidity, psychological pain treatment methods should always be used.
- Relaxation methods, cognitive behavioural treatment methods and biofeedback can also be used instead of medication prevention treatment.
- In a multimodal approach, both medication and psychological prevention treatment can be combined.
- Psychological methods were equally effective compared to conventional medication-based prevention treatment (this does not apply to monoclonal antibodies) and can be used instead.
- Endurance sports are effective in preventing migraines.

*Nutrition and diets*

- Most dietary supplements and probiotics are not effective in preventing migraine.
- Low-sugar, low-fat or ketogenic diets may be effective.

*Apps and internet-based offers*

- Smartphone applications and telemedicine services can support the diagnosis and treatment of migraine.
- They can document the course of migraine and headache and thus support the monitoring of progress and success.
- Information tools can provide knowledge and behavioural treatment options.
- Internet-based services and apps can be helpful when time or location constraints (e.g. pandemic, rural areas, long waiting times) make face-to-face care difficult.
- Results from randomised controlled trials on clinical efficacy or improvement of the quality of care are currently not available.

# Contents

# 1 Overview and introduction

## 1.1 Introduction

Migraine is a common condition with a point prevalence of 20% in women and 8% in men. As a result, guidelines for the treatment of migraine attacks as well as the medicinal and behavioural prevention treatment of migraine are of great practical importance. The aim of this guideline is to optimise the treatment of acute migraine attacks and the prevention treatment of migraine with and without medication. The guideline is evidence-based, takes into account the clinical experience of the guideline authors and is a further development of the following guidelines and recommendations:

- Guidelines of the European Headache Federation 2022 (1)
- DGN and DMKG guidelines on migraine treatment 2018 (2)
- DMKG guidelines: Relaxation therapy and behavioural intervention for treating migraines 2017 (3)
- American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice 2021 (4)
- Scottish Intercollegiate Guideline 2018 (5)

## 1.2 Definitions

Migraine is characterised by attacks of severe, often unilateral, pulsating, throbbing headaches that increase in intensity with physical activity (6). Holocranial headaches occur in one third of patients. The individual attacks are accompanied by loss of appetite (almost always), nausea (80%), vomiting (40-50%), photophobia (60%), sensitivity to noise (50%) and hypersensitivity to certain smells (10%). Signs of parasympathetic activation were found in up to 82% of patients, most commonly mild eye tearing (7). If the headache is unilateral, it may change sides during an attack or from one attack to the next. The intensity of the attacks can vary greatly from one attack to the next. The duration of attacks, according to the definition of the International Headache Society, is between 4 and 72 hours if untreated. In children, the attacks are shorter and may be accompanied only by severe nausea, vomiting and dizziness, even without a headache (8, 9). The localisation of the headache is more often bilateral.
Accompanying symptoms such as photophobia and phonophobia can occasionally only be inferred from behaviour in children.

## 1.3 Epidemiology

Migraine is one of the most frequent forms of headache. The 1-year prevalence of migraine lies between 10% and 15% (10-12). Before puberty, the 1-year prevalence of migraine is 3-7% (13, 14). Boys and girls are affected about equally often.

The highest prevalence is between the ages of 20 and 50. In this phase of life, women are affected up to three times more often than men. The difference in prevalence between the two sexes was greatest at around 30 years.

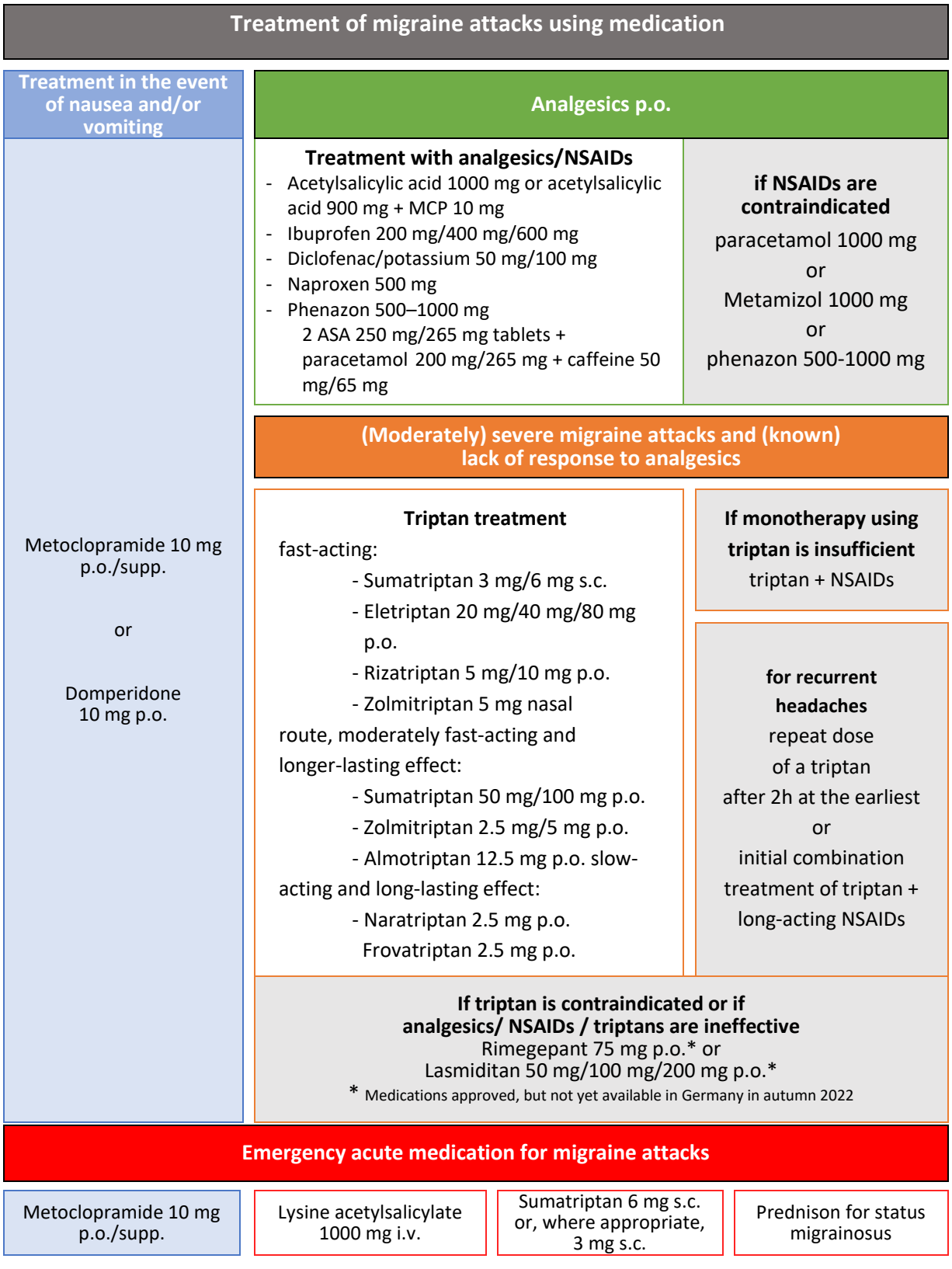
## 1.4 Diagnosis

The diagnosis is based on medical history and an unremarkable neurological examination result. Additional diagnosis and especially imaging are necessary for headaches with an unusual clinical presentation (e.g. to exclude subarachnoid haemorrhage).

# 2 Acute treatment using medication

**Figure 1: Treatment of acute migraine attacks using medication**

p. o. = per os, Supp. = suppository, i. v. = intravenous, NSAIDs = non-steroidal anti-inflammatory drug, ASA = acetylsalicylic acid, CI = contraindications, s. c. = subcutaneous



## 2.1 5-HT$_{1B/1D}$ agonists (triptans)

**Recommendations**

- The triptans almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan are the substances with the highest degree of effectiveness for the acute treatment of the headache phase in migraine attacks with or without aura. They should be used for severe headaches that do not respond to analgesics, combination analgesics or non-steroidal anti-inflammatory drugs (NSAIDs). Triptans are superior to analgesics for the freedom-from-pain endpoint after two hours. There are no differences as regards the headache-relief endpoint after two hours.
- Sumatriptan 3 mg or 6 mg administered subcutaneously is the most effective and fastest-acting treatment for acute attacks of migraine.
- Eletriptan 40 mg and rizatriptan 10 mg are the fastest-acting oral triptans according to the results of meta-analyses.
- Almotriptan 12.5 mg and eletriptan 40 mg have the best side-effect profiles.
- Naratriptan and frovatriptan have the longest half-life and are the longest-acting.
- If a patient does not respond to one triptan, another triptan may be tried.
- Combining triptans with naproxen is more effective than monotherapy. However, the additional treatment effects were not considerable. Side effect rates were higher with combined treatment than with monotherapy.
- Triptans are superior to ergot alkaloids in terms of efficacy.
- The efficacy of medications for treating acute migraine attacks, including triptans, is higher if they are taken early in the headache phase.
- The threshold for the development of headache due to overuse of analgesics or migraine medications is ≥ 10 days of use per month for triptans and combination analgesics and ≥ 15 days of use per month for monoanalgesics.

The serotonin 5-HT$_{1B/1D}$ receptor agonists (triptans) almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan are the first-choice treatment for the acute treatment of the headache phase in moderate and severe migraine attacks with or without aura that do not respond or do not respond sufficiently to treatment with analgesics, combined medication or non-steroidal anti-inflammatory drugs. For recurrent headaches after initial efficacy of a triptan, a second dose of a triptan may be given after two hours at the earliest.

Triptans are specific migraine medications. However, the efficacy of triptans is not diagnostic, as triptans can also be ineffective for migraine and effective for secondary headaches such as subarachnoid haemorrhage (15).

The efficacy of triptans has been proven in numerous large placebo-controlled trials. The data on the efficacy of oral triptans collected in clinical trials have been summarised in large meta-analyses, so these studies are not reviewed in detail here (16-22). Cochrane analyses are available for the various non-oral forms of sumatriptan administration, which also show efficacy (23-26). Zolmitriptan as a nasal spray has been shown to be effective in placebo-controlled trials (27-29); the efficacy of nasal and oral zolmitriptan has also been shown in a Cochrane analysis (30).

In long-lasting migraine attacks, migraine headache may recur after the successful pharmacological effect of a migraine medication has ended (headache recurrence). Recurrent headache is defined as a worsening of headache intensity from no headache or mild headache to moderate or severe headache in a period of 2-24 hours after the first effective medication (31). By definition, the likelihood of recurrent headache increases with the efficacy of the medication. Recurrent headache is more common with the triptans than with ergotamine tartrate or acetylsalicylic acid (ASA). For example, 15-40% of patients experience a recurrence of headache after oral administration of triptans, in which case a second dose of the substance is effective again (32).

Triptans with a longer half-life such as frovatriptan and naratriptan tend to have slightly lower recurrence rates than those with a short half-life (33). However, their efficacy is somewhat lower. If the initial administration of a triptan is not effective in an attack within 2 hours, a second dose should not be taken during this attack because the efficacy for this has not been sufficiently proven in clinical trials. The exception is if the first dose has been regurgitated. In these cases, an analgesic should be used as a substitute medication. Studies show that patients who do not respond to treatment during one attack can still be successfully treated during another attack.

Table 1 gives an overview of the available triptans. Almotriptan 12.5 mg, naratriptan 2.5 mg and sumatriptan 50 mg are also available over the counter.

**Table 1: Treatment of acute migraine attacks with triptans**

| Triptans | | | |
|---|---|---|---|
| **Active substance** | **Dose and application route** | **Adverse effects (selection)** | **Contraindications (selection)** |
| Sumatriptan | 50 or 100 mg p. o.<br>10 or 20 mg nasal route<br>6 mg, 3 mg s. c. | Tightness in the chest and throat, paraesthesia of the extremities, feeling of coldness<br><br>in the case of sumatriptan s. c. additionally: Local reaction at the injection site<br><br>Adverse effects with naratriptan, almotriptan and frovatriptan (somewhat) lower compared to sumatriptan | Inadequately treated hypertension, coronary artery disease, angina, history of myocardial infarction, Raynaud's disease, PAOD, TIA or stroke, pregnancy, lactation, severe hepatic or renal insufficiency, multiple vascular risk factors, concomitant treatment with ergotamine, within two weeks of stopping an MAO inhibitor. |
| Zolmitriptan | 2.5 or 5 mg<br>Tablet or orodispersible tablet p. o.<br>5 mg nasal route | | |
| Naratriptan* | 2.5 mg p. o. | | |
| Rizatriptan | 5 or 10 mg<br>(Orodispersible) tablet p. o.<br>5 mg in the event of co-medication with propranolol or where liver or kidney function is impaired. | | |
| Almotriptan* | 12.5 mg p. o. | | |
| Eletriptan | 20 or 40 mg p. o. | | |
| Frovatriptan | 2.5 mg p. o. | | |

*also available as OTC

### 2.1.1 Comparison of triptans with each other and with other substances for the treatment of acute migraine attacks

**Recommendations**

- There were only minor differences in efficacy between the individual orally administered triptans. However, the efficacy can vary considerably from one individual to another.
- Triptans are more effective than analgesics or NSAIDs for the "pain-free after 2 hours" endpoint in most randomised trials. In meta-analyses, however, only minor differences in efficacy were observed.
- Triptans are superior to ergot alkaloids in terms of efficacy.

The shortest time to onset of action was for subcutaneous administration of 6 mg sumatriptan (10 minutes) (34). Oral sumatriptan, almotriptan and zolmitriptan take effect after 45-60 minutes (18). Rizatriptan and eletriptan taken orally were fastest-acting (after 30 minutes) (35). If an initial dose of eletriptan 40 mg is not effective, 80 mg (2 times 40 mg) can also be given (80 mg tablets are available in Switzerland). A second 80 mg dose may be not given for recurrent headache within 24 hours.

Naratriptan and frovatriptan take up to 4 hours to take effect (36). Zolmitriptan 5 mg as a nasal spray has a more rapid onset of action than oral zolmitriptan 2.5 mg (27).

The reduction in headache after two hours, the most important parameter in clinical trials for the efficacy of migraine medication, is highest with subcutaneous application of 6 mg sumatriptan (70-80%) (37). Sumatriptan nasal spray is as effective as sumatriptan tablets (38, 39). Sumatriptan 50 mg and 100 mg are comparably effective. Naratriptan and frovatriptan (2.5 mg each) are less effective than sumatriptan, rizatriptan and zolmitriptan for improving headache after two hours (17, 40), but also show fewer adverse effects and a slightly lower rate of recurrent headache. The onset of action of naratriptan and frovatriptan is likely to be delayed compared with the other triptans, although some trials have shown no difference between frovatriptan and other triptans (41). After 4 hours, the efficacy is comparable to that of sumatriptan. Zolmitriptan 2.5 and 5 mg and almotriptan 12.5 mg are moderately effective. Rizatriptan 10 mg is slightly more effective than 100 mg sumatriptan (42–44) and almotriptan 12.5 mg (45). In dosages of 40 mg and 80 mg (2 x 40 mg), eletriptan is the most effective oral triptan (46). In a meta-analysis, eletriptan 40 mg and rizatriptan 10 mg showed the highest rate of freedom from pain after two hours; eletriptan additionally showed the highest rate of freedom from pain over 24 hours (16) (Table 2).

**Table 2: Selected results of a meta-analysis on the efficacy of triptans (22) and analgesics for the treatment of migraine attack**

| | RR for pain-free after two hours | Number of patients |
|---|---|---|
| Sumatriptan 100 mg | 3.85 | 6571 |
| Sumatriptan 6 mg s. c. | 3.85 | 2522 |
| Rizatriptan 10 mg | 2.43 | 3328 |
| Naratriptan 2.5 mg | 2.52 | – |
| Zolmitriptan 2.5 mg | 2.06 | 4904 |
| Almotriptan 12.5 mg | 1.68 | 1429 |
| Acetylsalicylic acid | 2.08 | 2027 |
| Ibuprofen 400 mg | 1.91 | 1815 |
| Paracetamol | 1.89 | 729 |
| ASA plus paracetamol plus caffeine*(47) | 2.2 | 3306 |
| Eletriptan 40 mg* (17) | OR 3.35 | 3143 |

RR = relative risk compared to placebo, OR = odds ratio; *not mentioned in the meta analysis

The incidence of recurrent headaches is between 15% and 40% for the different triptans. In menstrual migraine, frovatriptan showed a lower rate of recurrent headaches after two hours than rizatriptan and almotriptan with the same efficacy (48, 49). If a triptan is not effective for three consecutive attacks, another triptan may still be effective (46, 50-52).

In comparative trials, the higher dose of a triptan is more effective than an analgesic or an NSAID for the freedom-from-pain endpoint after two hours. Triptans are effective in about 60% of non-responders to NSAIDs (53). Sumatriptan 6 mg s.c. was slightly more effective than 1000 mg ASA i.v., but had more adverse effects (54). Sumatriptan 3 mg s.c.is better tolerated than 6 mg s.c.and is also characterised by a rapid onset of action (55, 56).

Among the drugs containing ergotamine, ergotamine tartrate was less effective than sumatriptan (57), rizatriptan (58), eletriptan (59) and almotriptan (60) in comparative trials.

### 2.1.2 Combinations

**Recommendations**

- The initial combination of a triptan with a long-acting NSAID (e.g. naproxen) works better than the individual components and can partly prevent the recurrence of migraine attack.
- If one triptan is not effective enough, it can be combined with a fast-acting NSAID.
- In patients with long migraine attacks and recurrent headaches when treated with a triptan, a long-acting NSAID can be given with a time lag.

Combination treatment for the combination of sumatriptan and naproxen (61, 62) was best studied, the efficacy of which has also been confirmed in a Cochrane analysis (63).
Compared with placebo, the number needed to treat (NNT) was 4.9 when the initial headache was moderate or severe. Alternatively, the NSAID can also be given with a time delay, but no placebo-controlled trials are available on this. The combination of naproxen and sumatriptan is also effective in patients with "probable" migraine according to IHS criteria (64). In contrast, the combination of rizatriptan and paracetamol was not significantly more effective than rizatriptan alone (65). Frovatriptan and dexketoprofen in combination are more effective than frovatriptan alone (66). The administration of metoclopramide not only improves the accompanying vegetative symptoms, but also leads to better absorption and efficacy of sumatriptan (67).

### 2.1.3 Time the triptans are administered

**Recommendations**

- Triptans work better if they are taken early in the headache phase of the migraine attack.
- If triptans are taken during the aura phase, while there is still no headache, they are not effective.

Triptans can work at any time during the attack, which means they do not necessarily have to be taken immediately at the beginning of the pain phase. However, triptans work better the earlier they are taken in a migraine attack (68-73). To prevent the development of a headache from medication overuse, early use should only be recommended if attacks are not too frequent (<5 headache days per month) and if the patient can clearly identify their headache as a migraine attack. If triptans are taken during the aura phase, while there is still no headache, they are not effective (74, 75).

### 2.1.4 The safety of triptans

**Recommendation**

- Triptans should not be used in patients with serious cardiovascular disease such as angina, coronary artery disease, after myocardial infarction, transient ischaemic attack (TIA), stroke or advanced peripheral arterial disease (PAOD).

Life-threatening adverse effects (myocardial infarction, severe cardiac arrhythmia, stroke) are extremely rare and have been reported with sumatriptan application with a frequency of 1:1,000,000 (76). Almost all patients affected either had clear contraindications (e.g. pre-existing coronary artery disease) or the diagnosis of migraine was incorrect (77). Since the mechanism of action of the different triptans is approximately the same, a similar incidence of life-threatening adverse effects can be expected with all triptans. In terms of adverse event reports, oral forms of administration have a lower risk than subcutaneous administration (78). For safety reasons, patients suffering from migraine with aura should apply a triptan only after the aura has subsided and the headache has started. In addition, triptans are probably not effective when used during aura (74, 75). Population-based trials showed no increased risk of vascular events with the use of triptans compared with analgesics (79, 80). This was also found in a retrospective analysis of patients with migraine with brainstem aura and hemiplegic migraine (81).

In Germany, orally administered almotriptan, naratriptan and sumatriptan 50 mg are available OTC and thus without a prescription. There are very few reports of serious adverse effects for these substances.

Theoretically, all antidepressants that inhibit the reuptake of serotonin can trigger serotonergic syndrome in combination with a triptan. Rizatriptan and sumatriptan are metabolised predominantly via the MAO-A system and can thus lead to elevated effect levels and increased adverse effects in combination with MAO inhibitors and other serotonergic antidepressants. Almotriptan and zolmitriptan are metabolised via other cytochrome-linked systems in addition to a strong MAO component, so that fewer complications are to be expected here with polypharmacy. Eletriptan, naratriptan and frovatriptan, on the other hand, are not metabolised to any significant extent via the MAO system, so that they should be preferred for serotonergic concomitant medication. In principle, the choice of a single triptan should also be based on concomitant medication and metabolisation.
Serotonergic syndromes, however, have only been described in very few individual cases (82-84). Triptans and ergot alkaloids must not be combined.

## 2.2 Ergot alkaloids

**Recommendations**

- Ergotamine is effective in the treatment of acute migraine. However, its effectiveness is poorly documented in controlled trials.
- The adverse effects of ergotamine are greater compared to triptans and other acute therapy drugs. Ergot alkaloids should therefore no longer be used as a 1st-line treatment.
- Ergot alkaloids must not be combined with triptans.
- In view of the poorer efficacy and the increased adverse effects, ergotamines should only be used as an exception for the treatment of acute migraine attacks.
- Patients who benefit from the longer-lasting action of ergotamine compared to that of triptans can continue to take ergotamine.

Ergotamine has been used in clinical practice for more than 70 years for the acute treatment of migraine. A European expert group had reviewed the preclinical and clinical data on ergotamine in the treatment of migraine (85). Based on the analysis of 18 randomised trials of acute migraine attack treatment, ergotamine is found to be superior to placebo and comparably effective to most analgesics. Ergotamine is considered for patients with long-lasting headaches. For most migraine sufferers who require specific migraine treatment, a triptan is the better choice, both in terms of efficacy and adverse effects.

## 2.3 Antiemetics

Table 3: Antiemetics in the treatment of acute migraine attacks

| Antiemetics | | | |
|---|---|---|---|
| **Active substance** | **Dose and application route** | **Adverse effects (selection)** | **Contraindications (selection)** |
| Metoclopramide | 10 mg p. o.<br>10 mg<br>rectally<br>10 mg i. m. or i. v. maximum daily dose 30 mg | Early dyskinetic syndrome, restlessness | Children and adolescents under 18 years, hyperkineses, epilepsy, pregnancy, prolactinoma |
| Domperidone | 10 mg p. o.<br>maximum daily dose: 30 mg | Less frequent than with etoclopramide | Children under 12 years and under 35 kg, otherwise see metoclopramide, but side-effects less pronounced and less frequent. QTc interval prolongation, medication that prolongs the QTc interval |

**Recommendations**

- Antiemetics such as metoclopramide or domperidone are effective in treating nausea and vomiting during a migraine attack.
- Metoclopramide has little independent effect on the headache of a migraine attack.
- Prokinetic and antiemetic drugs should not generally be combined with analgesics or triptans, but should be used for the targeted treatment of severe nausea or vomiting (89).

Nausea and vomiting are among the characteristic accompanying symptoms of migraine. Pharmacokinetic trials suggested that during migraine attacks the absorption of analgesics such as paracetamol (86) or acetylsalicylic acid (87) may be delayed. The cause is thought to be disturbed gastric peristalsis in the migraine attack (88). This led to the rationale for combining analgesics or triptans with prokinetic antiemetics: an increase in effect via accelerated and possibly also improved absorption. In fact, this hypothesis has only been investigated in a few, predominantly small trials with sobering results. In a Cochrane review, the combination of acetylsalicylic acid and metoclopramide was shown to have a better effect on the migraine accompanying symptoms of nausea and vomiting (89). When administered i.v., metoclopramide also appears to have an independent analgesic effect on migraine; domperidone taken in the prodromal phase of migraine reduced the occurrence of a subsequent headache phase of migraine in two studies (90, 91). A single dose of domperidone is 10 mg. The maximum daily dose is 30 mg.

In a randomised, open-label trial, a combination of 900 mg acetylsalicylic acid with metoclopramide 10 mg orally (n = 7) was more effective than acetylsalicylic acid alone (n = 8) (92). 50 mg of sumatriptan plus metoclopramide 10 mg orally was more effective than sumatriptan 50 mg alone in a double-blind cross-over study (n = 16) (67). In a larger study (n = 118, cross-over design), a soluble fixed combination of 650 mg acetylsalicylic acid and metoclopramide 10 mg was superior to placebo but not to acetylsalicylic acid as monotherapy in reducing pain (93). A similar result was found for domperidone. In a placebo-controlled study in a cross-over design (n = 46), the combination of paracetamol with domperidone was not superior to paracetamol as monotherapy in terms of pain reduction (94). Accordingly, a Cochrane review from 2010 concluded that, although the combination with 10 mg metoclopramide orally substantially improves the effect of acetylsalicylic acid on the migraine accompanying symptoms of nausea and vomiting, the additional administration of metoclopramide has no additional effect on pain (95).

Numerous case series or comparative trials with other substances without placebo control have been conducted on the efficacy of metoclopramide 10-20 mg i.v. in the acute treatment of migraine, and the results are consistently positive (96-100). Placebo-controlled trials, however, came to contradictory results (101). In one study (n = 50), metoclopramide 10 mg i.v. was superior to placebo (102), and in another study (n = 40), to both placebo and ibuprofen 600 mg orally (103). In contrast, metoclopramide 10 mg i.v. was not superior to prochlorperazine and placebo in a comparative study (n = 70) (104), nor was it superior to magnesium sulphate and placebo in a comparative study (n = 113) (105). Metoclopramide 10 mg i.m. was also no more effective than placebo in a comparison with prochlorperazine and placebo (n = 86) (106). In a comparative study, metoclopramide in a dose up to 4 x 10 mg i.v. was effective to a comparable extent to 6 mg sumatriptan s.c. in the first two hours (97). Nevertheless, a meta-analysis from 2004 concluded overall that metoclopramide i.v. was a therapeutic option for acute migraine attacks in the emergency situation (107). Metoclopramide is approved in Germany for the symptomatic treatment of nausea and vomiting caused by acute migraine. It can be used with oral analgesics to promote absorption in acute migraine.

A controlled trial (n = 330) compared valproate 1000 mg with metoclopramide 10 mg and ketorolac 30 mg, both administered intravenously, in the emergency treatment of acute migraine attack (108). Metoclopramide showed significant superiority over both comparators for several endpoints. Valproate was less effective than metoclopramide or ketorolac in emergency treatment. Intravenous rehydration after severe vomiting by administration of fluids is often performed in emergency situations. In a post-hoc analysis, the short-term effect (1 hour) and the long-term effect (24 hours) were compared between patients with (n = 112) and without rehydration (n = 458) given metoclopramide. The additional rehydration did not improve pain parameters in patients with acute migraine attack treated with metoclopramide (109). However, rehydration may be necessary in the event of significant fluid loss due to repeated vomiting.

In a small double-blind, placebo-controlled study in a cross-over design (n = 19), it was shown that taking domperidone 30 mg orally in the prodromal phase of the migraine attack significantly reduced the occurrence of migraine headaches compared to placebo (90). The same author was able to reproduce this effect in a later double-blind cross-over study without placebo control (n = 19) for domperidone at doses of 20, 30 or 40 mg orally (91). It should be noted that domperidone is only licensed for single doses of 10 mg and the maximum daily dose must not exceed 30 mg.

Only small trials are available for the antiemetic dimenhydrinate. It is preferred for nausea associated with dizziness and balance disorders or when a mild sedative effect is desired (110-114). Dimenhydrinate is a salt of diphenhydramine and 8-chlorotheophylline. It has not been shown to be significantly effective in treating nausea when taken additionally during an acute migraine attack in a controlled study (115).

## 2.4 Analgetic agents

**Recommendations**

- Analgesics such as acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs) and the combination of analgesics and caffeine are effective in treating acute migraine.
- The best evidence is available for the effect of acetylsalicylic acid and
- Mild and moderate migraine attacks should be treated with these substances first. They also work for some patients with severe migraine attacks.
- The efficacy of medications for treating acute migraine attacks, including triptans, is higher if they are taken early in the headache phase.
- Opioid analgesics should not be taken in the treatment of acute attacks of migraine.
- The threshold for the development of headache due to overuse of analgesics or migraine medications is ≥ 10 days of use per month for triptans and combination analgesics and ≥ 15 days of use per month for monoanalgesics.

About 80% of all patients treat headaches with (mainly over-the-counter) analgesics (116). Table 4 gives an overview of the currently recommended analgesics, NSAIDs and coxibs for the treatment of acute migraine attack.

**Table 4: Analgesics/NSAIDs/COX-2 inhibitors with proven efficacy for the treatment of acute migraine attacks In descending order of evidence**

| Active substance or combination of substances | Comment |
|---|---|
| **Acetylsalicylic acid (ASA) (p. o.)**<br>Single dose: 900–1000 mg | ASA with and without metoclopramide |
| **Acetylsalicylic acid (ASA) (i. v.)**<br>Single dose: 1000 mg | i. v. emergency medication with and without metoclopramide |
| **Ibuprofen (p. o.)**<br>Single dose: 200 mg, 400 mg and 600 mg | 200 mg less effective than 400 mg; flat dose-response curve between 400 and 600 mg ibuprofen. |
| **Phenazone**<br>Single dose: 1000 mg | Can be used in patients with contraindications to NSAIDs |
| **Diclofenac/potassium (p. o.)**<br>Single dose: 50 mg and 100 mg | very flat dose-response curve between 50 and 100 mg diclofenac/potassium |
| **Acetylsalicylic acid (250 or 265 mg) + Paracetamol (200 or 265 mg) + caffeine (50 or 65 mg)**<br>Single dose: Two tablets of the fixed combination | In trials, the combination was more effective than the individual substances. Threshold for development of medication overuse headache at ≥ 10 days of use/month (monoanalgesics ≥ 15 days of use/month). |
| **Diclofenac sodium (p.o.)**<br>Single dose: 50 mg, 100 mg | Conflicting results on efficacy for 100 mg diclofenac/sodium |
| **Metamizole (p. o.)**<br>Single dose: 1000 mg | For the treatment of severe pain when other analgesic measures are not suitable |
| **Metamizole (i. v.)**<br>Single dose: 1000 mg | i. v. emergency medication with and without metoclopramide |
| **Paracetamol (p. o.)**<br>Single dose: 1000 mg | No robust evidence of efficacy for 500 mg paracetamol |
| **Naproxen (p. o.)**<br>Single dose: 500 or 825 mg | Comparison with placebo only in three smaller, older RCTs |
| **Soluble celecoxib (p. o.)**<br>Single dose: 120 mg | Two RCTs |

RCT = Randomised Controlled Trial

Analgesics are available in different formulations. The resulting pharmacokinetic profiles may influence therapeutic efficacy. Effervescent tablets, with an active substance already dissolved outside the stomach, lead to faster absorption, faster pain reduction and functional action. Since there is no high concentration of active substance in the gastric mucosa, there is also better tolerability. Appropriate formulations should therefore be preferred (117).

A Cochrane review investigated the efficacy of acetylsalicylic acid alone or in combination with an antiemetic in the acute treatment of migraine (118). For the single dose of 500 mg ASA, no study is available for efficacy in the treatment of migraine. In 13 trials (n = 4222), ASA 900 mg or ASA 1000 mg alone or in combination with metoclopramide 10 mg were compared with placebo or active comparators, especially sumatriptan 50 mg or 100 mg. The NNT for freedom from pain after two hours was 6.6 for acetylsalicylic acid 1000 mg as monotherapy and 6.2 in combination with metoclopramide. Sumatriptan 50 mg did not show a significantly better effect. Sumatriptan 100 mg was significantly superior to the combination of acetylsalicylic acid with metoclopramide for freedom-from-pain after two hours. Acetylsalicylic acid was confirmed to be effective in migraine acute treatment, similar to sumatriptan 50 mg or 100 mg. The efficacy of the i.v. formulation of 1000 mg lysine acetylsalicylate (54) or of 900 mg in combination with 10 mg metoclopramide (119) for the treatment of severe migraine attacks has been demonstrated in placebo-controlled randomised trials.

Ibuprofen was also evaluated in a Cochrane review for efficacy in acute migraine attack alone or in combination with antiemetics (120). Nine trials (n = 4373 attacks) compared ibuprofen with placebo or other active substances. The NNT for 2-hour significant headache improvement for ibuprofen 400 mg vs. placebo was 7.2. Ibuprofen leads to pain relief in about half of the patients, but only in a minority to complete freedom from pain and accompanying symptoms. Soluble forms lead to faster pain relief. In a large RCT, there was no significant difference between doses of 200 mg, 400 mg and 600 mg ibuprofen in the primary endpoint of pain reduction two hours after taking the study medication (121). Only older trials are available for the doses of 800 mg and 1200 mg ibuprofen (122, 123), which do not meet the current requirements for an RCT. No headache or migraine trials are available for ibuprofen lysinate, an active ingredient also frequently used in self-medication.

A Cochrane systematic review compared the use of paracetamol and ibuprofen in specific pain situations, including migraine and tension-type headache. Ibuprofen was consistently superior to paracetamol in mean comparisons (124). Since neither drug is effective for every patient, both are needed. The frequent practice of using paracetamol as the first analgesic is not supported by the data; the efficacy of paracetamol is not sufficiently proven (124). A Cochrane review investigated the efficacy of acetylsalicylic acid alone or in combination with an antiemetic in the acute treatment of migraine (125). 11 trials (n = 2942) compared paracetamol 1000 mg alone or in combination with an antiemetic, with placebo or an active comparator. The NNT for freedom from pain after two hours was 12. The NNT of paracetamol was higher than that for other analgesics. It should therefore only be considered in the acute treatment of migraine if there are contraindications or intolerability to acetylsalicylic acid or other NSAIDs. In a smaller RCT, 1000 mg paracetamol i.v. was not superior to placebo treatment (126) and should therefore not be used for treating attacks.

According to an extensive study (n = 1021), three main subgroups of headache patients are found in self-medication (127). 48.8% of self-medication patients are of a relatively young age, most suffer from migraine and have the lowest frequency of medication overuse headache (MOH).

29.5% were older patients, mainly without migraine headaches. 21.7% of patients form a subgroup with high impairment from the headache, pain additionally in several body regions and a proportion of medication overuse headache of 73% (127). The data make it clear that results of trials in the context of self-medication cannot be directly transferred to the specific indication of migraine.

The fixed combination of 250 mg ASA, 200 or 250 mg paracetamol and 50 or 65 mg caffeine (APC) has been studied in several trials (128-131). The efficacy over placebo is also shown in a meta-analysis of the available trials (47). Seven trials with 3306 participants were included and 2147 patients were treated with APC and 1159 with placebo. For the primary efficacy outcome, freedom from pain after two hours, APC was superior to placebo (19.6% vs 9.0%, RR 2.2, 95% CI 1.4-3.3). For the co-primary efficacy outcome, pain relief after two hours, APC was also superior to placebo (54.3% vs. 31.2%, RR 1.7, 95% CI 1.6-1.9). Adverse events occurred more frequently in the APC group than in the placebo group (10.9% vs. 7.8%, RR 1.7, 95% CI 1.3-2.2). A trial conducted in Germany (128) only included patients who had already self-medicated with analgesics and were satisfied with this. A specific headache diagnosis as an inclusion criterion, such as migraine, was not applied. The trial dealt with headaches classified on the basis of the diaries and which had previously been treated satisfactorily by the patients under self-medication.
Patients who were previously treating their headaches with prescription drugs were excluded. Some trials describe a slightly increased risk of medication-overuse headache (132-141) with the use of combination analgesics.

Combination analgesics with fixed dosages aim for a higher analgesia than the individual agents. It is not clear whether oral combinations have only additive or also synergistic effects. Moore et al. analysed available trials with regard to these possible effects (142). For the treatment of acute migraine attacks, additive effects were found for sumatriptan plus naproxen. Evidence for synergistic effects of other combinations was not found.

Evidence has shown efficacy in headache relief and improvement of associated symptoms (such as sensitivity to noise and light, nausea and vomiting), as well as its greater efficacy over 400 mg ibuprofen (130) and over 50 mg sumatriptan (129). The fixed combination of 500 mg ASA, 400 mg paracetamol and 100 mg caffeine is superior to a combination of 500 mg ASA and 400 mg paracetamol and to monotherapy with 100 mg caffeine (128). Two post-hoc analyses report efficacy under the conditions presented of the fixed triple combination in patients with severe migraine attacks (143, 144), one also in patients with menstruation-associated migraine (145).
For ketoprofen, the data available is limited. No RCT is available for the 50 mg, 100 mg and 200 mg peroral formulations. For the i.m. formulation of 100 mg, only one older, very small study without placebo control is available (146), for 25 mg dexketoprofen p. o. only one open, uncontrolled trial (147). A recent RCT shows that a "dual-release" formulation with 75 or 150 mg ketoprofen, which is not available in German-speaking countries, is effective in the acute treatment of migraine (148).

Metamizole (novaminsulphone) 1000 mg orally is shown to be effective in the treatment of acute migraine attack in a placebo-controlled study (149). An i.v. formulation of 1000 mg metamizole is rated by a Cochrane review as effective in migraine and episodic tension-type headache based on few clinical trials (150). In a controlled trial, 1000 mg of phenazone was found to be effective in treating an acute migraine attack (151).

A Cochrane review of naproxen in doses of 275 mg, 500 mg or 825 mg alone or with additional antiemetic showed statistical superiority of naproxen compared with placebo. The high NNT of 11 for freedom from pain after two hours contradicts clinically significant efficacy. No RCTs are available for the over-the-counter doses of 200-250 mg naproxen, so there is no evidence of their efficacy.

An updated Cochrane review analysed the efficacy of diclofenac with and without an antiemetic in the treatment of migraine attacks (152). In recent years, new drugs (potassium salt, water solubility, drop form) with accelerated absorption have become available. For a single dose of 50 mg diclofenac potassium, an NNT of 6.2 is calculated for freedom from pain after two hours. Oral diclofenac potassium 50 mg has been proven to be effective in migraine treatment, but only a minority of patients achieve pain relief over 24 hours with a single dose, so repeated doses may be necessary.

Diclofenac potassium is approved for the treatment of the headache phase of migraine attacks with and without aura. The active substance is also available in drop form, which can favour absorption and tolerability. Efficacy is proven for oral application of 50 mg in a controlled trial (153). No RCTs have been conducted on diclofenac potassium for the doses 12.5 and 25 mg for the treatment of migraine. In two RCTs, diclofenac potassium at doses of 50 and 100 mg proved effective.

There are conflicting results for diclofenac sodium at 100 mg, with an older trial finding diclofenac sodium effective at 50 and 100 mg (154). In a more recent RCT, 100 mg diclofenac sodium was only effective in combination with 100 mg caffeine, but not as a monotherapy (155). For 75 mg diclofenac sodium as an i.m. formulation, only one open-label (156) and one blinded but not placebo-controlled trial are available (157).

There are no RCTs for the following active substances or combinations of active substances for the acute treatment of migraine: ASA + vitamin C, ASA + caffeine, aceclofenac, acemetacin, etoricoxib, ibuprofen-lysine, indometacin, meloxicam, paracetamol + caffeine, parecoxib, piroxicam, propyphenazone and tiaprofenic acid.
The efficacy of the selective COX-2 inhibitors etoricoxib and parecoxib that are currently available in German-speaking countries has not been studied in a controlled manner.

No RCTs have been conducted with these coxibs for the treatment of acute migraine attacks. For the oral soluble form of celecoxib, there is evidence of efficacy from two placebo-controlled trials (158-160). This form of celecoxib is not yet available in Germany (as of summer 2022).

## 2.5 Lasmiditan and rimegepant for treating migraine attacks (substances approved in Germany but not yet available in December 2022)

**Recommendations**

- Lasmiditan is more effective than placebo in treating acute migraine attacks.
- Lasmiditan can be used if the use of triptans is contraindicated.
- Lasmiditan acts both centrally and peripherally and does not cause vasoconstriction.
- Lasmiditan is an agonist at the 5-$HT_{1F}$ receptor and can cause central adverse effects, including drowsiness, fatigue and dizziness. Patients are not permitted to drive a vehicle or engage in any activity requiring increased alertness for up to eight hours after the administration of lasmiditan.
- Rimegepant, a CGRP receptor antagonist, is more effective in the treatment of acute migraine attacks than placebo. No comparative trials with triptans are available as yet.
- Rimegepant demonstrates good tolerability in the treatment of acute migraine attacks. Rimegepant does not cause vasoconstriction.
- Rimegepant can be used in patients for whom analgesics or triptans are not effective or are not tolerated.

**Table 5: Lasmiditan and rimegepant with proven efficacy for the treatment of acute migraine attacks**

| Active substance or combination of substances | Comment |
|---|---|
| **Lasmiditan (per os)**<br>Single dose:<br>50 mg, 100 mg, 200 mg | Standard dose 100 mg, note central adverse effects, in rare cases serotonin syndrome, bradycardia and transient increase in blood pressure. Status September 2022: approved in Germany, but not yet available |
| **Rimegepant (per os)**<br>Single dose: 75 mg | Standard dose 75 mg, contraindications: severely impaired kidney or liver function, use of strong CYP3A4 inhibitors.<br>Status September 2022: approved in Germany, but not yet available |

### 2.5.1 Lasmiditan

The vascular contraindications to triptans made it necessary to develop new migraine drugs without the vasoconstrictive properties mediated by the 5-$HT_{1B}$ receptor. One therapeutic target was the 5-$HT_{1F}$ receptor. This receptor is found in the trigeminal ganglion and the caudal trigeminal nucleus (161, 162). In preclinical models, 5-$HT_{1F}$ agonists inhibited dural plasma protein extravasation and c-Fos induction in the caudal nucleus of the trigeminal nerve after stimulation of the trigeminal ganglion (163). Lasmiditan is a high-affinity and highly selective serotonin (5-HT) 5-$HT_{1F}$ receptor agonist (164) developed for the treatment of acute migraine attacks (161).

#### 2.5.1.1 Lasmiditan: Phase III trials

For the first double-blind phase III trial, 2231 migraine patients were recruited exclusively in the USA. The safety population comprised 1856 patients (165). Patients are randomly assigned to receive a moderate or high intensity attack with lasmiditan 200 mg, lasmiditan 100 mg or placebo. The trial had no active comparator. The patients had to note which accompanying symptom of the migraine attack was the most bothersome symptom (MBS) for them. In most cases this was light sensitivity. The primary endpoint, freedom from pain at two hours, was achieved in 32.2% for lasmiditan 200 mg and in 15.3% for placebo (odds ratio 2.6, 95% CI 2.0-3.6, p <0.001). The corresponding figures for the 100 mg dose of lasmiditan were 28.2% compared with 15.3% (OR 2.2, 95% CI 1.6-3.0, p <0.001). Rapid resolution of the MBS in the migraine attack was achieved by 40.7% of patients with 200 mg lasmiditan, 40.9% with 100 mg lasmiditan and 29.5% with placebo (OR for 200 mg vs. placebo 1.6, 95% CI 1.3-2.1, p <0.001; OR for 100 mg vs. placebo 1.7, 95% CI 1.3-2.2, p <0.001).

The second phase III trial was a prospective, double-blind, multicentre trial in which patients with migraine with and without aura from the USA, UK and Germany were treated with oral lasmiditan 200 mg, 100 mg, 50 mg or placebo (166). The trial had two primary endpoints: the proportion of patients who were pain-free two hours after administration of the trial medication and free from the accompanying symptom of the attack that was most bothersome.

For the trial, 3005 patients were recruited and 2583 treated. 1938 patients received lasmiditan (200 mg, n = 528; 100 mg, n = 532; 50 mg, n = 556) and 540 placebo. The patients were 42 years old on average and 84% were female. Approximately 80% had at least one cardiovascular risk factor. The most bothersome symptom of the migraine attack at two hours was resolved in 21.3% on placebo, 38.8% on lasmiditan 200 mg (OR 2.3, 95% CI 1.8–3.1, p <0.001), 31.4% on lasmiditan 100 mg (OR 1.7, 95% CI 1.3–2.2, p <0.001) and 28.6% on 50 mg lasmiditan (OR 1.5, 95% CI 1.1–1.9, p = 0.003). The most bothersome symptom of the migraine attack at two hours was resolved in 33.5% on placebo, 48.7% on lasmiditan 200 mg (OR 1.9, 95% CI 1.4–2.4, p <0.001), 44.2% on lasmiditan 100 mg (OR 1.6, 95% CI 1.2–2.0, p <0.001) and 40.8% on 50 mg lasmiditan (OR 1.4, 95% CI 1.1–1.8, p = 0.009).

In summary, lasmiditan was shown to be effective in treating an acute migraine attack at doses between 50 mg and 200 mg in the two phase III trials (table 6). The adverse effects point to a central mechanism of action.

**Table 6: Percentage of patients who were pain-free after two hours**

| | Lasmiditan | | | Placebo |
|---|---|---|---|---|
| | 50 mg | 100 mg | 200 mg | |
| Kuca et al. (165) | | 28.2% | 32.2% | 15.3% |
| Goadsby et al. (166) | 28.6% | 31.4% | 38.8% | 21.3% |
| Ashina et al. (167) | | 25.8% | 29.3% | 8.4% |

The CENTURION trial investigated the efficacy and consistency of response to 100 or 200 mg lasmiditan in the treatment of migraine across four acute attacks compared with two control groups who received placebo in three of four attacks and 50 mg lasmiditan only in the 3rd or 4th attack (168). The primary endpoints of the study were freedom from pain after two hours (1st attack) and freedom from pain after two hours for ≥ 2/3 attacks. 1471 patients treated ≥ 1 migraine attack with lasmiditan. Both primary endpoints were met for lasmiditan 100 mg and 200 mg ($p < 0.001$). The results showed a consistent response of lasmiditan across multiple migraine attacks. In a subgroup analysis, the efficacy of lasmiditan was investigated in patients who previously had an inadequate response to triptan treatment (169). The subgroup also included patients who had shown intolerability or had a contraindication to triptans. The results regarding freedom from pain after two hours were comparable in triptan non-responders and triptan responders. It must be critically noted here that non-response to the administration of triptans was not recorded long-term. Lasmiditan was also effective for perimenstrual migraine attacks in a post-hoc analysis (170)

A meta-analysis evaluated four trials on the treatment of acute migraine attacks with lasmiditan (171). The use of lasmiditan was associated with a significantly higher percentage of patients with freedom from pain (OR 2.02; 95% CI 1.72-2.39; $p < 0.00001$), sustained freedom from pain (OR, 1.93; 95% CI, 1.55-2.39; $p < 0.00001$), a lower degree of clinical disability (OR, 1.36; 95% CI, 1.20-1.55; $p < 0.00001$), better overall patient impression (OR, 1.88; 95% CI, 1.69-2.10; $p < 0.00001$) and significantly lower use of emergency medication (OR, 0.49; 95% CI, 0.38-0.63; $p < 0.00001$) compared with placebo. The subgroup analysis showed a dose-dependent effect of lasmiditan on freedom from pain, sustained freedom from pain, overall patient impression and the occurrence of adverse drug reactions. In an analysis of 12 RCTs, the probability of achieving both freedom from pain and pain relief at two hours was higher with lasmiditan 200 mg than with rimegepant 75 mg. The adverse effects with lasmiditan are mainly dizziness, fatigue, paraesthesia, and sedation.

Nausea is the most common adverse effect of rimegepant (172).

### 2.5.1.2 Tolerability of lasmiditan

Adverse effects occur in a dose-dependent manner and indicate that lasmiditan crosses the blood-brain barrier and has a central point of action. A meta-analysis of four trials evaluated the occurrence of adverse drug reactions to lasmiditan (171). The incidence of adverse effects was compared between lasmiditan (n = 3416) and placebo (n = 3469). For dizziness as an adverse event, OR was 6.54 (95% CI, 4.24-10.07; p <0.00001), for paraesthesia OR was 4.28 (95% CI, 2.97-6.17; p <0.00001) and for fatigue OR was 5.67 (95% CI, 3.78-8.52; p <0.00001).

The most common adverse events (AEs) with lasmiditan compared to placebo in the first phase III trial were dizziness (16.3% and 12.5% vs. 3.4%), paraesthesia (7.9% and 5.7% vs. 2.1%), nausea (5.3% and 3.0% vs. 1.9%), fatigue (3.1% and 4.1% vs. 0.3%) and lethargy (2.5% and 1.9% vs. 0.3%) (165). In the second phase III trial, the same adverse effects were observed and there was some dose dependence (166).

In the CENTURION trial, 1471 patients treated 4494 migraine attacks (173). The incidences of treatment-related serious adverse events (SAEs) were: placebo, n = 2 (0.4%); lasmiditan 100 mg, n = 1 (0.2%); lasmiditan 200 mg, n = 2 (0.4%). The most common treatment-related adverse events with lasmiditan were dizziness, paresthesias, fatigue, nausea, vertigo and somnolence. Most of the adverse effects were mild or moderate. The incidence of adverse effects was highest during the first attack and decreased during subsequent attacks.

### 2.5.1.3 Cardiovascular safety of lasmiditan

From a pharmacological point of view, no effects of lasmiditan on the coronary arteries are expected (174). Both phase III trials of lasmiditan for acute migraine attacks included patients with cardiovascular risk factors. The SPARTAN trials were able to include patients with coronary artery disease, cardiac arrhythmias or poorly controlled hypertension. In the pooled analysis of both trials, 3500 patients (78.8%) had at least one cardiovascular risk factor and 1833 patients (41.3%) had two or more vascular risk factors at baseline (175). There were few cardiovascular adverse events (AEs) with lasmiditan (n = 30, 0.9%) and placebo (n = 5, 0.4%). The most commonly reported AEs were palpitations, tachycardia and elevated heart rate. Considering the mode of action of lasmiditan, vascular adverse effects would also not be expected.

### 2.5.1.4 Long-term efficacy and tolerability of lasmiditan

In the prospective, randomised, open-label GLADIATOR trial, patients who had completed either phase III trial were offered the option of continuing randomised treatment with lasmiditan 100 mg or 200 mg (176). The duration of the trial was 1 year. Patients were asked to use lasmiditan as first-line treatment for any migraine attack with at least moderate headache. Results were collected at baseline and at predefined time intervals of up to 48 hours using electronic diaries.

At the time of the published interim analysis, 1978 patients had taken at least one dose of lasmiditan. 19,058 treated migraine attacks were recorded and analysed. Adverse drug reactions occurring during treatment included dizziness (18.6%), somnolence (8.5%) and paraesthesia (6.8%). These frequencies are similar to the rates observed in the placebo-controlled trials. No serious treatment-related adverse events were observed. Across all migraine attacks treated, freedom from pain was observed after two hours in 26.9% of attacks treated with lasmiditan 100 mg and in 32.4% of attacks treated with lasmiditan 200 mg. The interim results of this open-label, long-term trial showed similar rates of freedom from pain after two hours and adverse events as in the randomised, placebo-controlled trials.

In summary, lasmiditan is effective in the treatment of acute migraine attacks. In indirect comparisons, it is effective to a similar degree as the triptans and more effective than gepants (see table 7). Lasmiditan can be used in patients for whom NSAIDs are not effective and have contraindications to triptans. The central adverse effects are limiting factors.

Lasmiditan is approved in Europe under the brand name Rayvow© but is not yet available in Germany as of December 2022. The recommended initial dose is 100 mg. Contraindications are severe liver dysfunction, pregnancy and lactation. Impaired kidney function does not count as a contraindication. Data on the efficacy and tolerability of lasmiditan in children and adolescents is not available. Lasmiditan can cause significant impairment of the ability to drive a vehicle. A placebo-controlled trial examined driving performance 90 minutes after taking lasmiditan 50 mg, 100 mg, 200 mg, alprazolam 1 mg and placebo in a randomised, double-blind, five-way cross-over trial in 90 healthy volunteers (mean age 34.9 years) (177). Driving ability was assessed using a validated threshold established in a population with a blood alcohol concentration of 0.05%. The primary endpoint was driving ability. A dose-dependent impairment of computer-assisted simulated driving ability was observed at all lasmiditan doses 90 minutes after administration. As a result, patients are advised not to engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery, for at least 8 hours after a dose of lasmiditan. Simultaneous use with other serotonergic drugs, e.g. selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) or monoamine oxidase (MAO) inhibitors, may lead to serotonin syndrome.

### 2.5.2 Treatment of migraine attacks using rimegepant

The gepants are small molecules that act as antagonists at the CGRP receptor (178). Gepants of the 1st generation were not further developed because of liver value increases (179). Rimegepant, ubrogepant and zavegepant have been and are currently being studied as 2nd generation gepants for the acute treatment of migraine. Rimegepant and ubrogepant have been approved by the FDA for the treatment of acute migraine attacks in the USA, and rimegepant has been approved in Europe.

Rimegepant is also approved for the preventive treatment of migraine. Atogepant – another gepant of the 2nd generation is currently only being studied for the preventive treatment of migraine. It is currently in the approval process in Europe.

There are several phase III trials for rimegepant. In one trial, one migraine attack in each patient with 2 to 8 migraine attacks/month was treated with either 75 mg rimegepant or placebo (180). The primary endpoints were freedom from pain and absence of the most bothersome symptom other than pain (MBS, e.g. nausea, vomiting, sensitivity to light or noise) two hours after taking the trial medication. A total of 1186 patients were randomised. In the intention-to-treat analysis, two hours after receiving the dose, 19.6% of patients treated with rimegepant and 12.0% of patients in the placebo group were pain-free ($p < 0.001$). The percentage of patients who were relieved of their most distressing symptom two hours after the dose was 37.6% in the rimegepant group and 25.2% in the placebo group. A second trial investigated the efficacy of a 75 mg rimegepant orodispersible tablet (181). The primary endpoints were again freedom from pain and freedom from MBS after two hours. A total of 1466 patients were randomised. In terms of freedom from pain (21% vs. 11%, $p < 0.0001$) and freedom from MBS (35% vs. 27%), $p = 0.0009$), rimegepant was superior to placebo. The most common adverse events in both trials were nausea (rimegepant n = 11 [2%]; placebo n = 3 [<1%]) and urinary tract infections (rimegepant n = 10 [1%]; placebo n = 4 [1%]).
Rimegepant was well tolerated. The most common adverse effects are nausea, urinary tract infections and dizziness (182). In extremely rare cases, an allergic reaction may occur. Elevated liver values have only been described in very rare cases (183). However, rimegepant should not be used in cases of severe hepatic impairment and end-stage renal failure. To date, very few patients with concomitant vascular diseases have been included in the trials (182). In a long-term trial over one year, 1040 patients with at least six monthly migraine days treated their migraine attacks with 75 mg of rimegepant as needed (184). There was a slight decrease in migraine days over one year (10.9 monthly migraine days at baseline, 8.9 monthly migraine days after one year). There was no evidence of more frequent use of rimegepant over time. To date, there is no published data on the efficacy of a second dose of rimegepant if the first dose was not effective. Data on the efficacy and tolerability in children and adolescents is not available.

### 2.5.3 Specific aspects of lasmiditan and rimegepant

The substance class of gepants and ditans was developed with the proviso that they have no vasoconstrictive properties, in order to close therapeutic gaps in the case of contraindications, insufficient effect or intolerability of triptan treatment. However, trials in populations at high cardiovascular risk were lacking and there are no direct comparative trials with triptans to date.

Currently, vascular disease is not considered a contraindication for lasmiditan. Patients with cardiovascular disease were excluded from the rimegepant trials.

However, animal data show a marked worsening of cerebral ischaemia in mice treated with gepants (185). It should be noted by way of restriction that the doses used in animal experiments significantly exceed the doses used in humans. It is further postulated that gepants do not lead to medication overuse headaches (186). To date, there are no concerns about fitness to drive after taking a gepant.

Looking at the rates for freedom-from-pain after two hours, in indirect comparisons lasmiditan was equally effective or slightly less effective than the triptans. Rimegepant was less effective (Table 7). The first generation of CGRP receptor antagonists led to a significant increase in liver enzymes in some patients, which meant that development had to be discontinued (187). Whether this could also be the case with the modern gepants will only be clarified when several tens of thousands of patients have been treated over a long period of time. However, in vitro experiments and the registry trials conducted to date show no evidence of hepatotoxicity of the new gepants (179). Pharmacovigilance data from the USA show no risk signal for liver toxicity so far.

**Table 7: Comparison of the efficacy of selected triptans, lasmiditan and rimegepant**

| Substance | Verum | Placebo | TB |
|---|---|---|---|
| | freedom from pain after two hours | freedom from pain after two hours | |
| Eletriptan 40 mg (188) | 35% | 7% | 28% |
| Sumatriptan 100 mg (189) | 32% | 11% | 22% |
| Lasmiditan 100 mg (166) | 31% | 21% | 10% |
| Rimegepant 75 mg (180) | 20% | 12% | 8% |

TB = therapeutic benefit Verum minus placebo

# 3 Special situation in treatment of acute cases

## 3.1 Treatment of migraine attacks in children and adolescents

**Recommendations**

- For short migraine attacks (<3 hours) in childhood, the headache can be treated by cooling the forehead and temples as well as by sleep.
- Migraine attacks in children were best treated with ibuprofen 10 mg/kg body weight or paracetamol 15 mg/kg body weight (bw) (second-best option). For paracetamol, attention to critical cumulative dosages was of particular importance.
- Sumatriptan nasal spray 10 mg and zolmitriptan nasal spray 5 mg are approved in Germany for the treatment of migraine attacks with triptans in adolescents over the age of 12.
- Local cooling and the possibility to retire and sleep are sufficient for the treatment of an acute migraine attack in some children and therefore represent the basic treatment.

Local cooling and the possibility to retire and sleep are sufficient for the treatment of an acute migraine attack in some children. For the treatment of migraine attacks in children, ibuprofen 10 mg/kg bw or paracetamol 15 mg/kg bw (second-best option) are recommended, from the age of 12 also acetylsalicylic acid (500 mg).
The critical cumulative dose of paracetamol is max.1 g for a body weight of 17-32 kg, and 2 g for a body weight of 33-43 kg.
If antiemetics are necessary, domperidon should be preferred to metoclopramide because of the lower risk of acute extrapyramidal movement disorders. Domperidone is only permitted for administration to children from the age of 12.

Sumatriptan 10 mg and zolmitriptan 5 mg are approved as a nasal spray for the treatment of migraine in adolescents aged 12 and over. In the trials on the use of triptans in children and adolescents, the high response rate to placebo and the short attack duration were methodological problems in demonstrating an effect of triptans in children under 12 years of age (190). There is now sufficient data to justify the use of the triptans (sumatriptan 10 or 20 mg as a nasal spray, zolmitriptan 2.5 or 5 mg as tablets, rizatriptan 5 or 10 mg as tablets and almotriptan 12.5 mg as tablets) before the age of 12 years if there is an inadequate response to acute analgesic treatment (191, 192). Studies on the combination treatment of sumatriptan and naproxen in 12- to 17-year-olds with migraine showed a slight superiority over placebo, but this was not significant (193). Ergotamine tartrate and oral triptans are not approved for use in children. Ergotamin is approved from the age of 16. If acute migraine attacks in children and adolescents cannot be treated effectively enough, therapy with subcutaneously injected sumatriptan is also possible after informed patient consent (194, 195).

Both patients and their parents should be informed about the treatment options for migraine attacks and advised to take acute medication at an early stage. In addition, counselling should be given on lifestyle factors that can exacerbate migraine and how to deal with migraine triggers. The possibility of developing a headache due to medication overuse when analgesics or triptans are taken too frequently must be pointed out (acute medications no more than three days in a row and less than 10 days per month). In the event of frequent migraine, non-medicated preventive treatment should be initiated.

## 3.2 Treatment of migraine attacks as emergencies

**Recommendations**

- Patients who call a doctor to treat their migraine attacks or go to A&E have usually used oral medication before without success. As a result, studies available in connection with emergency treatment tend to focus on parenterally administered substances.
- The following treatments can be applied: ASA i.v., triptans s.c., metoclopramide i.v. (as well as other dopamine antagonists), metamizole i.v. and, in the case of status migraenosus, steroids.

The first-line treatment is intravenous administration of 1000 mg ASA with or without metoclopramide (196). At a dose of 10-40 mg, metoclopramide administered i.v. has been shown to have an independent analgesic effect (97). If there are no contraindications, sumatriptan 6 mg can also be given subcutaneously. If the patient has already taken oral triptans for several days before treatment, however, repeated administration of a triptan, including sumatriptan s.c., is not expected to have a significant effect. At the same time, repeated use increases the risk of headache due to overuse of migraine medicines.
Triptans are significantly more effective at the onset of an attack than during the course of an attack or when administered repeatedly during an attack. Sumatriptan s.c. is slightly more effective than ASA i.v., but leads to significantly more adverse effects. With regard to the occurrence of recurrent headaches, the two substances do not differ (196). Intravenous administration of 1000 mg metamizole is significantly more effective than placebo, but may cause hypotension and allergic reactions (197, 198). It is therefore particularly suitable for use in hospitals.

Intravenous administration of 1000 mg paracetamol was not more effective than placebo in acute migraine attacks in a randomised trial (126) and should therefore not be used. There is evidence that intravenous administration of valproic acid at a dose of 300 mg or 800 mg is also effective in the treatment of acute migraine attacks (199, 200). However, valproic acid is not approved for the treatment of migraine attacks. Opioids cannot be recommended for the treatment of acute migraine attacks.

They are inferior to other medications for the treatment of acute migraine attacks (201), have numerous adverse effects, very often lead to recurrent headaches and have a high potential for dependence (156, 202-208).

According to expert consensus, the treatment of status migraenosus is a single dose of 50-100 mg prednisone or 4-8 mg dexamethasone i.v. (209). This is confirmed by a review of trials on the treatment of migraine attacks with corticosteroids (210).

## 3.3 Treatment of migraine attacks during pregnancy

**Recommendations**

- Mild migraine attacks can be treated without medication through stimulus shielding and rest.
- For nausea and vomiting, metoclopramide can be used throughout gravidity. In cases of severe nausea and ineffectiveness of metoclopramide, ondansetron can be used while applying strict diagnostic criteria.
- In pregnancy, migraine attacks in the 1st and 2nd trimesters can be treated with acetylsalicylic acid, ibuprofen or metamizole. Acetylsalicylic acid, NSAIDs and metamizole should not be used in the 3rd trimester.
- Paracetamol should only be given in pregnancy if no other options are available. It is not approved for severe attacks, and significant efficacy is not expected. Studies suggest risks for neurodevelopmental disorders, atopy and reproductive disorders in the unborn child.
- To date, there is no epidemiological evidence that triptans lead to malformations or other complications in pregnancy. The most extensive experience is available for sumatriptan. Sumatriptan (oral, nasal, s.c.) can therefore be used as the drug of choice for migraine attacks in pregnancy. Where this is ineffective and there is urgent need for treatment, other triptans can also be used.

Mild migraine attacks during pregnancy can sometimes be treated non-medically by stimulus shielding, rest, relaxation and ice packs.

Women who suffer from severe nausea and vomiting during pregnancy have a poor quality of life and an increased risk of maternal and foetal complications. For nausea and vomiting, metoclopramide can be used throughout gravidity. In cases of severe nausea and ineffectiveness of metoclopramide, ondansetron can be used while applying strict diagnostic criteria.

The first-line analgesic for the treatment of migraine attacks in the 1st and 2nd trimesters is ibuprofen, the second-choice alternative is acetylsalicylic acid (212). These substances should be avoided in the 3rd trimester.

In exceptional cases, single doses of metamizole may be acceptable during the 1st and 2nd trimesters for severe pain if no other treatment options are available (213). Use during the 3rd trimester may be associated with fetotoxic effects (restriction of renal function, constriction of the ductus arteriosus), which is why the use of metamizole in the 3rd trimester of pregnancy is contraindicated (214-216).

A large trial investigated associations between in utero exposure to five over-the-counter analgesics (paracetamol, ibuprofen, acetylsalicylic acid, diclofenac, naproxen) and adverse effects on the newborn child. Taking paracetamol in combination with other non-steroidal anti-inflammatory drugs was associated with the highest risk (217). Recent evidence suggests that intrauterine paracetamol exposure may be associated with urogenital/reproductive disorders in offspring (218, 219). Studies suggest a possible link between prenatal paracetamol exposure and an increased risk of neurodevelopmental disorders, atopy and reproductive disorders (220). Paracetamol is not approved for severe pain (off-label), and efficacy was not expected for severe migraine attacks, even in pregnancy. It should only be given in pregnancy if there is a need for treatment and no other options are available.
Pregnant women should be warned of the risks at the beginning of pregnancy. They should avoid paracetamol unless its use is urgently indicated medically. Treatment should be administered at the lowest dose for as short a time as possible and not in combination with other medicines. Pregnant women should consult a doctor and not self-medicate with paracetamol (219).

To date, there is no epidemiological evidence that triptans lead to malformations or other complications in pregnancy (221, 222). For sumatriptan, the results of several pregnancy registries are available and report no increased complication rates during pregnancy and no increased risk of malformations (222-225). The registries for naratriptan (224, 226) and rizatriptan (227) also show similar results. No unfavourable effects of triptans were observed for the further motor and emotional development of children up to 3 years of age (228). The most extensive experience is available for sumatriptan. Sumatriptan (oral, nasal, s.c.) can therefore be used as the drug of choice for severe migraine attacks in pregnancy. Where this is ineffective and there is urgent need for treatment, other triptans can also be used. Ergotamines are contraindicated in pregnancy, and this also applies to gepants and lasmiditan.

In individual cases, additional information can be found at https://www.embryotox.de/.

## 3.4 Treatment of migraine during lactation

**Recommendations**

- Whenever possible, mild migraine attacks during lactation should be treated non-medically with stimulus shielding, rest, relaxation and ice packs.
- Antiemetics such as metoclopramide or dimenhydrinate should not be taken during lactation.
- Only small amounts of the active substance and degradation products of acetylsalicylic acid and ibuprofen pass into breast milk. In the case of short-term use, interruption of lactation is not usually necessary.
- Use of sumatriptan and eletriptan is possible during lactation without the need for pumping.
- There is no clear evidence that the other triptans are safe. As an additional safety measure, it may be recommended to pump off the breast milk used to breastfeed the infant before taking the drug.

During lactation, migraines often return to their previous pattern of frequency and severity. Whenever possible, mild migraine attacks during lactation should be treated non-medically with stimulus shielding, rest, relaxation and ice packs.

Metoclopramide, dimenhydrinate and ondansetron are not recommended during lactation. The substances pass into breast milk and can cause adverse effects in the infant.

Only small amounts of the active substance and degradation products of acetylsalicylic acid and ibuprofen pass into breast milk. In the case of short-term use, interruption of lactation is not usually necessary. Interruption of breast-feeding is necessary in the event of prolonged use or intake of a higher dose. Paracetamol can be given during lactation, but it should only be used if other options are not available because of its low efficacy.

Drug exposure through lactation of the infant from triptans taken by the mother appears to be low. This suggests that the use of triptans is compatible with lactation (229). Use of sumatriptan is possible during lactation without the need for pumping. The exposure of the infant is very low at 0.5% of the maternal dose. No adverse effects on the breastfed infant have been reported so far (230). For eletriptan, a dose in breast milk after 24 hours of only 0.002% has been described, so this substance can be considered safer (231).
There is no clear controlled evidence for the other triptans. As an additional safety measure, it may be recommended to pump off the breast milk before taking the drug in order to breastfeed the infant. Breastfeeding should be interrupted 24 hours after taking the drug and that milk should be discarded (232).

Rimegepant is found only in very minimal concentrations in breast milk after oral ingestion (233). However, clinical experience of use during lactation is still lacking.

## 3.5 Treatment of menstruation-associated migraine

**Recommendation**

- The acute treatment of a migraine attack during menstruation is basically no different from the usual treatment of migraine attacks.

Menstrual migraine is by definition a migraine in which the attacks occur exclusively in the time window between two days before and three days after the onset of bleeding in at least two out of three cycles. If attacks occur independently of menstruation, this is called a menstruation-associated migraine. Menstruation-associated attacks are considered to be particularly severe and prolonged, with poorer response to acute treatment and more frequent recurrence of headache after initially successful treatment (234).

The acute treatment is basically no different from the usual treatment of migraine attacks. All triptans were shown to be superior to placebo in acute treatment. This applies in particular to the combination of sumatriptan and naproxen (235, 236). In comparative trials, within the group of triptans, frovatriptan (2.5 mg) had a lower recurrence rate than 10 mg rizatriptan and 12.5 mg almotriptan, with equally good efficacy (49, 237). Another trial showed that the combination of 10 mg rizatriptan with 4 mg dexamethasone was more effective, but also had more adverse effects than rizatriptan alone (238). Dexamethasone alone was inferior to monotherapy with rizatriptan and therefore cannot be recommended. If the response of menstrual migraine to the usual acute treatment is insufficient, the indication for general or short-term preventive treatment should be considered (see below).

## 3.6 Non-medication procedures for treating acute migraine attacks

The focus of the non-medicinal and psychological procedures is preventive treatment. However, there are also ways to use some of these procedures during an acute attack, although reports are partly anecdotal (239).

## 3.6.1 Non-medication methods for the treatment of acute attacks

### 3.6.1.1 Supraorbital stimulation, vagus nerve stimulation, TNS and acupuncture

**Recommendations**

- External transcutaneous stimulation of the trigeminal nerve in the supraorbital region (Cefaly®) is effective in treating acute migraine attacks.
- There is evidence of an effect of acupuncture in the treatment of acute migraine attacks, but the quality of the available studies does not allow any clear recommendations.

Transcutaneous supraorbital stimulation has also been studied for the treatment of acute migraine attacks. Stimulating electrodes are applied supraorbitally and stimulation is applied continuously for two hours. In a randomised trial of sham stimulation in 538 patients, 25.5% were pain-free after two hours with active stimulation compared with 18.3% with sham stimulation. Verum stimulation was also more effective for the endpoint improvement of headache after two hours (240). This method was particularly suitable for patients who do not want to take medication.

The vagus nerve can be stimulated directly in the area of the sternocleido mastoid muscle in the neck (nVNS). Due to the stimulus thresholds, the efferent autonomic fibres are activated less and the myelinated afferent sensory fibres, which have a lower stimulation threshold, are activated (241). GammaCore® (electroCore Medical, LLC, Basking Ridge, NJ, USA) offers such stimulation.

The largest randomised trial of the effect of nerve vagus stimulation on migraine attacks was the PRESTO trial. This included 248 patients who underwent nVNS or sham-nVNS bilaterally for 120 seconds each within 20 minutes. For the primary endpoint freedom from pain after 30 minutes there was a significant difference of 12.7% versus 4.2%, also after 60 minutes (21% versus 10%). In contrast, the difference after 120 minutes was not significant (30.4% to 19.7%) (242). The tolerability of nVNS stimulation was good. The only adverse reaction reported was dizziness in two patients (1%). No serious adverse events occurred. Further results of the trial were reported in two subsequent publications. It was shown that patients in the verum group needed pain medication less often and that the effect of freedom from pain and pain reduction was also observed over multiple treated attacks (243, 244).

In a retrospective case series (n = 18), bilateral stimulation over 2 x 120 seconds using GammaCore® led to an improvement in both vertigo symptoms (from 5.2 (scale 0–10) to 3.1) and headache (6 to 2.4 (scale 0–10)) (245). A reduction in spontaneous nystagmus during vestibular migraine attacks was also demonstrated in four patients by stimulation of the vagus nerve (2 x 120 seconds bilaterally) in the neck region (246). In a small trial of nine young migraine patients (aged 13-18 years), stimulation of the vagus nerve (1 x 120 seconds unilateral) for the treatment of acute migraine attacks also proved to be effective (40.4% pain relief after 60 minutes; 6.3% pain relief after 120 minutes; 46.8% with no need for emergency medication) and well tolerated (no adverse events) (247).

One of the largest trials of a neuromodulatory procedure in the treatment of migraine attacks investigated whether the application of two transcranial magnetic pulses (TMS) over the visual cortex (30 seconds apart) had an effect on pain relief after two hours in patients with migraine with aura (248). A total of 201 patients were randomised. They treated up to three attacks with TMS stimulation or sham stimulation. The proportion of patients who were pain-free after two hours was significantly higher at 39% than in the control group at 22%. Sustained freedom from pain after 24 hours was also significantly higher in the stimulation group. Device-related adverse effects were not reported.

A systematic review on the effect of non-invasive neuromodulation on acute migraine attacks concludes that both simple occipital TMS and transcutaneous stimulation of the trigeminal nerve were significantly superior to the control condition in randomised trials (249).

There are approaches in traditional Chinese medicine also to use acupuncture in the acute treatment of migraine attacks (250). For example, a trial in two German centres for Chinese medicine compared the efficacy of acupuncture with the subcutaneous injection of sumatriptan (6 mg) or saline solution (placebo) in the acute attack. Acupuncture and sumatriptan were about equivalent in preventing the development of a full-blown attack and significantly superior to placebo treatment (251). In a multicentre Chinese trial, acupuncture was shown to be superior to sham acupuncture in reducing pain and acute medication use (252). A recent paper found significant effects mainly in the first hour after acupuncture, but not afterwards in the period after one hour (253). Recent reviews (250, 254) summarise that acupuncture is an effective option also for the treatment of acute headache because it has a low side effect profile compared to medication. However, the quality of the trials was not sufficient to be able to make clear recommendations. There is limited evidence that traditional Chinese acupuncture is effective in the treatment of acute migraine attacks.

### 3.6.2 Psychological methods for the treatment of acute migraine attacks

**Recommendations**

- Vasoconstriction training (blood volume pulse biofeedback) is recommended for the treatment of an acute attack.
- A distinction must be made between acute behavioural treatment and preventive treatment.

Behavioural treatments for the treatment of acute migraine attacks have very rarely been studied. Pain management training with strategies for an acute attack, relaxation techniques and biofeedback treatment are used. Dealing with acute migraine attacks should be addressed in behavioural preventive treatment procedures. A more recent cognitive-behavioural programme (255) refers to the analysis of possible triggers of a migraine attack and addresses coping and communication strategies during the attack.

#### 3.6.2.1 Pain management training

Pain management methods aim to achieve distancing from pain during the attack through cognitive strategies (e.g. attention control in the form of imagination exercises). The individual treatment steps are practised in the pain-free interval so that they can then be applied in an acute migraine attack. No usable trial results are available for these procedures.

#### 3.6.2.2 Relaxation techniques

Relaxation methods and individual relaxation techniques play an important role in preventive treatment. They are rarely used during acute attacks. However, there are reports that some patients can counteract a slow-onset migraine attack with these techniques (239). In a recent trial, it was shown that, in the treatment of an acute attack with a neuromodulation procedures, the group that received additional guidance consisting of explanation and relaxation (PMR, diaphragmatic breathing, imagination) performed significantly better in terms of pain relief and functional improvement two hours after the start of treatment than the group that received neuromodulation alone (256).

#### 3.6.2.3 Biofeedback

Acute treatment of a migraine attack can also be effected using a special biofeedback method called vasoconstriction training (blood volume pulse biofeedback, BVP) (257). Whereas in most other biofeedback procedures in the prophylactic treatment of migraine, general relaxation is the goal to be achieved, in BVP biofeedback, sufferers learn voluntary constriction of the right or left superficial temporal artery (258). The background to this is the assumption that constricting the blood vessels during an acute attack can lead to a reduction in migraine pain.

The basis of the migraine attack is complex cerebral processes based on a genetic disposition with activation in the area of the hypothalamus (prodromal) and in the attack of trigeminal nuclei. This releases neuropeptides such as CGRP, which then trigger a cascade of vasodilation and inflammation. Today we know that the vascular reaction is associated with the pain, but is not the cause of it. BVP biofeedback training is carried out in pain-free intervals so that imaginations or cognitive strategies with which the affected person can achieve vasoconstriction are learnt. These acquired strategies are then executed during an acute attack. Nestoriuc et al. published a meta-analysis on BVP in 2008; more recent trials were not available in this regard (259). BVP biofeedback is rated as one of the most effective biofeedback procedures with a Cohen's "d" = 0.7 (0.5-0.8) (259).

Overall, it can be assumed that the procedure is not effective if there are not even slight effects after ten sessions. No conclusions can be drawn about factors such as adherence and the occurrence of possible recurrence headaches after successful coping through imagination or cognition. There is no data available in this regard. When reviewing the trials, it is important to note that influencing artery width during attacks is only one of the possible biofeedback applications. Since BVP biofeedback is also used as preventive treatment, the different forms of application must be differentiated.

# 4 Migraine prevention (Fig. 2)

## 4.1 Indication for prevention of migraine using medication and duration of migraine prevention

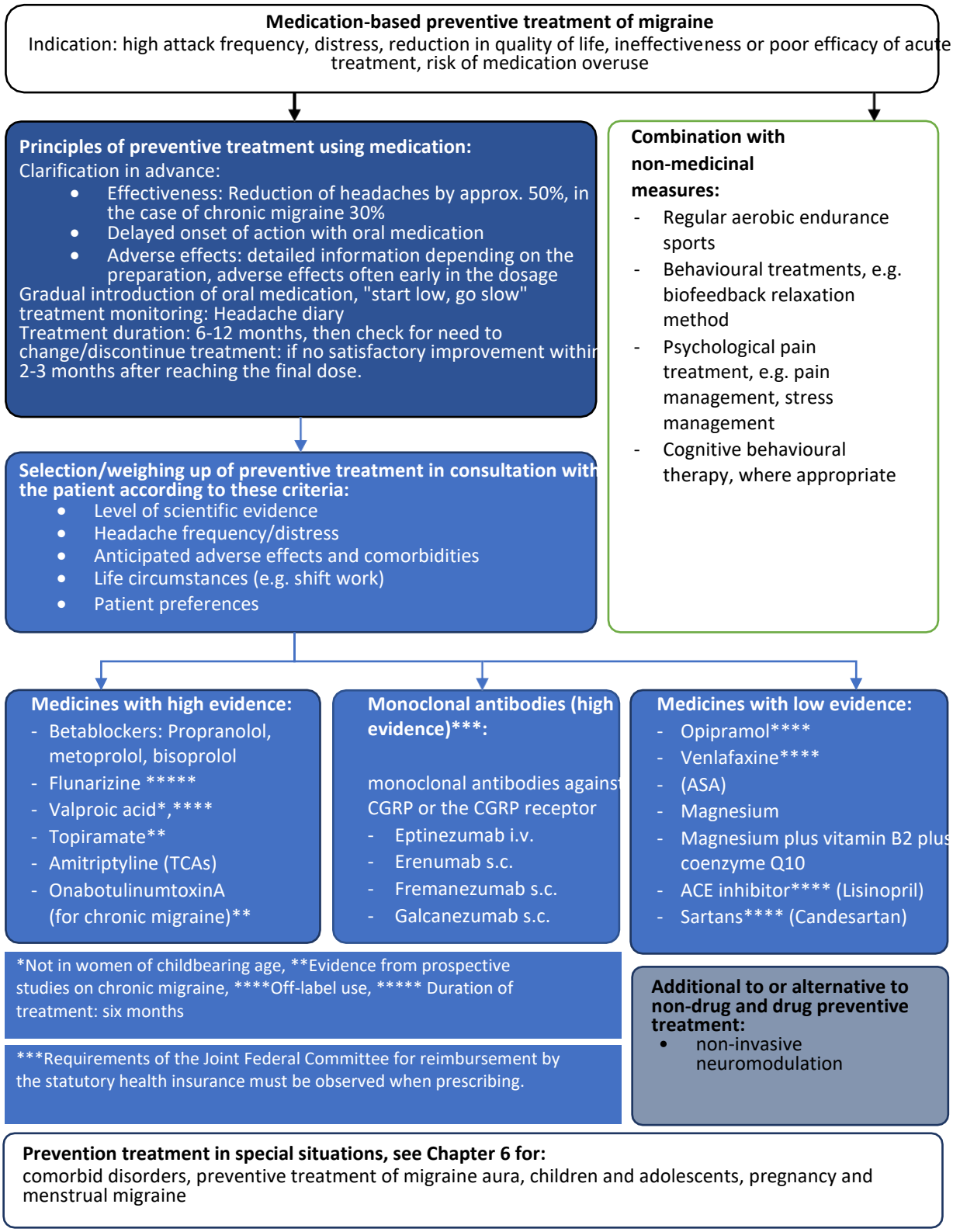
The indication for preventive treatment medication of migraine results from the particular extent of distress, restriction of the quality of life and the risk of medication overuse. Additional criteria (not evidence-based) are:

- Three or more migraine attacks per month that affect quality of life
- Migraine attacks that regularly last longer than 72 hours
- Attacks that do not respond to treatment according to the recommendations given above for acute treatment (including triptans)
- If patients cannot tolerate the adverse effects of acute treatment
- If the frequency of attacks increases and the patient is taking analgesics or migraine medicines
- In complicated migraine attacks with debilitating (e.g. hemiplegic) and/or long-lasting auras.
- After a migrainous cerebral infarction when other causes of infarction have been excluded

The purpose of preventive treatment medication is to reduce the frequency, severity and duration of migraine attacks and to prevent headaches caused by overuse of analgesics and migraine medications. Migraine preventive treatment is said to be effective when the frequency of attacks is reduced by 50% or more for episodic migraine and by 30% or more for chronic migraine. Patients should keep a headache diary to document attack frequency and the success or failure of each attack medication.

The duration of effective migraine prevention treatment depends on the severity of the migraine, comorbidities (e.g. MOH) and the substance administered. Flunarizine should not be taken for longer than six months, according to the product information. All other substance classes are usually administered for at least nine months. The indication for each prevention treatment must be reviewed throughout the treatment, at the latest after a treatment duration of 24 months.

Figure 2. Medication-based preventive treatment of migraine



## 4.2 Substances administered orally to prevent migraine (Table 8)

**Recommendations**

- The beta-blockers propranolol and metoprolol, the calcium antagonist flunarizine as well as the anticonvulsants valproic acid and topiramate and the antidepressant amitriptyline are effective in migraine prevention treatment.
- Valproic acid must not be prescribed to women of childbearing age because of its teratogenic properties.
- Valproic acid may only be used off-label.
- Betablockers bisoprolol, ACE inhibitors and sartans are also effective but less well studied.

### 4.2.1 Betablockers

Betablockers are effective in the preventive treatment of migraine. Most data is available on propranolol and metoprolol, with more than 50 trials each. Meta-analyses and reviews also confirm the preventive treatment effect of betablockers (260-262). At a dose of 160 mg, Holroyd et al. calculated an average reduction in migraine activity of 44% for propranolol (260). A meta-analysis included 108 randomised controlled trials, 50 placebo-controlled trials and 58 comparative efficacy trials. Compared with placebo, propranolol reduced headache days by 1.5 days/month in episodic migraine (95% CI: -2.3 to – 0.65). The 50% responder rate had a relative risk of 1.4 (95% CI: 1.1–1.7) (262). In a Cochrane analysis, the relative risk of responding to treatment with propranolol was reported as 1.94 (95% CI 1.61-2.35) in the placebo-controlled trials (263). Response rates tend to increase with dose, where doses of propranolol between 60 and 320 mg/d were studied. However, the criterion "response to treatment" was not defined uniformly in the trials, which explains the partially heterogeneous results. Compared to other migraine preventive treatment substances (other betablockers, calcium antagonists), no significant difference in potency was found. However, this result could also be methodological (small number of cases).

Superiority to placebo has been demonstrated for the 200 mg/d dose of metoprolol in several trials (264, 265). The potency of metoprolol was comparable to that of propranolol (263).

A double-blind controlled trial from India compared the effect of propranolol 160 mg with 100 mg topiramate in patients with chronic migraine (266). In the topiramate group, 55.9% of patients met the criteria and also the criteria for medication-overuse headache, compared with 47.6% in the propranolol group. Recruitment had to be terminated prematurely due to the COVID-19 pandemic, so the trial was hampered somewhat.

93 patients received topiramate and 82 propranolol. The primary endpoint was the mean change in migraine days over each 28-day period from baseline, compared with weeks 25-28 on treatment. The number of migraine days decreased by 2.9 ± 0.7 days with topiramate and by 4.6 ± 0.8 days with propranolol. The difference was not statistically significant. The secondary endpoints also did not differ significantly between the two treatment groups.
Adverse effects were reported in the topiramate group by 32 of the 93 patients and in the propranolol group by 30 of the 82 patients. Concomitant medication overuse had no influence on the results. Statistically, propranolol was neither inferior nor superior to topiramate. This was the only trial that has explicitly investigated the migraine preventive treatment effect for chronic migraine with and without medication overuse. The evidence for the preventive treatment effect of other betablockers is less well established. Bisoprolol was significantly superior to placebo in one trial and equally effective to metoprolol in another (267-269). Positive trials are also available for timolol (270-272), atenolol (273-275) and nebivolol (276). However, these trials are older and of lower quality, which means that these betablockers can only be considered as alternative drugs. Acebutolol (277), alprenolol (278), oxprenolol (279) and pindolol (280) (211) are not effective in preventing migraine.

### 4.2.2 Flunarizine and other calcium channel blockers

Flunarizine was the only calcium channel blocker that has been shown to have a significant effect in migraine preventive treatment (262, 281-291). The potency of flunarizine does not differ from that of metoprolol, but adverse effects (depression, weight gain) were more common when taking flunarizine (291). Flunarizine is a calcium antagonist from the class of calcium overload blockers. Other, "pure" calcium channel blockers such as nifedipine (292) and nimodipine (293) were not effective in migraine preventive treatment. Verapamil has only been studied in very small trials and is probably not effective either.

The recommended dose of flunarizine is 10 mg at night. However, 5 mg is just as effective. As a result, to reduce adverse effects, the dose should be reduced to every 2nd day. Only the 5 mg dose should be used in patients over 65 years of age. After six months, a break in treatment should be taken. Flunarizine has also been adequately studied in children (294). For children, the dose is 5 mg a day or every 2nd day. However, there is no approval for use in children.

Flunarizine was shown to be as effective as topiramate in reducing non-headache migraine symptoms, possibly due to effects on the dopamine/prolactin system (295).

A meta-analysis (25 trials) examined the evidence for the efficacy, tolerability and safety of flunarizine. This showed that flunarizine reduced headache frequency by 0.4 attacks per 4 weeks compared to placebo (5 trials, 249 participants: mean difference – 0.44; 95% CI -0.61 to -0.26). The analysis also showed that the efficacy of flunarizine preventive treatment was comparable to that of propranolol (7 trials, 1151 participants, mean difference-0.08; 95% CI -0.34 to 0.18) (296).

Population-based trials of flunarizine-induced parkinsonism in Taiwan with 6470 migraine patients show an incidence rate of parkinsonism in the control group without flunarizine exposure of 1.92 and in the flunarizine-treated group 8.72 per 1000 person-years (hazard ratio 4.07; 95% CI: 2.84–5.85). In 45- to 64-year-old and ≥ 65-year-old subjects, the risk of flunarizine-induced parkinsonism was 3.18-fold (95% CI = 1.63-6.20) and 4.89-fold (95% CI = 3.09-7.72) higher, respectively, than in controls (297). Overall, the risk can thus be classified as low, but flunarizine should not be used in patients with Parkinson's disease or familial Parkinson's syndromes. If extrapyramidal motor symptoms occur, the treatment should be stopped. Only the 5 mg dose should be used in patients over 65 years of age. Flunarizine should not be used in people with pre-existing depression or a history of recurrent depression.

As treatment with flunarizine is often accompanied by tiredness, flunarizine is taken in the evening. Treatment can be started with 5 mg in the evening and increased to 10 mg in the evening if it is effective. The long half-life of flunarizine must be taken into account, which is why the treatment can also be adjusted to every 2nd day. This switch should be effected after 4-8 weeks if there is a response to treatment. After half a year, the further indication for treatment should be checked by a discontinuation test; if the migraine increases again, the treatment can be restarted.

**Table 8: Substances for migraine preventive treatment with high/good scientific evidence**

| Active substance | Dosage | Adverse effects (selection) | Contraindications (selection) |
|---|---|---|---|
| Propranolol | 40–240 mg | H: Fatigue, arterial hypotension<br>G: Sleep disorders, dizziness<br>S: Hypoglycaemia, bronchospasm, bradycardia, gastrointestinal complaints, erectile dysfunction | A: AV block, bradycardia, heart failure, sick sinus syndrome, bronchial asthma<br>R: Diabetes mellitus, orthostatic dysregulation, depression |
| Bisoprolol* | 5–10 mg | | |
| Metoprolol | 50–200 mg | | |
| Flunarizine ** | 5–10 mg | H: Fatigue, weight gain<br>G: Gastrointestinal complaints, depression<br>S: Hyperkineses, tremor, parkinsonoid | A: Focal dystonia, pregnancy, lactation, depression<br>R: M. Parkinson's in the family |
| Topiramate | 25–100 mg | H: Fatigue, cognitive disorders, weight loss, paresthesias<br>G: Taste changes, psychoses, kidney stones, depression<br>S: Narrow-angle glaucoma | A: Renal insufficiency, kidney stones, narrow-angle glaucoma<br>R: Depression, anxiety disorder, low body weight, anorexia |
| Valproic acid* | 500–1000 mg | H: Fatigue, dizziness, tremor<br>G: Skin rash; hair loss, weight gain<br>S: Liver dysfunction | A: Liver dysfunction, pregnancy (neural tube defects), women of childbearing age, alcohol abuse. |
| OnabotulinumtoxinA in chronic migraine | 155–195 U i.m. | G: Muscle soreness, cosmetic undesirable effects, neck muscle weakness. | A: Myasthenia gravis<br>R: Anticoagulation |
| Amitriptyline | 50–75 mg | H: Fatigue, dry mouth, dizziness, weight gain | A: Heart failure, glaucoma, prostatic hypertrophy, adenoma |

Adverse effects divided into these categories: H: Frequent; G: Occasional; S: Rare; contraindications divided into: A: Absolute, R: Relative, *off-label, **for flunarizine treatment pause after six months

### 4.2.3 Anticonvulsants

**Recommendations**

- Topiramate is effective in preventing migraines.
- Topiramate is also effective for the preventive treatment of chronic migraine and MOH.
- Valproic acid has also been shown to be effective in trials. However, the substance has not been approved for this indication and no pharmaceutical manufacturer of a valproic acid drug has agreed to off-label use. According to the G-BA decision, there is an off-label indication for migraine preventive treatment in adults aged 18 years and older, except for patients of childbearing age, if treatment with other medicinal products authorised for this purpose has not been successful, or is contraindicated.

The effect of topiramate in migraine preventive treatment has been proven by numerous randomised trials (298-300). In a meta-analysis of six randomised, placebo-controlled trials, the 50% response rate ratio was 2.67 (50% CI 1.94-3.66) for the comparison of topiramate with placebo (301). According to the expert information, topiramate should be used for the preventive treatment of migraine headaches in adults after careful consideration of possible alternative treatment methods. The dosage of topiramate should be slowly phased in at 2 × 12.5 or 2 × 25 mg. The target dose should be 2 × 50 mg (if necessary, up to 2 × 100 mg) per day. There is a dose-response relationship regarding efficacy and weight loss (302). Limiting factors in the use of topiramate are above all cognitive adverse effects, which occur almost exclusively in the titration phase (303), but also depressive moods.

The HER-MES trial prospectively investigated the tolerability and effect of topiramate compared to erenumab using a double-blind, placebo-controlled, double-dummy design. A total of 777 patients were randomised. With a very rigid up-dosing regimen for topiramate up to a daily dose of 50-100 mg/day, erenumab at the 70- or 140-mg dose proved to be more tolerable (discontinuation due to adverse effects in 38.9% of the topiramate group vs. 10.6% in the erenumab group) and more effective. The proportion of patients who experienced at least a 50% reduction in migraine headache days was 55.4% in the erenumab group vs. 31.2% in the topiramate group (304).

There was also evidence from smaller trials and subgroup analyses for efficacy in medication overuse and in chronic migraine (300, 305, 306). The TOP-PRO trial was a double-blind, randomised comparison of the efficacy of 100 mg topiramate with 160 mg propranolol in CM. However, due to the COVID-19 pandemic, fewer patients were randomised than planned. On average, migraine days decreased by 5.3 ± 1.2 days in the topiramate group (n = 46) and by 7.3 ± 1.1 days in the propranolol group (n = 49) after the 24-week treatment period compared with baseline (p = 0.226). The effects of the two substances were comparable. In a phase IV open-label trial, headache discomfort, productivity limitations and depression were assessed by means of questionnaires.

Both groups improved, with patients treated with topiramate performing significantly worse. Compared to baseline, at week 30, the HIT-6 score improved by 5.6 vs. 1.3 points, the PHQ-9 (9-item Patient Health Questionnaire Quick Depression Assessment) score improved by 2.1 vs. 0.5 points and the FIMQ (Functional Impact of Migraine Questionnaire) score improved by 16.5 vs. 5.1 points (307). In combination with nortriptyline, topiramate was effective in patients who did not respond to monotherapy (308).

Valproic acid has been shown in several trials to significantly reduce the frequency, but not the intensity, of migraine attacks (309, 310). In a meta-analysis of 7 placebo-controlled trials with 782 participants and 7 controlled trials against active comparators with 554 participants, active treatment with valproate medication was significantly superior to placebo for the 50% response rate (odds ratio, 4.02; 95% CI 2.17- 7.44; I2 = 66%) (311).

However, valproic acid is not approved for the preventive treatment of migraine. According to the G-BA decision of 18.8.22, the off-label use of valproic acid in adults was determined as follows: migraine preventive treatment in adults aged 18 years and older, except for patients of childbearing age, if treatment with other medicinal products authorised for this purpose has not been successful, or is contraindicated. Prescription and supervision of treatment may only be carried out by specialists in neurology and/or psychiatry or in psychiatry and psychotherapy."

Lamotrigine (312) and levetiracetam (313, 314) have been shown to reduce the frequency of migraine attacks in patients with migraine in small non-placebo-controlled trials. Lamotrigine is effective in reducing the frequency of migraine attacks in patients with migraine with but not without aura (315). In a comparative trial, zonisamide showed similar efficacy to topiramate (316).

### 4.2.4 Antidepressants

**Recommendations**

- Amitriptyline is effective in preventing migraines
- SSRIs are not effective in preventing migraines.

Amitriptyline was only proven in migraine preventive treatment in older trials of methodologically lower standard (317-323). However, a meta-analysis from 2015 proves the efficacy (302). In a 2017 meta-analysis, amitriptyline also showed a significant decrease in headache frequency and a significantly higher 50% response rate in a pairwise comparison with placebo recent comparative trial, 25 mg amitriptyline and 3 mg melatonin were equally effective in reducing monthly migraine days after 3 months of treatment for episodic migraine (327).
(324). Amitriptyline has comparable efficacy to topiramate (325). Amitriptyline was also effective in treating chronic migraine according to the post-hoc evaluation of an older trial (326). In a

The best effect was found after taking it for 4 months, so it was crucial that the drug was used for a sufficient period of time. Amitriptyline should preferably be given as preventive treatment when combined with tension-type headache, chronic neuropathic pain or chronic back pain, or if – as was often the case with chronic pain – there was additional depression. Opiramol (50-150 mg) has shown efficacy in an older trial (328). Venlafaxine is a serotonin and noradrenaline reuptake inhibitor for which two small controlled positive trials are available (329, 330). In a non-inferiority trial, 25 mg amitriptyline and 37.5 mg venlafaxine per day for eight weeks reduced the number of migraine attacks comparably (331). Opipramol and venlafaxine are not approved for migraine preventive treatment in Germany.

### 4.2.5 Medicines for migraine preventive treatment with lower evidence

**Recommendations**

- Acetylsalicylic acid has a low efficacy for migraine preventive treatment.
- Dietary supplements with efficacy in migraine preventive treatment include magnesium, butterbur, riboflavin and coenzyme Q10. However, the scientific evidence is limited.
- Gabapentin and levetiracetam have low efficacy.
- Some sartans and ACE inhibitors have a migraine preventive effect. They are especially suitable in patients with arterial hypertension.

#### 4.2.5.1 Analgetic agents

In principle, the use of analgesics for preventive treatment contradicts the concept of medication-overuse headache, as every day of analgesic preventive treatment taken would have to be counted formally as a day taken. The trials on analgesics were all of slightly shorter duration, so this problem cannot be reflected in the trial data. Consequently, this substance class plays a very minor role in everyday clinical practice and was at best suitable for short-term preventive treatment. However, since there is a certain amount of evidence available, it will nevertheless be discussed here. Overall, the evidence base is only moderate. In special situations such as menstrual migraine, the use of e.g. naproxen in short-term preventive treatment is justified, see separate chapter in the guideline.

**Acetylsalicylic acid**

Acetylsalicylic acid (ASA) at a low dose of 100-300 mg/d probably has a small migraine preventive effect.

A phase III, multinational, multicentre, double-blind, active-controlled trial evaluated the efficacy and safety of 300 mg acetylsalicylic acid (n = 135) compared with 200 mg metoprolol (n = 135) in preventing migraine (with 2-6 attacks per month) (332). A total of 270 patients aged 18 to 65 years were included. The primary endpoint was equivalence of efficacy, defined as 50% response. A 4-week placebo phase was followed by a 16-week verum phase. In both treatment groups, attack frequency improved during the trial period. There was a reduction from 3 to 2 attacks in the ASA group and a reduction from 3 to 1 in the metoprolol group. 45.2% of all metoprolol patients were responders compared to 29.6% on ASA. Drug-related adverse events occurred less frequently in the ASA group (37) than in the metoprolol group (73). The results of this trial show that metoprolol was superior to ASA in migraine preventive treatment. The ASA responder rate in this trial was comparable to the placebo rate of other trials.

In an older and very small double-blind cross-over trial, 28 patients aged 31 ± 14 years were treated with acetylsalicylic acid for three months and metoprolol for a further three months after an eight-week baseline phase (333). Attack frequency was significantly reduced with both treatment regimens. A 50% response was observed with metoprolol in 14 cases and with ASA in only three cases.

ASA use (325 mg every other day) was also studied in the randomised, double-blind, placebo-controlled Physicians' Health Study (334) conducted in the USA. Among other things, the occurrence of migraine attacks was queried in annual follow-up questionnaires. Of those randomised to receive ASA, 6.0% reported migraine, while 7.4% of participants in the placebo group reported the occurrence of migraine. The difference is significant. Overall, however, the chosen endpoint was unusual and no longer sufficient from today's viewpoint.

An evaluation of the randomised Women's Health Study with use of low-dose aspirin and vitamin E in 39,876 female healthcare professionals aged >45 years, women with frequent migraine attacks were given either 100 mg aspirin every other day (n = 525) or placebo (n = 476) (335). Frequency of attacks, like the other endpoints, was assessed by means of questionnaires at 12 months and 36 months after randomisation and by means of monthly diaries. Women who received aspirin reported a reduction in migraine frequency (59.6% vs. placebo 56.4%,) after 36 months. This reduction, as well as the severity of the migraine attacks, the duration of the attacks and the migraine-related incapacity to work were not statistically significantly different.

#### Nonsteroidal anti-inflammatory drugs (NSAIDs)

The data for NSAIDs covers a somewhat broader range. There are at least 23 controlled trials on 10 different NSAIDs. However, the concerns about MOH were similar. Overall, a small but significant benefit was shown for naproxen. Similar trends were seen for flurbiprofen, ketoprofen and mefenamic acid. The studies are mostly old. The endpoints and data quality do not meet today's requirements. Some trials are listed below as examples.

In a very early trial, naproxen sodium was investigated in a double-blind, placebo-controlled cross-over trial in 34 patients for migraine preventive treatment. Preference for the drug and therapeutic effect were assessed by both patients and investigators. An endpoint that does not do justice to today's conditions. In the trial, both groups preferred the drug to placebo. An index of migraine activity was calculated from the patients' daily records, which showed a significant reduction in headache severity, duration, disability and medication needed.

A 20-week, placebo-controlled, double-blind cross-over trial investigated a dose of 100 mg flurbiprofen two times daily versus placebo for eight weeks each (336). The substance significantly reduced migraine intensity ($p < .05$), the total number of hours with migraine ($p < .015$) and the frequency of taking other analgesics ($p < .015$). The reduction in migraine frequency did not reach statistical significance ($p < .10$).

### 4.2.5.2 Other substances

#### Magnesium

Magnesium is used relatively frequently because of its minimal adverse effects and some people’s reluctance to take a "real" drug as preventive treatment.

At a dose of 10 mmol 2 x daily, no efficacy was shown in multicentre, prospective, randomised, double-blind, placebo-controlled trials (337). 35 patients had received magnesium and 34 placebo. The number of responders was 10 in each group (28.6% on magnesium and 29.4% on placebo).

In a slightly larger trial, 81 patients were studied for 12 weeks after a 4-week baseline phase and treated with either 1 x 600 mg (24 mmol) magnesium trimagnesium citrate or placebo (338). In weeks 9-12, attack frequency decreased by 41.6% in the magnesium group and by only 15.8% in the placebo group ($p < 0.05$). The number of days with acute medication also decreased significantly in the magnesium group. Adverse events were diarrhoea (18.6%) and stomach irritation (4.7%).

A monocentre, randomised, controlled, cross-over trial investigated the efficacy of magnesium oxide compared to valproate (339). Magnesium oxide 500 mg and 2 x 400 mg valproate were compared for 8 weeks each. The final phase of the eight weeks was compared with the baseline. It was possible to analyse 63 patients. This trial has some weaknesses and is accordingly of limited informative value. The authors concluded that 500 mg of magnesium oxide appeared to be similarly effective to valproate in migraine preventive treatment and without significant adverse effects.

In a second comparative trial of the substances, 82 patients were randomised to a valproate group, 70 to a magnesium-plus-valproate group and 70 to a magnesium group (340). Baseline was followed by three months of treatment. There was a significant reduction in all studied migraine parameters for all groups compared to baseline. In direct comparison to the other groups, the magnesium group was shown to be inferior to both other groups in terms of headache days. Quality of life parameters (MIDAS and HIT-6) showed significant improvement in all groups compared to baseline. Again, in a direct comparison, the magnesium group performed significantly worse than the other two trial arms. However, this does not demonstrate ineffectiveness because no placebo arm was included.

Overall, the trial data was not completely conclusive and the reduction in attack frequency by magnesium was not very pronounced. However, the acceptance and tolerability of the treatment were very good in everyday clinical practice. However, higher dosages were not always possible due to diarrhoea. All in all, magnesium is suitable for patients who do not want a treatment with a drug approved for this purpose.

#### Butterbur extract

Butterbur extract (Petadolex) has proven its efficacy in two placebo-controlled trials.

In a secondary analysis of a randomised, placebo-controlled, small parallel-group trial on the efficacy and tolerability of a special butterbur extract (Petadolex) for migraine preventive treatment, after a 4-week baseline phase, patients were treated either with two capsules of butterbur (25 mg) twice daily (33 patients) or with placebo (27) (341). The attack frequency/month decreased within 3 months in the butterbur group from 3.4 to 1.8 ($p = 0.0024$) and in the placebo group from 2.9 to 2.6 (n.s.). The responder rate was 45% in the verum group and 15% in the placebo group.

There was also evidence for the higher dosage. In a slightly larger (n = 245), three-arm randomised trial, 75-mg butterbur extract 2 x daily was compared with 50 mg 2 x daily and placebo (342). The primary endpoint was defined as the percentage reduction in migraine attacks/month after four months. There was a 48% reduction for the 2 x 75 mg dose and a 36% reduction for the 2 x 50 mg dose. Only the higher dose was superior to placebo (minus 26%). The 50% response rate of 68% in 2 x 75 mg was also superior to placebo (49%, $p < 0.05$).

In extremely rare cases, serious liver dysfunction has occurred in the past. The substance butterbur extract is no longer available as a medicinal product in Germany and Austria.

### Other substances

Feverfew as CO2 extract was also effective in two trials (343-345). Feverfew is not distributed in this form in Germany. The use of other forms of feverfew has not been studied and cannot be recommended.

Two prospective, open-label trials and two smaller randomised, double-blind trials investigated the efficacy of memantine (346-348). The double-blind trials examined a dosage of 5-10 mg/day and were able to show a reduction of 3.6 and 5.07 migraine days/month, respectively (349).

Three monocentric trials (all from the same centre) report the efficacy of subcutaneous histamine for migraine prevention (350-352). According to these authors, the injection of N-alpha-methylhistamine (1-10 ng 2 times/week) reduces the frequency of migraine attacks compared to placebo. Headache frequency decreased from 3.8 to 0.5 in the histamine group after 4 weeks, while it only decreased from 3.6 to 2.9 attacks in the placebo group ($p < 0.0001$). Itching at the injection sites was the only reported and significant adverse effect.

Of the dopamine agonists, alpha-dihydroergocryptine may be effective (353).

Only small placebo-controlled trials were available on high-dose vitamin B2 (daily dose 2 × 200 mg), which suggest that this substance was effective. Both trials were published by the same group of authors (354, 355). In addition, there was some evidence from open trials and trials with children. An intense yellowing of the urine was described as a side effect; beyond this, there were no serious adverse effects or contraindications.

The efficacy of coenzyme Q10 (daily dose 3 × 100 mg) has previously been positively tested in a small bicentre placebo-controlled trial (356). There was a reduction in attack frequency that was significantly more effective than placebo up to 4 months after treatment. The 50% response was 47.6% for CoQ10 versus 14.3% for placebo ($p = 0.02$).

In contrast, no superiority of coenzyme Q10 over placebo could be shown in a double-blind, placebo-controlled trial in children and adolescents (357). In Germany, coenzyme Q10 was available as a dietary food in combination with magnesium and vitamin B2 as well as in combination with omega-3 fatty acids and other berry extracts and vitamins. The combination reduced the severity of migraine attacks compared to placebo, but not the frequency (358). Migraine days per month decreased from 6.2 to 4.4 days in the verum group and from 6.2 to 5.2 days in the placebo group ($p = 0.23$). The HIT-6 decreased by 4.8 points compared to 2 points in the placebo group ($p = 0.01$).

The results for gabapentin were mixed to contradictory (359, 360). Various double-blind trials investigated 1200-3000 mg/day. An early trial showed a reduction in migraine frequency (38.4% vs. 13% placebo) and intensity. A second trial showed a 50% response in monthly migraine frequency ($P = 0.006$) and a decrease in average migraine days ($p = 0.008$) in 46.4% of patients. The largest study with a total of 523 patients, who were, however, distributed over several study arms, found no statistically significant difference between active treatment and placebo with regard to the reduction of migraine headache days (361).

A more recent open-label trial investigated the use of levetiracetam in the preventive treatment of episodic migraine in 50 patients (362). The data suggest that levetiracetam has some potential for the preventive treatment of episodic migraine. However, the quality of evidence was low.

#### 4.2.5.3 ACE inhibitors and angiotensin receptor blockers (sartans)

In the context of migraine preventive treatment, the mechanism of action of sartans and ACE inhibitors is not yet understood. Preclinical trials suggest that the renin-angiotensin system in the brain plays a role in the transmission of nociceptive signals, neurogenic inflammation, endothelial dysfunction and oxidative stress (363). Overall, however, dose-response trials and larger efficacy trials are lacking.

##### ACE inhibitors

To date, 3 ACE inhibitors have been studied in double-blind randomised trials and each has been compared with placebo. Lisinopril (2 x 10 mg) was studied in a double-blind, placebo-controlled cross-over trial in 60 patients aged 19-59 years with migraine with two to six attacks per month for 12 weeks (364). There was a reduction in hours and days with headaches, migraine days and the headache severity index. ITT analysis confirmed the differences in favour of lisinopril. Enalapril showed a 50% response superior to placebo and reduced headache severity and duration (365). This was compared in a randomised, double-blind, placebo-controlled Iranian trial of 10 mg enalapril vs. placebo in 40 migraine patients over a two-month period.
An older captopril trial with a total of 26 participants showed a reduction in the migraine index (number of attacks*duration*severity). In this randomised double-blind trial, treatment was 25 mg captopril (three times daily) or placebo for four months (366).
The trials consistently reported cough as a side effect. With lisinopril, significantly more patients in the verum arm reported dizziness as a side effect.

##### Angiotensin (AT) blockers

A small placebo-controlled cross-over trial of 60 patients suffering from 2-6 migraine attacks monthly investigated candesartan (367). After a 4-week placebo phase, they were randomised to receive either 16 mg candesartan or placebo once daily for three months, followed in each case by the other medication. The primary endpoint was the number of headache days. During the 12 weeks of treatment, the patients suffered from pain on 18.5 days with placebo and on 13.6 days with verum. Candesartan also performed better in terms of migraine and headache duration, pain severity and disability, but did not have a favourable effect on quality of life. In a second trial, candesartan was compared with propranolol and placebo in terms of efficacy and adverse effects (368). The main endpoint was the number of days with moderate or severe headaches that lasted at least four hours or had to be treated by taking the usual medicines. Secondary trial parameters were the number of headache days, the duration of headaches in hours, their intensity, the dosage of analgesics and triptans, the number of days missed due to illness and finally the number of responders – defined as patients who at least halved the number of migraine days compared to baseline.

For the primary endpoint, candesartan and propranolol were almost equally effective and both better than placebo. The baseline average of 4.82 migraine days in four weeks decreased to 2.95 with candesartan and 2.91 with propranolol (placebo 3.53). The two drugs were also clearly superior to the placebo in most secondary outcomes, with the exception of days with headache for propranolol, number of analgesic doses for candesartan and days missed from work, which neither drug was able to significantly reduce.

The second angiotensin receptor blocker studied was telmisartan (369). Here, 80 mg was randomised and double-blinded against placebo in 95 migraine patients with three to seven migraine attacks in three months. The primary endpoint was the reduction in the number of migraine days in the last four weeks of the 12-week treatment period compared with the four-week baseline. The reduction was 1.65 for telmisartan and 1.14 for placebo. Corrected post-hoc analyses showed a 38% reduction in migraine days with telmisartan vs. 15% with placebo ($p = 0.03$) and a borderline significant difference in 50% responders (40% vs. 25%, $p = 0.07$). The frequency of adverse events was similar for both treatments.

## 4.3 Monoclonal antibodies against CGRP or the CGRP receptor to prevent episodic migraine

**Recommendations**

- The monoclonal antibodies against CGRP (eptinezumab, fremanezumab and galcanezumab) or against the CGRP receptor (erenumab) are superior to treatment with placebo in the prevention of episodic migraine.
- The at least 50% responder rate ranges from 30% to 62% after 3-6 months. The at least 50% responder rate for placebo ranges from 17% to 38%.
- The efficacy of monoclonal antibodies can be evaluated within 4–12 weeks. In chronic migraine, a delayed response may occur, so that a response can still be observed after 5-6 months. According to the approval, treatment success is to be reviewed after 3 months (for eptinezumab after six months).
- A direct comparison of the monoclonal antibodies with each other is not possible due to the data currently available.
- Erenumab is discontinued less frequently due to adverse reactions compared to topiramate.
- Erenumab was better tolerated and more effective than topiramate in a direct comparison. Comparative studies with other migraine prevention treatments to date are not available.
- The efficacy of the monoclonal antibodies has also been demonstrated for patients with headaches associated with overuse of analgesics or migraine medications (MOH).
- All monoclonal antibodies are approved for migraine prevention treatment in adults experiencing at least four migraine days per month.
- With regard to reimbursement by the SHI, the G-BA determined a considerable added benefit for fremanezumab and galcanezumab for adult patients only if they do not respond to, were not suitable for, or cannot tolerate any of the above-mentioned drug treatments with the active class substances metoprolol, propranolol, flunarizine, topiramate, amitriptyline (and, in the case of chronic migraine, onabotulinumtoxinA). For both products, a national special case in practice was also agreed for this population, meaning that prescriptions do not weigh heavily on budgets. For erenumab, the G-BA determined a considerable additional benefit compared to migraine preventive treatment with topiramate on the basis of the submitted benefit dossier, based on the results of the HER-MES trial. Reimbursement by the state health system is thus possible for erenumab without prior treatments. This regulation applies retroactively from 1.4.2022. A budget-neutral prescription within the framework of a nationwide special case in practice is only granted if at least one previous therapy (metoprolol, propranolol, flunarizine, topiramate, amitriptyline or onabotulinumtoxinA) was not effective or was not tolerated or if there are contraindications to all of the above-mentioned active substances.

- For episodic migraine, treatment success is defined as a reduction in average monthly migraine days of 50% or more compared to pre-treatment over a period of at least three months. In chronic migraine, a reduction in migraine days of 30% or more is considered a therapeutic success. Documentation using an analogue or digital headache calendar is recommended.
- Alternative clinically acceptable criteria include significant improvements in validated, migraine-specific, patient-reported outcome measurements such as a 30% reduction in MIDAS score for those with baseline scores above 20 or a reduction in the score on the 6-item Headache Impact Test (HIT-6) of at least 5 points.
- If there is no response to one monoclonal antibody, a switch to another monoclonal antibody may be considered. Here, the differences in the amounts reimbursed with regard to previous treatments must be taken into account.
- Monoclonal antibodies against CGRP or the CGRP receptor should not be administered to pregnant women and during lactation. They should not be used in women who are not using contraception or not using adequate contraception.
- Furthermore, monoclonal antibodies should be used with caution in patients with coronary heart disease, ischaemic insult, subarachnoid haemorrhage or peripheral arterial occlusive disease as well as inflammatory bowel disease, COPD, pulmonary hypertension, Raynaud's disease, wound healing disorders and after organ transplants until appropriate safety data are available. For children and adolescents, there is as yet insufficient information on tolerability and safety. None of the antibodies has yet been approved for use in children and adolescents.

Until the approval of monoclonal antibodies against CGRP or the CGRP receptor (mAbs), the beta-receptor blockers propranolol, metoprolol and bisoprolol, the calcium antagonist flunarizine, the anticonvulsants valproic acid and topiramate, and the tricyclic antidepressant amitriptyline were available for migraine preventive treatment with a high level of evidence (370). OnabotulinumtoxinA was also effective in chronic migraine. The drugs used so far for migraine preventive treatment have a comparable effect. According to the current recommendations of the International Headache Society, the target criterion was the 50% responder rate (371). This describes the percentage of migraine patients who usually experience a reduction in migraine days/month of ≥ 50% from baseline after three months of treatment.

The migraine preventive treatments available so far are effective for many patients. However, one problem with most migraine preventive treatments to date is adverse drug reactions. This explains why adherence and persistence are low (372). Initial analyses of health insurance data suggest that treatment adherence is significantly higher with the use of monoclonal antibodies against CGRP or the CGRP receptor compared to classical preventive treatments. Thus, adherence was 56.5% higher in the CGRP antibody group than in the conventional preventive treatment group, and persistence was 61.1% higher (373).

### 4.3.1 Calcitonin gene-related peptide (CGRP) and migraine

In 1990, Goadsby and Edvinsson identified the important role of CGRP in the pathophysiology of migraine (374, 375). They systematically examined neuropeptides in blood samples from the jugular vein during acute migraine attacks. They found that CGRP was released during migraine attacks and that CGRP levels decreased when the attack was successfully treated with sumatriptan. The release of CGRP was inhibited by the activation of 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors. These receptors are targeted by the triptans as part of attack treatment. Interventions in the CGRP circuit are effective against migraine attacks, as shown, among others, in a trial by Olesen and Diener, in which a CGRP antagonist ended migraine attacks significantly more often than placebo (376).

Four monoclonal antibodies – eptinezumab, erenumab, fremanezumab and galcanezumab – have undergone extensive clinical trials in episodic and chronic migraine and have shown superiority to placebo (377). Monoclonal antibodies have a molecular weight of around 150 kDa and cannot cross the intact blood-brain barrier to any relevant extent (378). As a result, these are called "large molecules" in contrast to conventional pharmaceuticals and the "gepants" (379), which are "small molecules". Due to the production process, fully human, recombinant antibodies (ending in "umab") are distinguished from humanised antibodies that still contain murine parts (ending in "zumab"). Fully human and humanised monoclonal antibodies are specific, lead only minimally to the formation of autoantibodies and have a favourable side-effect profile. Due to their size, no relevant central nervous adverse effects are to be expected. Due to the degradation to amino acids, they do not interact with other drugs in that they bypass hepatic and renal elimination steps. Monoclonal antibodies must be administered either subcutaneously or intravenously, with corresponding dosing intervals ranging from four weeks to three months. There are no trials so far that have demonstrated a possible difference in efficacy, tolerability and safety. However, imaging trials suggest different sites and modes of action in the brain between erenumab and galcanezumab (380).

The four monoclonal antibodies are presented in Table 9 with regard to dosage, use, adverse drug reactions and restrictions on use.

**Table 9: Dosage, use, adverse drug reactions and limitations of use of monoclonal antibodies, modified from (381)**

| Active substance | Dosage | Adverse effects (UAW) | Contraindications (CI) and restrictions on use (RU) |
|---|---|---|---|
| Erenumab | 70 mg s. c. pre-mixed pen or syringe<br>140 mg s. c. pre-mixed pen or syringe<br>every four weeks | Frequently: Hypersensitivity reactions such as rash, swelling/oedema, angioedema and urticaria; constipation, pruritus, muscle spasms, reaction at the injection site, anaphylactic reaction possible, increase in blood pressure possible. | **CI:** Hypersensitivity to the substance or other ingredients<br>**RU:** Age <18 years (no data available); avoid use during pregnancy to stay on the safe side.<br>No safety data available for patients with severe cardiovascular disease. |
| Fremanezumab | 225 mg s. c. pre-mixed pen or syringe<br>1 x monthly<br>675 mg s. c. (3 x 225 mg pre-mixed pen or syringe) quarterly | Very frequently: Pain at the injection site, induration at the injection site, erythema at the injection site<br>Frequently: Itching at the injection site<br>Occasionally: Rash at the injection site, hypersensitivity reactions such as rash, pruritus, urticaria and swelling. | **CI:** Hypersensitivity to the substance or other ingredients<br>**RU:** Age <18 years (no data available); to stay on the safe side, avoid use during pregnancy and in severe cardiovascular disease. |
| Galcanezumab | Initially: 240 mg s. c.<br>(2 x 120 mg pre-mixed pen)<br>Thereafter: 120 mg<br>s. c. pre-mixed pen monthly | Very frequently: Pain at the injection site, reactions at the injection site<br>Frequently: Vertigo, constipation, pruritus<br>Occasionally: Urticaria, Rarely: anaphylactic reaction possible | **CI:** Hypersensitivity to the substance or other ingredients **RU:** Age <18 years (no data available); avoid use during pregnancy and in cases of severe cardiovascular disease to stay on the safe side |
| Eptinezumab | 100 mg i.v. every 12 weeks or 300 mg i.v. every 12 weeks possible | Very frequently: Nasopharyngitis<br>Frequently: Hypersensitivity reactions, fatigue<br>infusion-related reactions (usually occur during the infusion) | **CI:** Hypersensitivity to the substance or other ingredients, hereditary fructose intolerability (HFI).<br>**RU:** Age <18 years (no data available); avoid use during pregnancy, as well in cases of cardio-vascular disease and serious neurological disease to stay on the safe side |

With the exception of the HER-MES trial (see below), there have been no trials comparing the individual antibodies with each other or with the previously established migraine preventive treatments. To enable an indirect comparison, the 50% responder rate was used across the trials. However, it must be taken into account that the inclusion criteria and definitions of the endpoints in the peer-reviewed trials were in part different and therefore a direct comparison of the efficacy of the individual antibodies is not possible. The second part of the review describes the results for important subgroups of patients.

### 4.3.2 Erenumab for the preventive treatment of episodic migraine

In the STRIVE trial, a phase III trial in episodic migraine, migraine patients received either erenumab 70 mg, 140 mg or placebo subcutaneously once a month for six months (382). The primary endpoint of the trial was the change in migraine frequency between baseline and months four to six, measured with the mean number of migraine days per month. Secondary endpoints were 50% responder rate, number of days on acute medication and change in quality of life as measured by the migraine physical function impact diary (MPFID).

A total of 955 patients were included in the trial (382). 319 received placebo, 317 the low dose (70 mg) and 319 the high dose (140 mg) of erenumab. The mean age of the patients was 41 years and 85% were women. 60% used triptans and 78% analgesics to treat migraine attacks. 40% of the patients had experience with other medications for migraine preventive treatment. 40% reported that previous migraine preventive treatment was either not effective or had unacceptable adverse effects. In the baseline phase, patients had a mean of 8.2 migraine days per month and 9.3 headache days. On average, they took triptans on 3.4 days per month. The reduction in migraine days per month was 3.2 in the 70 mg erenumab group and 3.7 in the 140 mg erenumab group. This was significantly greater compared to 1.8 days in the placebo group. The difference was statistically significant. The 50% responder rate, based on monthly migraine days, was 43.3% for the low dose and 50% for the high dose of erenumab, compared with 26.6% in the placebo group. The difference was also statistically significant. Significant differences were also seen for use of specific migraine medications (e.g. triptans), which decreased by 1.1 days in the 70 mg treated group and by 1.6 days in the 140 mg treated group, compared to 0.2 days in the placebo group. Scores on the MPFID (migraine physical function impact diary) scale, which measures physical impairment, improved significantly by 4.2 and 4.8 points in the erenumab groups, compared with 2.4 points in the placebo group. The incidence of adverse drug reactions was not significantly different between erenumab and placebo.

The second phase III trial (ARISE) was a randomised, double-blind, placebo-controlled trial that enrolled 577 patients with episodic migraine (383). Patients received either 70 mg of erenumab subcutaneously or placebo every four weeks. The primary endpoint was a decrease in migraine days per month. Secondary endpoints were the 50% responder rate for migraine days, the change in days on which migraine-specific symptomatic acute medication was taken (e.g. triptans), and an improvement of 5 or more points of the "Migraine Physical Function Impact Diary Score". These endpoints were recorded at the end of the three-month treatment phase.
The patients were 42 years old on average and 85% were female. Migraine had existed for an average of 20 years. About half of the patients had migraine with aura. Half of the patients had not received any migraine preventive treatment so far. 60 percent of the patients took specific migraine medications such as triptans to treat acute migraine attacks. The average number of migraine days per month at baseline was 8.2 days.

There was a significant reduction of 2.9 migraine days per month within 3 months with erenumab compared to 1.8 days with placebo. The 50% responder rate was 39.7% for erenumab and 29.5% for placebo, with an odds ratio (OR) of 1.9, a 95% confidence interval between 1.12 and 2.27. There was also a significant reduction in days of specific migraine medication, with a reduction of 1.2 days with erenumab and 0.6 days with placebo. This difference was significant with a p-value of 0.002. Performance as measured by the physical impairment and impact on everyday activities domain score measured by the migraine physical function impact diary was not significantly different. Erenumab had a side effect profile comparable to placebo. Occasionally, upper respiratory tract infections occurred and some patients complained of injection site pain (12/289 with placebo, 17/283 with erenumab). Only 5 patients in the erenumab group discontinued treatment due to adverse effects.

The LIBERTY trial prospectively investigated the administration of erenumab 140 mg every 4 weeks in patients for whom between two and four migraine preventive treatment agents had been ineffective or intolerable in the past (384). The trial enrolled 246 patients and treated them with erenumab or placebo for 12 weeks. Subsequently, the patients were treated openly for 156 weeks. The primary endpoint was at least a 50% reduction in migraine days at weeks 9-12.

In the trial, 39% of patients had two unsuccessful attempts at treatment with migraine preventive treatments, 38% had three attempts and 23% had four attempts. The most commonly discontinued treatments were topiramate (85%), amitriptyline (45%), propranolol (45%) and metoprolol (38%). At week 12, the 50% response rate was 30.3% with erenumab and 13.7% in the placebo group. This corresponds to an odds ratio of 2.73 with a 95% CI of 1.43-5.19. Erenumab was also significantly more effective than placebo for all secondary endpoints. In addition, patient-oriented endpoints were investigated. Erenumab was shown to be superior on the HIT-6 scale (headache impact test) and a score measuring productivity at work (WPAI = work productivity and activity impairment score).

Summarising the randomised trials on the efficacy of erenumab in episodic migraine, both doses of 70 and 140 mg are significantly more effective than placebo. The reduction in migraine days per month ranged from 2.9 to 3.7 days, compared to 1.8 to 2.3 days for placebo. Across the three trials, the mean number of migraine days at baseline was 8.4 and was reduced by a mean of 3.3 days with erenumab. The median 50% responder rate was 45% for erenumab and 24-27% for placebo.
The speed of onset of action of erenumab was assessed in a post-hoc analysis of the phase III trials for episodic migraine (STRIVE) (382) and chronic migraine (385). For episodic migraine, a significant reduction in weekly migraine days was found even after the first week of treatment for the 140 mg dose (reduction of -0.6 days vs. -0.1 under placebo) and a higher rate of patients with ≥ 50% reduction in weekly migraine days (386).

The HER-MES trial is currently the only direct comparison trial of a CGRP (receptor) antibody with a conventional migraine preventive treatment (304). There were 777 patients with migraine on ≥ 4 days per month randomised 1:1 into two treatment groups (erenumab 70 or 140 mg or topiramate 50-100 mg). The primary endpoint was discontinuation of medication due to adverse effects during the 24-week double-blind phase. The rate of treatment discontinuation was significantly lower in the erenumab group than in the topiramate group (10.6% vs. 38.9%; OR 0.19; p <0.001). The secondary endpoint, the proportion of patients with ≥ 50% reduction in monthly migraine attacks, was achieved by significantly more patients taking erenumab compared with topiramate (55.4% vs. 31.2%, OR 2.76; p <0.001).

The first long-term data from open-label trials of erenumab in episodic migraine (387) come from the open-label follow-up trial that tracked participants over 5 years (388). After 5 years of continuous treatment, there was a sustained reduction of 5.3 days in monthly migraines from 8.7 days. The monthly intake of acute medication was reduced from 6.3 days by 4.4 days with sustained improvement in several patient reported outcomes (PROs, evaluation of a treatment measure by subjective assessment, e.g. structured questionnaires). However, it must be taken into account that patients with a lack of efficacy or adverse effects did not continue the trial. No new safety signals were found after five years compared to previous trials.

To date, no comparative trial on the efficacy of the two dosages has been conducted. A network meta-analysis showed significantly better efficacy, in terms of a 50% responder rate and the number of monthly days taking migraine-specific acute medication, at a 140 mg dose with a comparable side effect profile, compared with the 70 mg dose (389). In clinical practice, some patients may benefit from a dose of 140 mg of erenumab once monthly compared with 70 mg, particularly patients with difficult-to-treat migraine and previous treatment failure. Erenumab at 140 mg had numerically better efficacy than 70 mg (390).

### 4.3.3 Erenumab for the preventive treatment of episodic migraine

Fremanezumab was compared to placebo in the HALO-EM trial (391). This was a double-blind, placebo-controlled, parallel-group trial conducted at 123 headache centres in nine countries. After a 28-day baseline, treatment was given for 12 weeks with subcutaneous administration of fremanezumab. Inclusion criteria included an age between 18 and 70 years and episodic migraine with 6-14 headache days per month, of which at least four days had to fulfil the criteria of migraine. Only patients who had a history of either not responding to or not tolerating two or more classes of migraine preventive treatment or for whom the corresponding class of medication was contraindicated were included. About 20% of the trial participants were stable on migraine preventive treatment medication and continued that treatment in the trial. Patients were randomised into three groups. 290 patients received 225 mg fremanezumab every four weeks, 291 patients received a single dose of 675 mg fremanezumab and 294 patients received placebo. The primary endpoint was the mean change in migraine days per month over the 12-week treatment period.

The patients were 42 years old on average and 85% were female. Migraine had existed for an average of 20 years. At baseline, the patients had a mean of 9 migraine days and on 7.7 days the patients took medication to treat the migraine attack. Specific migraine medication was taken on 6-7 days. In the treatment group receiving fremanezumab once a month, there was a significant reduction of 3.7 migraine days compared to 2.2 migraine days with placebo. With the single higher dose of fremanezumab, there was a decrease in migraine days per month of 3.4 days. Here, too, the difference compared with placebo (decrease of 2.6 days) was significant. The 50% responder rate, based on migraine days per month, was 47.7% in the fremanezumab 3-injection group, 44.4% in the patients treated only once with 675 mg fremanezumab, and 27.9% in the placebo group. These differences were significant. Significant differences in favour of fremanezumab were also seen for all secondary endpoints, such as days of headache medication use and migraine impairment as measured by the MIDAS score. There were no significant differences in adverse drug reactions between the three treatment groups. Pain at the injection site and upper respiratory tract infections were reported most frequently. Therapy was discontinued by five patients in each treatment group due to adverse effects.

In patients in a follow-up trial of the HALO-EM (391) and the HALO-CM trial (392) and in other patients, Blumenfeld et al. investigated whether there was a wearing-off effect of fremanezumab towards the end of the dosing interval of one or three months. Regardless of the underlying migraine pattern (EM, CM) and dosing interval, there was no increase in weekly migraine days towards the end of the dosing interval (393).

### 4.3.4 Galcanezumab for the preventive treatment of episodic migraine

The two EVOLVE (evaluation of LY2951742 in the prevention of episodic migraine) trials were double-blind, randomised, placebo-controlled trials that compared subcutaneous injections of galcanezumab with placebo (394, 395). Patients received a subcutaneous injection of galcanezumab 120 mg, 240 mg or placebo once a month for six months, with a starting dose of 240 mg in the 120 mg treatment arm. Patients with 4-14 migraine days/month were included. The primary endpoint of the trials was the mean reduction in migraine days during the trial period, compared to baseline. In addition, the 50%, 75% and 100% responder rates were calculated, migraine days with the use of acute medication as well as the quality of life and the restriction in everyday life caused by the migraine. Pre-existing migraine preventive treatment had to be discontinued before inclusion in the trial.

The EVOLVE-1 trial enrolled 858 patients. The mean age of the patients was 40.7 years and 84% were women. In the baseline period, the mean frequency of migraine days per month was 9.1. Both doses of galcanezumab were significantly more effective than placebo. The mean reduction in migraine days was 4.7 days (120 mg) and 4.6 days (240 mg) for galcanezumab, compared with placebo at 2.8 days ($p < 0.001$). The trial also showed significant differences for all secondary endpoints in favour of galcanezumab.

The EVOLVE-2 trial enrolled 915 patients and also treated them with 120 mg (n = 231) or 240 mg (n = 223) galcanezumab 1 x monthly. 461 patients received placebo. The patients were on average 41.9 years old and 85.4% were female. In the baseline period, the mean frequency of migraine days per month was 9.1. The mean reduction in migraine days was 4.3 days (120 mg) and 4.2 days (240 mg) for galcanezumab, compared with placebo at 2.3 days ($p < 0.01$). This trial also showed superiority of galcanezumab over placebo for the secondary outcome parameters. The at least 50% responder rates were 62.3% and 59.3% for the 120 mg dose of galcanezumab and 60.9% and 56.5% for the 240 mg dose in the two trials, compared with 38.6% and 36% with placebo. The 100% response rates were 15.6% and 11.5% (120 mg), 14.6% and 13.8% (240 mg), compared with placebo 6.2% and 5.7%. However, it must be taken into account that these rates do not refer to complete freedom from pain over the entire six months, but to at least one (or more) attack-free months. In a pooled analysis of the two EVOLVE trials, 0.7% of patients at 120 mg and 1.4% at 240 mg galcanezumab showed complete freedom from pain over all six months of treatment (396).

The treatment with galcanezumab was very well tolerated. Apart from injection site reactions, there were no differences in adverse drug reactions between verum and placebo. Only a few patients discontinued the trial because of adverse effects. The frequencies were 1.7% and 2.3% for placebo, 2.2% and 4.2% for the 120 mg dose, and 4.0% and 3.3% for the 240 mg dose of galcanezumab.

The monoclonal antibody against CGRP galcanezumab was more effective than placebo in preventing episodic migraine in two randomised, double-blind, placebo-controlled trials over a six-month period. There were no differences in efficacy between the two doses of 120 and 240 mg.

### 4.3.5 Eptinezumab for the preventive treatment of episodic migraine

The PROMISE-1 trial compared three doses of eptinezumab (30 mg, 100 mg and 300 mg) with placebo in patients with episodic migraine (397). The primary endpoint was the reduction in monthly migraine days over weeks 1-12. The trial lasted a total of 48 weeks. 888 patients were available for the evaluation. The mean number of migraine days per month at baseline was 8.4 to 8.7 days in all treatment groups. Eptinezumab 30, 100 and 300 mg vs. placebo significantly reduced migraine days per month from baseline at weeks 1-12. The percentage of patients with ≥ 50% reduction in migraine days per month was 50.2% for eptinezumab 30 mg, for 100 mg it was 49.8%, for 300 mg 56.3% and for placebo 37.4%. Adverse drug reactions were not significantly different between eptinezumab and placebo. Upper respiratory tract infections and nasopharyngitis were numerically more frequent with eptinezumab than with placebo.

For eptinezumab, the speed of onset of action was also investigated (398). Patients were randomised to receive 100 mg eptinezumab or placebo within one to six hours after the onset of a migraine attack. The primary endpoints of time to freedom from headache and time to freedom from the most bothersome symptom were achieved significantly earlier with eptinezumab (median four hours and two hours) compared with placebo (median nine hours and three hours). Eptinezumab is not approved for the acute treatment of migraine. However, the trial shows that the effect can occur very quickly. This effect may be relevant in the context of starting prophylactic treatment for refractory status migraenosus.

## 4.4 Studies on the preventive treatment of chronic migraine

### 4.4.1 OnabotulinumtoxinA and topiramate

In chronic migraine, a preventive treatment effect has been proven by methodologically sound placebo-controlled trials only for onabotulinumtoxinA and topiramate. The two PREEMPT trials with onabotulinumtoxinA included a total of 1384 patients with chronic migraine (399, 400). The double-blind trial investigated two treatment cycles at three-month intervals, followed by a six-month open-label treatment phase. In a pooled analysis (401), onabotulinumtoxinA significantly reduced days with headache, frequency of migraine attacks, days with marked headache, cumulative headache hours per day and subjective impairment compared to placebo. The number of headache days per month decreased by 8.4 days in the onabotulinumtoxinA group, from 19.9, and by 6.6 days in the placebo group, from 19.8. OnabotulinumtoxinA also showed good efficacy in patients with overuse of analgesics or migraine medications (402). However, secondary headaches caused by MOH were excluded in the PREEMPT trials.

The efficacy of topiramate in the treatment of chronic migraine has been demonstrated in two randomised, placebo-controlled trials. 59 patients were treated with placebo or topiramate 100 mg/day for 16 weeks (403). 22% of patients treated with topiramate showed at least a 50% reduction in headache days/month (0% in the placebo group, p = 0.012) (305, 404). Headache days reduced on average by -3.5 ± 6.3 per month in the verum group and by 0.2 ± 4.7 in the placebo group (p = 0.02). There was also a significant improvement in headache days (p <0.03) in the patients (78%) with medication overuse (3.5 ± 7.1 days). A similar result was shown in a larger (n = 306) American trial (405). In the topiramate group, there was also a significant reduction (6.4 +/- 5.8) in migraine days compared to placebo (4.7 +/- 6.1; p = 0.01).

### 4.4.2 Erenumab for the preventive treatment of chronic migraine

Erenumab has been studied in connection with chronic migraine in a phase II trial (385). This was a randomised, double-blind, placebo-controlled, multicentre trial that included patients with chronic migraine in the United States and Europe. The patients were treated in a ratio of 3:2:2 randomised to subcutaneous placebo, erenumab 70 mg or erenumab 140 mg every four weeks for 12 weeks. The primary endpoint was the change in migraine days per month from the four-week baseline to the last four weeks of the double-blind treatment phase.

A total of 667 patients were included in the trial. 286 received placebo, 191 the low dose and 190 the high dose of erenumab. The monthly reduction in migraine days was 6.6 days for the two doses of erenumab and 4.2 days for placebo. The absolute difference of minus 2.4 days was significant. Adverse effects were reported by 39% of patients in the placebo group, 44% in the low dose and 47% in the high dose of erenumab. The most common adverse effects were pain at the injection site, nausea and upper respiratory tract infection. Autoantibodies against erenumab were detected in 11 patients in the low-dose group and three patients in the high-dose group. No abnormalities were found in the laboratory values or the ECGs.

The CGRP receptor antibody erenumab was more effective than placebo in reducing migraine days in patients with chronic migraine at both doses of 70 and 140 mg.

### 4.4.3 Fremanezumab for the preventive treatment of chronic migraine

The HALO-CM trial was a randomised, placebo-controlled trial in patients with chronic migraine, in which patients were divided into three treatment groups (392). The first treatment group received an initial dose of 675 mg fremanezumab (quarterly) and placebo subcutaneously after four and eight weeks. In the second group, patients received 675 mg fremanezumab initially and 225 mg after four and eight weeks (monthly dosing), while the patients in the third group received the placebo. The primary endpoint was the mean change in headache days per month, defined as days with headaches that lasted at least four hours, had an intensity of at least moderate, or were treated with specific migraine medication such as triptans or ergot alkaloids. The primary endpoint was the frequency of headache days per month over 12 weeks.

A total of 1130 patients were included. A total of 376 received fremanezumab once (quarterly), 379 monthly and 375 placebo. The patients were on average 41 years old and 88% were female. 20% were taking migraine preventive treatment. 30% had experience with topiramate and 15% with botulinum toxin. The median number of headache days at baseline was 13 and the number of days with any headache intensity was 20. 16 migraine days were observed at baseline, medication for headache treatment was taken on 13 days and specific migraine medication on 11 days. The mean reduction in headache days per month was 4.3 after a single dose of fremanezumab, 4.6 with monthly dosing and 2.5 with placebo. The difference from placebo was statistically significant.

The at least 50% responder rate was 38% and 41% for fremanezumab and 18% for placebo. Adverse drug reactions were comparable. There was a transient increase in liver enzymes in five patients taking fremanezumab and in three patients in the placebo group.

### 4.4.4 Galcanezumab for the preventive treatment of chronic migraine

The REGAIN trial was a randomised, double-blind, placebo-controlled trial in patients with chronic migraine (406). The trial had a three-month double-blind, placebo-controlled phase and a nine-month open-label phase. Patients with chronic migraine between the ages of 18 and 65 years were randomised at a ratio of 2:1:1 to placebo (n = 558), galcanezumab 120 mg with an initial dose of 240 mg (n = 278) and 240 mg galcanezumab (n = 277). The treatment took place once per month. The primary endpoint was the reduction in monthly migraine days during the three-month double-blind treatment phase, compared to baseline.

Patients randomised to the 240 mg/month group that is not approved as maintenance treatment were on average 39-42 years old, while the group treated with galcanezumab 120 mg (after a single loading dose of 240 mg at baseline) were slightly younger than the placebo group. 85% of the trial participants were women. The migraine had persisted for a mean of 21 years and the mean number of migraine days per month during baseline was 19.4. The mean number of headache days per month was 21. 78% of patients had previous experience of preventive treatment and 31% of patients had failed two or more preventive treatments in the past. In 64% of the patients, there was an overuse of analgesics and migraine medicines. Galcanezumab resulted in a significantly greater reduction in the number of migraine days per month compared to placebo. The reduction in migraine days per month was 2.7 with placebo, 4.8 with the lower dose of galcanezumab and 4.6 with the higher dose. The at least 50% response rate was 15.4% with placebo, 27.6% with the low dose and 27.5% with the high dose of galcanezumab. There was also a significant superiority of galcanezumab for the quality-of-life instruments used. Galcanezumab was very well tolerated. The most common adverse effects were pain at the injection site and respiratory infections, although these did not differ between the three treatment groups.

### 4.4.5 Eptinezumab for the preventive treatment of chronic migraine

Eptinezumab was studied in a double-blind, randomised, placebo-controlled phase III trial in 1072 patients with chronic migraine (407). Patients were randomised to an injection of eptinezumab 300 mg, 100 mg or placebo. The primary endpoint was the reduction in monthly migraine days in weeks 1-12 compared with the 28-day screening period. This was achieved for all groups. The 50% responder rates over weeks 1-12 for eptinezumab 300 mg and 100 mg were 61.4% and 57.6%, respectively, versus 39.3% for placebo (each $p < 0.0001$ vs. placebo). Eptinezumab was well tolerated and side effect rates were similar to placebo.

## 4.5 Other guidelines on the use of monoclonal antibodies for preventing migraine

The 2022 European Headache Federation guideline recommends the use of monoclonal antibodies in patients with episodic or chronic migraine (1). For migraine patients who need preventive treatment, monoclonal antibodies targeting the CGRP pathway were considered the first treatment option. Although monotherapy is generally preferable, for some migraine patients a single medication does not provide sufficient pain relief. In these cases, a combination of different drugs can be considered, taking into account the pharmacological history and comorbidities. In people with episodic or chronic migraine, there was insufficient evidence to recommend combining monoclonal antibodies targeting CGRP with other medications for migraine preventive treatment. With the conventional oral preventive medications, migraine patients were usually treated for 6 to 12 months. In people with episodic or chronic migraine, it is suggested that a break in treatment with monoclonal antibodies be considered after 12-18 months of continuous treatment.

However, there is no data-based foundation for these recommendations.

The American Headache Society has only issued recommendations, not guidelines (409). The criteria for assessing the success of the treatment are taken from these recommendations.

## 4.6 Comparison of the efficacy of monoclonal antibodies in treating episodic and chronic migraine

A comparison of the individual monoclonal antibodies (mAbs) is methodologically critical, as there are multiple differences in the design of the trials and in the inclusion and exclusion criteria, and different methods are used to calculate the reduction in migraine days and the at least 50% responder rate. One of the meta-analyses showed the highest odds ratio based on 50% responder rate for fremanezumab (2.58), followed by galcanezumab (2.41), erenumab (2.25) and eptinezumab (2.02) (301), with overlapping 95% confidence intervals. Early real-world data from uncontrolled trials show that 50% responder rates across all antibodies were lower in patients with chronic migraine than in those with episodic migraine (410, 411).

## 4.7 Particular populations and queries

### 4.7.1 Previous failure of migraine preventive treatment

The value of mAbs in patients who have not responded to other preventive treatment has been investigated in several trials and subgroup analyses. Some pivotal trials have included patients who have not responded to previous preventive treatments for episodic and chronic migraine at sufficient doses and for sufficient durations. Ultimately, these data form the basis for the first evaluation by the Federal Joint Committee (G-BA), on which the specifications for reimbursability in the area of statutory health insurance were based.

The primary objective of the LIBERTY trial was to evaluate the response to 140 mg of erenumab in patients with refractory episodic migraine without concomitant medication overuse in a randomised, double-blind, placebo-controlled trial design (412). The main inclusion criterion for the trial was that the patients had not responded to and/or had not tolerated two to four of the following substances within the previous five years: propranolol or metoprolol, topiramate, flunarizine, valproate, amitriptyline, venlafaxine, lisinopril, candesartan or another locally approved preventive treatment such as cinnarizine, indoramine, oxeterone, nadolol or pizotifen. At least one of the failed treatments had to have been with propranolol, metoprolol, topiramate or flunarizine. For valproate, either the insufficient effect had to be proven or there had to be a contraindication. An insufficient effect required a sufficiently long treatment duration of at least two to three months. Intolerability was defined as any discontinuation of medication due to adverse effects. The other inclusion and exclusion criteria essentially corresponded to those of the pivotal trials already presented.

121 patients received erenumab, 125 patients received placebo. In both treatment groups, three patients dropped out prematurely. The trial population was balanced across both treatment arms. In both arms, 70% of patients had high-frequency episodic migraine with 8-14 migraine days per month. An insufficient response to 2, 3 or 4 substances was present in the verum group in 36%, 36% and 27% respectively, and in the placebo group in 42%, 39% and 18% respectively. The substances most frequently used without success in the past were in descending frequency: topiramate, propranolol, amitriptyline, metoprolol and valproate. The primary endpoint of at least a 50% reduction in migraine days in the 3rd month of treatment compared to baseline was met by 30% of patients in the erenumab group and 14% in the placebo group (OR 2.7 [95% CI = 1.4-5.2]).

All the secondary endpoints were also met: there was a significant decrease in monthly migraine days at weeks 1-4 (mean -1.8 days vs. 0.1 on placebo), weeks 5-8 (-2.3 vs. 0.1 days) and weeks 9-12 (-1.8 vs. -0.2 days). There was a significant decrease in the number of days on acute medication and a significant decrease in physical function impairment (MPFIT) and general headache impairment (HIT-6) during each of the 3 4-week treatment intervals.
This trial showed for erenumab that a significant preventive treatment effect with good tolerability can be achieved in the 140 mg dose even in patients with proven treatment resistance or treatment intolerability to two to four pre-treatments. In this patient population, too, the onset of action of erenumab was demonstrated within the first four weeks of treatment. Based on this data, the administration of erenumab is possible in patients with episodic migraine without concomitant medication overuse with existing intolerabilities and insufficient response to standard preventive treatments.

For patients with refractory chronic migraine, a subgroup analysis of the phase II trial of erenumab in chronic migraine is available (413). This analysed the monthly administration of 70 or 140 mg of erenumab versus placebo in the subgroup of patients who had failed to respond to preventive treatments with substances from at least one or two substance categories compared to patients without failure to preventive treatment. Of the total of 667 patients, 492 patients had received preventive treatment in the past. Of these, 360 had not responded and 326 had not tolerated the treatment because of adverse effects. Topiramate (n = 299), beta-receptor blockers (n = 231) and tricyclic antidepressants (n = 209) had been used most frequently without success. Three subgroups were formed: patients who had not previously been treated or who had been treated successfully (group 1), patients with intolerability or treatment failure to at least 1 substance class (group 2) or at least 2 substance classes (group 3). Patients in group 1 had been ill for less time, had fewer days of taking migraine-specific acute medication and overused medication less frequently than the other two subgroups. Numerically, monthly migraine days decreased more with erenumab treatment than with placebo treatment in all subgroups. In the groups with unsuccessful pre-treatment, the 140 mg dose was more effective than the 70 mg dose and the placebo response rate was lower than in patients without previous treatment failure. Adverse events were reported slightly less frequently in the group without treatment failure (30.6–37.5%) than in the groups with previous treatment failure (42.2–60.0%). However, there were no significant differences compared to the respective group treated with placebo.

There was also a subgroup analysis of the REGAIN trial in which patients with chronic migraine aged between 18 and 65 years were randomised at a ratio of 2:1:1 to placebo (n = 558), galcanezumab 120 mg with an initial dose of 240 mg (n = 278) or 240 mg galcanezumab (n = 277) (414). The treatment took place once per month. This analysed the two doses of galcanezumab versus placebo in the subgroup of patients who had failed to respond to preventive treatments with at least 1 or at least 2 preventive treatment agent(s) (American Academy of Neurology/American Headache Society recommendation grades A and B) including onabotulinumtoxinA compared to patients without failure to preventive treatment. Of the total of 1113 patients, 573 had not responded to at least one substance, 347 to at least two substances and 199 to at least three substances or had not tolerated the treatment due to intolerabilities in the previous five years. Topiramate (57.6%), amitriptyline (31.4%), propranolol (26.7%), valproate (20.1%) and onabotulinumtoxinA (17.3%) had been used most frequently without success. The criteria for medication overuse headache were met in 63.8% of the total collective. Three subgroups were formed: patients without a history of treatment failure, patients with intolerability or treatment failure of at least one or at least two substance classes. Treatment with galcanezumab was significantly superior to placebo treatment in all three groups over the entire three months at both doses. With the two groups with a history of one or more treatment failures, response to the 120 mg dose was better than response to the 240 mg dose. Only in the group without previous treatment failure was the response to the 240 mg dose better. Response rates to placebo were consistently highest in the group without a history of treatment failure and lowest in the group with at least two previous treatment failures.

The randomised, double-blind, placebo-controlled phase IIIb FOCUS trial recruited patients aged 18-70 years with episodic or chronic migraine with documented failure of two to four classes of migraine preventive treatment medications in the past ten years.

Patients received a single dose of fremanezumab (month 1: 675 mg; months 2 and 3: placebo), monthly fremanezumab (month 1: 225 mg for episodic migraine and 675 mg for chronic migraine; months 2 and 3: 225 mg in both migraine subgroups) or placebo for 12 weeks. The primary endpoint was the mean reduction in the monthly number of migraine days during the 12-week treatment period. Between November 2017 and July 2018, 838 participants with episodic (329 = 39%) or chronic migraine (509 = 61%) were included. The reduction in monthly migraine days over 12 weeks was higher for fremanezumab than for placebo. The reduction was -0.6 days for placebo, -3.7 days for quarterly fremanezumab (difference vs. placebo -3.1 [95% CI = -3.8 to -2.4]; p <0.0001) and -4.1 with monthly fremanezumab (difference vs. placebo -3–5 [95% CI = -4.2 to -2.8]; p <0.0001). Three subgroups were formed: patients with treatment failure of two (n = 414), three (n = 265) or four (n = 153) prior treatments. Treatment failure was defined as inadequate response after three months or discontinuation due to intolerability or contraindication or if the patient was not suitable for treatment. Treatment with galcanezumab was significantly superior to placebo treatment in all three groups over the entire three months at both doses. Response rates to placebo were highest in the group with two prior treatment failures and lowest in the group with four prior treatment failures (415).

The CONQUER trial recruited 462 participants with episodic (269 = 58%) or chronic (193 = 42%) migraine. Patients received at least one injection of placebo (n = 230) or galcanezumab (n = 232) (416). Patients treated with galcanezumab experienced a significantly greater reduction in migraine headache days compared to placebo in months 1–3. The galcanezumab group had an average of 4.1 fewer monthly migraine headache days compared with baseline (13.4), while the placebo group had an average of 1.0 fewer compared with baseline (13.0; difference between groups -3.1; 95% CI -3.9 to -2.3; p <0.0001). The type and number of treatment-related adverse events were comparable between galcanezumab and placebo. Treatment-related adverse events were reported in 122 (53%) of 230 patients in the placebo group and in 119 (51%) of 232 patients in the galcanezumab group. Eptinezumab was studied in migraine patients who had failed previous treatments in the DELIVER trial (417). There were 891 people randomised to receive eptinezumab 100 mg (n = 299), eptinezumab 300 mg (n = 294) or placebo (n = 298). The change in mean monthly migraine days from baseline to weeks 1-12 was -4.8 (SE 0.37) with eptinezumab 100 mg, -5.3 (SE 0.37) with eptinezumab 300 mg and -2.1 (SE 0.38) with placebo. The difference from placebo in the change from baseline in mean monthly migraine days was significant for eptinezumab 100 mg and eptinezumab 300 mg.

Treatment-related adverse events occurred in 127 (42%) of 299 patients in the eptinezumab 100 mg group, 120 (41%) of 294 in the eptinezumab 300 mg group and 119 (40%) of 298 in the placebo group.

Based on the subgroup analyses available so far, there was evidence that treatment with eptinezumab, erenumab, fremanezumab and galcanezumab was also effective in patients with previously treatment-resistant chronic migraine with and without concomitant medication overuse or MOH.

### 4.7.2 Onset of action of the monoclonal antibodies

Early onset of action was shown for all four monoclonal antibodies. This was an advantage over the previously established preventive treatments, where the effect can also set in quickly, but usually several weeks of slow up-titrating were necessary and the first efficacy assessment was usually not until 8–12 weeks after a tolerable target dose has been reached. **Up-titrating is not necessary for any of the antibodies.** Administration of galcanezumab begins with an on-off loading dose of 2 x 120 mg. In the case of erenumab, treatment begins with 140 mg and, for fremanezumab, with a 675 mg dose administered at 3-month intervals. The early onset of action of erenumab was investigated in a trial that analysed data for chronic and episodic migraine (386). Compared to placebo, the onset of action was proven in the first week of treatment. Both the 70 mg and 140 mg doses were significantly superior to placebo in both episodic and chronic migraine from week two onwards after the start of treatment. A comparable situation was seen in the patients who achieved at least a 50% reduction in migraine days. In the first week after injection, erenumab 140 mg was already significantly superior to placebo for episodic migraine, and after two weeks for both doses. For chronic migraine, both doses were significantly superior to placebo from the first week.

For fremanezumab, a post-hoc analysis also shows a rapid onset of action in chronic migraine (418). The headache hours as recorded with an electronic diary were analysed. Statistical superiority was shown for the administration of 225 mg and 675 mg compared to placebo from day seven. In addition, the proportion of patients with at least a 50% reduction in headache hours or days with headache of moderate to severe intensity from week one was higher than with placebo.

A post-hoc analysis also demonstrated a rapid onset of action for galcanezumab (420). Already in the first week of treatment, galcanezumab proved to be significantly superior to placebo.

Possibly due to the intravenous administration, a very early onset of action was shown for eptinezumab (407). There was a superior effect compared to placebo from day one after administration of the trial medication (421).

### 4.7.3 Initial response and minimal duration of treatment with monoclonal antibodies

In a post-hoc analysis, the effect of galcanezumab on initial non-responders to treatment was analysed (422). In that analysis, study participants who did not achieve a 50% reduction in monthly migraine days in month one of treatment showed a response in months two and three more frequently than participants on placebo, justifying treatment for three months.
Looking at the trial results of the papers published so far on the response to the monoclonal antibodies against CGRP or the CGRP receptor, chronic migraine seems to respond somewhat later than episodic migraine. For patients with chronic migraine, a subgroup analysis of a real-world study showed that the conversion rate from patients with chronic migraine to episodic migraine increases by month five after starting therapy with erenumab (423).

Overall, the data on all antibodies justifies a treatment trial over three months, even if a very early response was often seen. A response can still occur in the 2nd or 3rd month, even if no therapeutic success has been demonstrated beforehand. For eptinezumab, treatment should initially be given for six months. This is in line with the guidelines in the Summary of Product Characteristics (see table 10), so the treatment should initially be given for three months (or, in the case of eptinezumab, for six months). If there is no sufficient therapeutic success, the treatment is terminated. In the case of chronic migraine, a treatment trial over 5–6 months may be useful.

**Table 10: Guidelines for reviewing treatment with mAbs or discontinuation of treatment according to the applicable Summary of Product Characteristics**

| Substance | EMA (D, A) | Swissmedic (CH) |
|---|---|---|
| Erenumab | At regular intervals after the first three months of treatment, it is recommended to evaluate whether to continue treatment. | If there is no response to treatment or after 12 months at the latest, a re-evaluation should be carried out as to whether the treatment should be continued. |
| Fremanezumab | The benefit of the treatment is to be evaluated within three months of the start of treatment. Any further decision regarding a continuation of treatment must be weighed up individually for each patient.<br>It is recommended that the need to continue treatment be assessed regularly thereafter. | If there is no response to treatment or after 12 months at the latest, a re-evaluation should be carried out as to whether the treatment should be continued. |
| Galcanezumab | The success of the treatment should be assessed three months after the start of treatment. Any further decision to continue treatment should be made individually for each patient. It is recommended to check regularly afterwards whether further treatment is necessary. | A re-evaluation should be made regarding the need to continue treatment if there is no response to treatment, or at least once a year. |
| Eptinezumab | The benefits and continuation of treatment should be assessed six months after the start of treatment. | If there is no response to treatment or after 12 months at the latest, |

| | | |
|---|---|---|
| | Any further decision regarding a continuation of treatment must be weighed up individually for each patient. | a re-evaluation should be carried out as to whether the treatment should be continued. |

### 4.7.4 Further target parameters for the efficacy of migraine preventive treatment with medication

In addition to the target parameter of > 50% responders, significant results for the reduction in the number of days taken for acute medication and for the impairment of quality of life due to migraine were also demonstrated in all pivotal trials. These aspects should be included in the assessment of the efficacy of the treatment.

### 4.7.5 Dose interval (one versus three months)

Erenumab is injected subcutaneously at four-week intervals, galcanezumab at monthly intervals. For fremanezumab, there is the option of monthly and trimonthly administration. The dose is 225 mg for monthly treatment and 675 mg for quarterly treatment. There is no significant difference between monthly and quarterly dosing, while there is a slight tendency towards better efficacy for the shorter treatment interval. Trimonthly treatment is not recommended for women of childbearing age without adequate contraception. Eptinezumab is infused every 12 weeks; no trial results are available on other dosing intervals.

### 4.7.6 Combination treatment

Evidence for a beneficial effect of combination treatment with other preventive treatment medications for both episodic (EM) and chronic migraine (CM) is currently drawn from a post-hoc analysis of pooled data from two trials of fremanezumab (424). In both trials, fremanezumab or placebo was administered s.c. every 28 days for three months. In both trial arms, patients used their preventive treatment medications (taken for at least three months). These included betablockers, calcium channel blockers, anticonvulsants, candesartan, tricyclic antidepressants, venlafaxine, mirtazapine, triptans, opioids and non-steroidal anti-inflammatory drugs (when taken daily as preventive treatment). Headache characteristics were recorded electronically 28 days before the first dose of fremanezumab (screening phase) and during the three treatment cycles. The primary analysis was the average number of migraine days and at least moderate headache days within each month of treatment and the average change in these parameters in each month, compared to baseline. The secondary endpoint was the number of acute medications used in each treatment arm and treatment cycle. There were 133 patients (66 with placebo, 67 with a preventive treatment) included in the analysis. In the patient group treated with fremanezumab, mean migraine days/month decreased from 14.6 to 10.5 (-4.12) and in the placebo group from 14.6 to 12.1 (-2.47) ($p = 0.0321$).

Moderate to severe migraine days (12.3 vs. 11.7) were also statistically significantly reduced in the verum group compared to the placebo group (-4.16 vs. -2.37; p = 0.0058). The number of days on which an additional acute medication had to be taken was statistically significantly reduced in the group of patients treated with fremanezumab (-3.88 vs. - 2.52; p = 0.0414). At least a 50% reduction in migraine days was achieved in 40% of patients in the verum group (vs. 24% in the placebo group). The adverse event rate was low, and not specific to dose and medication. The authors concluded from these results that fremanezumab as an add-on treatment compared to placebo statistically significantly reduces the number of migraine and headache days and that the combination should be considered in clinical practice, especially as no interactions between CGRP antibodies and other migraine preventive treatments are expected. When treatment with fremanezumab is initiated, treatment with a medicinal product for migraine prevention may be continued concomitantly if deemed necessary by the prescriber.

Based on pathophysiological considerations suggesting differential modulation of trigeminal activation in the context of a migraine attack by CGRP (receptor)-blocking substances (monoclonal antibodies against CGRP as a ligand or its receptor and gepants acting on trigeminal A-delta fibres) and onabotulinumtoxinA (acting on trigeminal C-fibres), the concept of a dual treatment is discussed. Initial uncontrolled trial data suggests a possible additive effect (425).

### 4.7.7 Reduction of the intake of acute medication

In all randomised trials, the days on which acute medication was taken were recorded. However, some trials only considered the administration of triptans. These were naturally higher in chronic migraine than in episodic migraine. Table 11 shows a reduction in days of medication for acute migraine attacks under placebo from +0.5 to -3.1 and under active treatment from -1.1 to -4.9. Although a direct comparison is not possible, there are no differences between eptinezumab, erenumab, fremanezumab and galcanezumab.

**Table 11: Reduction in the number of days per month that medicines are taken to treat acute migraine attacks**

| Substance | Trial | Placebo | Treatment 1 | Treatment 2 |
|---|---|---|---|---|
| Erenumab | EM (382) | -0.2 | 70 mg -1.1 | 140 mg -1.6 |
| | EM (383) | -0.6 | 70 mg -1.2 | |
| | EM (426) | +0.5 | 70 mg -1.3 | |
| | CM (385) | -1.6 | 70 mg -3.5 | |
| Fremanezumab | EM (427) | -3.1 | 225 mg -4.9 | 675 mg -4.8 |
| | EM (391) | -1.6 | 225 mg -3.0 | 675 mg -2.9 |
| | CM (392) | -1.9 | 675 mg -3.7 | 675/225/225 mg -4.2 |
| Galcanezumab | EM (394) | -2.2 | 120 mg -4.0 | |
| | EM (395) | -1.9 | 120 mg -3.7 | |
| | CM (406) | -2.2 | 120 mg -4.7 | |
| Eptinezumab | CM (428) | -5.0 | 100 mg -9.8 | 300 mg -8.5 |

### 4.7.8 Discontinuation test or pause in treatment after initial therapeutic response

According to the expert information, in Germany and Austria a regular review is to be carried out as to whether the treatment should be continued (for deviating regulation in Switzerland, see Table 12). In clinical practice, this means pausing the medication and waiting to see whether the therapeutic success continues after discontinuation of the medication and, if necessary, a resumption if the condition worsens again.

In the two EVOLVE trials, the course of migraine at the end of the six-month double-blind treatment phase was examined over a further four months (429). In month six, the number of migraine days in the month had decreased by 4.5–5 days. Four months after stopping, the migraine worsened again. However, the reduction in migraine days was still 3.5–4.1 days compared to baseline. A further analysis in patients who discontinued erenumab and galcanezumab at the end of the open-label long-term trials also showed that, although there may be an increase in monthly migraine days again from week five, these do not reach baseline levels (430).

In a longitudinal cohort trial with equal proportions of patients on erenumab, fremanezumab and galcanezumab, discontinuation after stabilisation to 8.2–6.6 migraine days at weeks 5–8 and (10.3 ± 6.8 days) and 13–16 (12.5 ± 6.6 days) again resulted in a statistically significant increase in migraine days (431). Migraine-related quality of life and migraine impairment also increased significantly again after discontinuation (432). After the treatment break of monoclonal antibodies, it was shown that the number of monthly migraine days increases again in many patients a few months after the end of treatment, whereby the initial level before the start of treatment was not always reached.

There is a consensus statement from the migraine and headache societies of the German-speaking countries on the duration of treatment for migraine preventive treatment with medication (433, 434) (see Table 12). In the event of a renewed increase, treatment with the last effective medication should be restarted. In an uncontrolled trial, it was shown that there was a significant decrease in monthly migraine days, monthly headache days and acute medication days after resumption of the last effective antibody treatment (435).

**Table 12: Recommended duration of treatment until migraine preventive treatment is discontinued**

| Recommended duration of treatment | |
|---|---|
| Patients with low-frequency (<8 monthly migraine days; MMDs) episodic migraine at baseline, shorter duration of disease and without comorbid conditions such as depression, anxiety disorder or chronic pain disorder. | Patients with a prolonged history of migraine, high-frequency episodic(≥ 8 MMDs), or chronic migraine at the start of treatment and concomitant disorders such as depression, anxiety disorder or chronic pain disorder |
| 9 to 12 months of treatment with clinically significant reduction in migraine (i.e. ≥ 50% reduction in MMD , ≥ 30% reduction in MIDAS, ≥ 5 points reduction in HIT-6) before attempting interruption | of the at least 12 to 24 months of treatment with clinically significant reduction in migraine (i.e. ≥ 30% to ≥ 50% reduction in MMD, ≥ 30% reduction in MIDAS, ≥ 5 points reduction HIT) before a migraine preventive treatment takes place |

| | |
|---|---|
| | discontinuation test of the migraine prevention treatment completed |
| Treatment with flunarizine must be interrupted after six months according to the recommendations in the summary of product characteristics. | Exceptions: Treatment with flunarizine must be interrupted after six months |

### 4.7.9 Switch from one antibody to another in the event of non-response

Data from uncontrolled trials suggests that switching from one monoclonal antibody to another was useful if one is ineffective, especially when accompanied by a change in drug class. For example, in non-responders, after three cycles of treatment, switching from erenumab to galcanezumab or fremanezumab resulted in at least a 30% reduction in monthly headache days in 32% of participants (436). At least a 50% reduction in headache days was found in 12% of patients. A closer look showed that no patient with daily headaches (n = 9) benefited from a change in treatment.
In contrast, 50% of patients with a "non-daily" headache benefited (n = 16).

Whether it makes sense to switch from one ligand antibody to another cannot be conclusively answered at present with the available literature, but can certainly be considered pragmatically in individual cases.

## 4.8 Safety and tolerability of monoclonal antibodies

Basically, few treatment-related adverse effects were observed when taking monoclonal CGRP antibodies over a period of use of one year. The adverse effects of CGRP antibodies were for the most part mild and cannot be attributed to the CNS. The latter fact contributes significantly to the acceptance of the substances. It must be noted that the trials mainly treated migraine patients who were otherwise healthy. There was hardly any previous experience in patients with additional diseases and the observed side effect spectrum thus essentially refers to otherwise healthy migraine patients.

The most common adverse effects of the CGRP receptor antibody erenumab across all trials were nasopharyngitis and upper respiratory tract infections, both of which were equally common as placebo (382, 385, 426). With placebo and active substance, local pain, reactions at the injection site and itching were found in about 2% of the patients.
Allergic adverse effects (anaphylaxis) were rarely seen. Slightly more constipation was observed in the STRIVE trial with the 140 mg dose (3.4%) than with 70 mg (1.6%) and 1.3% after placebo (382). However, this observation was not consistently observed across all erenumab trials (385, 426). Muscle spasms were observed in 2% of patients after administration of erenumab (385). The US Food and Drug Administration (FDA) points out that after the approval of erenumab in the USA, isolated cases of severe constipation, sometimes with the need for surgery, were observed. The problem of constipation in the case of pre-existing constipation or simultaneous intake of obstipating substances requires special clarification and must be taken into account.

When treating migraine patients with CGRP monoclonal antibodies, there is a subgroup of patients who are at risk for immunologically induced inflammatory complications from CGRP inhibition (437, 438). Inhibition of CGRP can cause both pro- and anti-inflammatory effects. This may promote local inflammation. Conversely, CGRP also induces the innate immune response in the skin. The immunological effects of inhibiting CGRP in the skin may therefore vary.

CNS adverse effects were rare and no more frequent than with placebo. This is another indication that the monoclonal antibodies do not cross the blood-brain barrier and do not become directly active in the CNS. Serious adverse events were most common in CM patients, with a maximum of 3% in the erenumab 70 mg group, but these were not significantly more common than with placebo and were generally not causally related to the administration of erenumab.
Adverse effects were also no more frequent with the use of erenumab over one year than in the double-blind trial phases (439). There were four cardiovascular events reported for erenumab. All events were explained by pre-existing severe coronary artery disease (n = 2), substance abuse (n = 1) or genetic predisposition (n = 1). Constipation is relevant with all monoclonal antibodies, but this is rarely severe.

Galcanezumab shows fewer treatment-related adverse effects compared to placebo (394, 395, 406). Here, up to about 15% of patients report pain or local reactions at the injection site (itching/erythema/swelling), which was slightly more frequent than with placebo. Constipation was observed in 1-1.5% and dizziness in 0.7-1.2% in the 120 mg and 240 mg doses, respectively. Numerically, this is more frequent than with placebo. The standard dosage was the monthly administration of 120 mg galcanezumab. No deaths have been reported, and likewise no serious adverse effects attributable to galcanezumab.

Approximately 24–30% of patients report pain on injection after administration of fremanezumab and similarly, slightly more patients report local injection site reactions such as erythema (up to 1%) or induration (<17%) after administration of the antibody in the trials than after placebo (391, 392, 440). The results for monthly and quarterly administration do not differ. Bladder infections were numerically more frequent with fremanezumab (3.4% quarterly dose) vs. 1.4% with placebo. In a pooled data analysis of all tolerability data, this effect was no longer evident (440).

All safety data was based on trials of over 2500 treated patients in each case. In addition, about 1500 patients were treated with erenumab for at least one year, 279 patients were treated with galcanezumab and 1400 with fremanezumab for one year. Patients over 65 years of age were excluded from the trials with erenumab and galcanezumab, and only 2% of the patients with fremanezumab were over 65 years of age, so no statements on adverse effects can be made for this patient group. Similarly, minors were excluded from the trials. Patients with relevant pre-existing conditions were not included in the trials, so special caution was urged in this regard.

Monoclonal antibodies can lead to an increase in blood pressure. This is particularly the case with erenumab. In individual cases, antihypertensive treatment may be necessary (441).

## 4.9 Contraindications and warnings

In the phase II and III trials, patients with acute or severe cardiovascular diseases and autoimmune diseases were excluded. In these patients, a CGRP antibody or CGRP receptor antibody should be prescribed only in justified individual cases, based on pathophysiological considerations, until safety data were available.

Erenumab at a dose of 140 mg i.v. was the only antibody studied in patients with stable angina pectoris in severe cardiovascular disease using an ergometer test (442). Here, there was no difference to placebo in all target parameters for placebo administration. Neither the time to ST-segment depression, nor the time to angina pectoris symptoms, nor the time to discontinuation of the ergometer test were affected by erenumab administration. Unfortunately, no comparable trials are available for direct CGRP antibodies.

Furthermore, antibodies against CGRP or the CGRP receptor should, as a precaution, not be used in patients with symptomatic coronary heart disease, ischaemic insult, subarachnoid haemorrhage, peripheral arterial occlusive disease, COPD, pulmonary hypertension, Raynaud's disease or after organ transplants.

Monoclonal antibodies against CGRP or the CGRP receptor must not be used during pregnancy and lactation. They can cross the placenta from day 90 via an active transport mechanism and should therefore be discontinued in any case when pregnancy occurs. In principle, women of childbearing age should use contraception. An interaction with contraceptives has been investigated for erenumab and is unknown. An interaction with other antibodies and immunologically active drugs is not known for the monoclonal antibodies.

There is currently no information on tolerability and safety for children and adolescents. Monoclonal antibodies should also not be used in patients with inflammatory bowel disease or wound healing disorders until further notice. This recommendation is based on the theoretical risk of inhibition of CGRP and not on published adverse drug reactions.

## 4.10 Details relating to cost reimbursements

The monoclonal antibodies eptinezumab, erenumab, fremanezumab and galcanezumab are approved in Germany for migraine preventive treatment in adults with at least four migraine days per month. Authorised and prescription-only medicinal products are in principle reimbursable, unless they have been explicitly excluded from reimbursement by the G-BA. These prescription restrictions and exclusions are defined in Annex 3 of the Medicines Directive. There are no regulations on CGRP antibodies in this appendix. All CGRP antibodies are therefore fully reimbursable in Germany within the scope of their approval. However, prescriptions can be subject to a performance audit like other medicines.

In the early benefit assessment procedure, the Federal Joint Committee (G-BA) identified an additional benefit for erenumab, fremanezumab and galcanezumab in certain subgroups. This process has not yet been completed for eptinezumab. The Statutory Health Insurance Association (GKV) and the manufacturers then negotiate the price on the basis of the benefit assessment. In addition to the amount of reimbursement, the Statutory Health Insurance Association (GKV) and the manufacturers can also agree that drug prescriptions for indications for which the G-BA has assigned an additional benefit to the active substance can be considered a special case in practice in performance audits. If a special case in practice can be considered for the drug, this reduces the prescription volume and lowers the probability of exceeding the guideline volume. A special case in practice has now been identified for erenumab, fremanezumab and galcanezumab. For recognition, detailed documentation is necessary, which can be requested from the Joint Examination Facilities in an audit procedure. In particular, indication according to the ICHD-3 criteria, the number of migraine days per month and the extent of disability in daily life as well as the individual previous treatments should be documented in the medical record so that the decision to prescribe a monoclonal antibody can be justified according to the above criteria.

In addition, health insurance companies have the option of concluding discount agreements on the various products, and individual selective contract regulations may exist to regulate the cost-efficacy of prescriptions for CGRP antibodies.

**Regulations for erenumab**

Prescriptions of Erenumab are to be recognised as special cases in practice from 01.04.2022 in accordance with Sec. 130b(2) German Social Code (SGB V) with an additional benefit according to the G-BA decision of 02.05.2019 as well as 21.10.2021 from the first case of treatment. The special cases in practice apply exclusively to:

- Adults with at least four migraine days per month for whom treatment with at least one migraine preventive treatment (metoprolol, propranolol, flunarizine, topiramate, amitriptyline or clostridium botulinum toxin type A) was unsuccessful or not tolerated.
- Adults with at least four migraine days per month for whom none of the above agents for migraine preventive treatment are suitable. Non-suitability must be documented.

All other patients are explicitly not covered by the special cases in practice. The specifications of the summary of product characteristics must be taken into account. For patients who have not shown a response after three months of treatment, the follow-up prescription is no longer covered by the special cases in practice.

**Regulations for fremanezumab**

According to the agreement pursuant to Section 130b (1) sentence 1 SGB V between the Statutory Health Insurance Association (GKV) and the manufacturer of fremanezumab, the medicinal product is to be prescribed exclusively for migraine preventive treatment in the patient group for which the G-BA has determined an additional benefit in the decision pursuant to Section 35a (3) SGB V of 19 September 2019. This patient group is:

- Adults with at least four migraine days per month who do not respond to, are not suitable for, or cannot tolerate any of the drug treatments/active substance classes mentioned (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A – the latter according to the approval only for chronic migraine).

Fremanezumab is to be recognised by the review body (Sec. 106c SGB V) from 15.05.2020 from the first treatment case exclusively in the above-mentioned patient group with additional benefit according to the G-BA decision of 07.11.2019 as a special case in practice.

**Regulations for galcanezumab**

Galcanezumab is to be prescribed exclusively in the patient group for which the G-BA has determined an additional benefit in the decision pursuant to Section 35a (3) SGB V of 19 September 2019. This patient group is:

- Adults with at least four migraine days per month who do not respond to, are not suitable for, or cannot tolerate any of the drug treatments/active substance classes mentioned (metoprolol, propranolol, flunarizine, topiramate, amitriptyline, clostridium botulinum toxin type A – the latter according to the approval only for chronic migraine).

Galcanezumab is to be recognised by the review body (§ 106c SGB V) from 01.04.2020 onwards as a special case in practice exclusively in the patient group with additional benefit according to the G-BA decision of 19.09.2019. This does not include other indications, patient groups or extensions of the indication for galcanezumab.

**General regulations**

Initiation and monitoring of treatment should be carried out by doctors experienced in the diagnosis and treatment of patients with migraine. The success of the treatment should be assessed three months after the start of treatment. Any further decision to continue treatment should be made individually for each patient. It is recommended to check regularly afterwards whether further treatment is necessary. Recognition as a special case in practice does not apply in the case of use outside the legally defined conditions in the context of non-intended use (off-label use). Doctors are not released from the requirements of Section 12 of the German Social Code, Book V (SGB V) (services must be economical and appropriate and must not exceed what is necessary) and Section 9 of the Medicines Directive.

**Prescriptions in the field of private health insurance**

The aforementioned regulations formally concern statutory health insurance, but not private health insurance. Unless otherwise stipulated in the individual insurance contract, medicines approved here are deemed eligible for reimbursement if the indication from the summary of product characteristics (at least four migraine days/month) is observed.

**Figure 3: Prescription criteria for fremanezumab and galcanezumab within the scope of the nationwide special cases in practice**

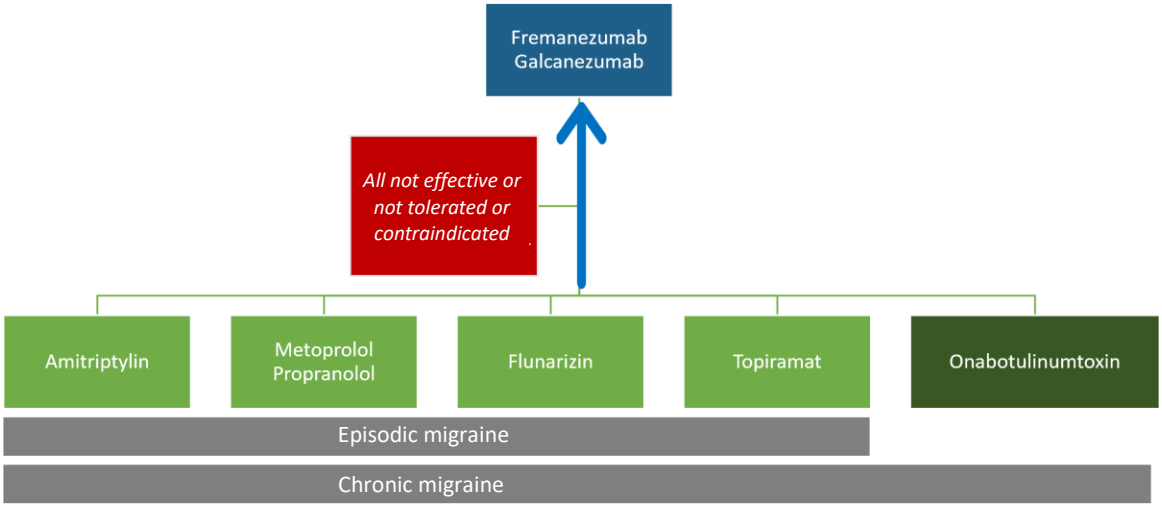
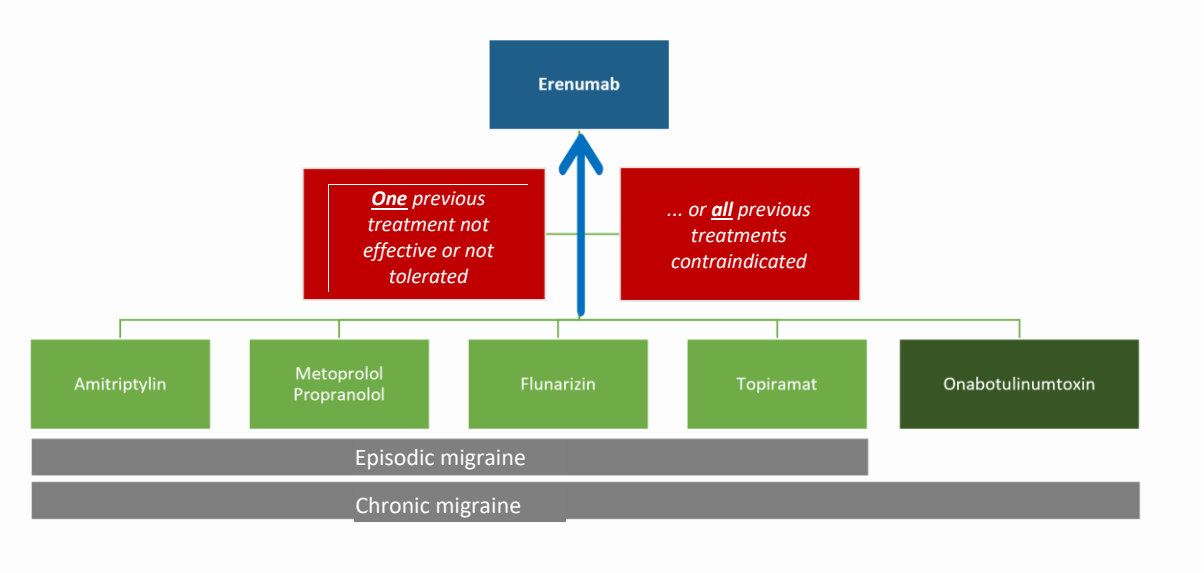


Figure 4: Prescription criteria for erenumab within the scope of the nationwide special cases in practice




## 4.11 OnabotulinumtoxinA as migraine prevention treatment

**Recommendations**

- OnabotulinumtoxinA is only effective in the treatment of chronic migraine with and without overuse of analgesics and migraine medications. OnabotulinumtoxinA should be used in this indication by neurologists experienced in the diagnosis and treatment of chronic headaches.
- OnabotulinumtoxinA should be used for 2–3 treatment cycles at three-month intervals before deciding on efficacy.
- There is evidence that the higher dosage (195 units) has a better effect than the lower dosage (155 units). The effect may increase with the duration of the treatment.
- If there is a good response, the dosing interval can be extended to e.g. four months or a discontinuation test can be made.

### 4.11.1 Indication and mechanism of action

OnabotulinumtoxinA (BoNT-A) is effective in the treatment of chronic migraine, that is, in the presence of 15 or more headache days of which at least eight fulfil the criteria of migraine, with or without overuse of analgesics and/or triptans. Treatment with BoNT-A is recommended if two previous oral preventive treatments were not sufficiently effective (443). Different mechanisms for the effect of BoNT-A in migraine preventive treatment are discussed: First, injections of BoNT-A into the trigeminal innervation area are thought to reduce peripheral sensitisation and neurogenic inflammation (444). Mediators such as glutamate, calcitonin gene-related peptide (CGRP) and substance P play a decisive role here. Pathophysiologically, in chronic migraine, it is hypothesised that the reduced secretion of these mediators by BoNT-A indirectly suppresses central sensitisation (445).

On the other hand, BoNT-A appears to block further peripheral sensitisation via a blockade of relevant nociceptive receptors and ion channels, including transient receptor potential cation channel subfamily V, subtype 1 (TRPV1) or transient receptor potential ankyrin 1 (TRPA1) (446). Alternative hypotheses could not be confirmed in vivo that BoNT-A has a direct effect on central pain processing via retrograde transport of peripheral nociceptive neurons and further central transcytosis (447). The injections of BoNT-A lead to an inhibition of the release of acetylcholine at the presynaptic vesicles. The effects are dose-dependent and reversible. It is assumed that the effect starts after 2–3 days, reaches its maximum after two weeks and ends after 2–4 months due to axonal sprouting (448).

### 4.11.2 OnabotulinumtoxinA for the treatment of chronic migraine

In two large phase III trials with a total of 1384 patients, the efficacy of BoNT-A in chronic migraine was demonstrated compared to placebo (phase 3 REsearch Evaluating Migraine Prevention treatment Therapy, PREEMPT 1 and 2) (449, 450). According to a standardised procedure, 155 or 195 IU were administered every 12 weeks to 31 sites from 7 specific sites of the head and shoulder muscles (add-on administrations of an additional 40 IU after "follow the pain" were possible). In PREEMPT 1, the frequency of headache attacks was defined as the primary endpoint, and in PREEMPT 2, the reduction in mean headache days from week 24 was defined as the primary endpoint. Pooled analyses showed a statistically significant difference for the primary endpoint, with a reduction of 8.4 headache days versus 6.6 days in the placebo arm ($p < .001$) (401). All other secondary endpoints were also positive except for the frequency of taking the acute treatment drugs. About one third of the patients did not respond to ≥ 3 oral preventive treatments. About 40% of the patients had no oral preventive treatment at baseline. Adverse effects occurred in 62.4% of patients in the verum arm (versus 51.7% in the placebo group). The most common treatment-related adverse events were neck pain (verum 6.7% versus 2.2% placebo), muscle weakness in 5.5% (0.3%) and ptosis in 3.3% (0.3%). In general, the adverse effects were mild and transient, and 3.8% (1.2%) of patients discontinued participation in the trial because of these adverse effects. There was a continuous decrease in headache frequency during the first year of treatment with 12 weekly injection intervals. In patients with acute treatment overuse (65.3% of patients) and chronic migraine, a reduction in the primary endpoint of -8.2 days versus -6.2 days ($p < .001$) was achieved (402).

The results of the efficacy and tolerability of the onabotulinumtoxinA treatment of the PREEMPT trials were able to be confirmed in several other trials: in a multicentre, single-arm, open-label, prospective phase IV COMPEL trial, 716 patients received up to 9 cycles of 155 IU BoNT-A at 12-week intervals according to the PREEMPT protocol. There was a sustained benefit of BoNT-A treatment for the primary endpoint in terms of reduction in monthly headache frequency at week 108 (-10.7 headache days; $p < .0001$) (451). The secondary endpoints HIT-6 score, migraine-related impairment (migraine disability assessment questionnaire), health-related quality of life, sleep disturbance (Pittsburgh sleep quality index), fatigue (fatigue severity scale), depression (9 item patient health questionnaire) and anxiety disorder (7 item generalised anxiety disorder assessment) also showed significant improvement between baseline and week 108 ($p < .001$). Although the trial designs were different, there was a comparable clinical benefit in the target parameters (451).

Several real-world trials support the efficacy of BoNT-A treatment for the treatment of chronic migraine. In a multicentre prospective REPOSE trial, 641 patients from 78 centres in Germany, Italy, Norway, Russia, Sweden, Spain and the UK received BoNT-A treatment for two years (452). 79.1% of patients received BoNT-A injections for at least one treatment 13 weeks after the last injection. Almost half of the patients suffered from overuse of acute medication at baseline. One third of the patients also received the "follow the pain" injections after PREEMPT, which was not the case in the COMPEL trial. Comparable to the results of the above clinical trials, BoNT-A therapy showed a significant and sustained reduction in monthly headache days compared to baseline (headache days baseline 20.6 (5.4) vs. 7.4 (6.6) headache days at 8th dose; p <.001). Other outcome parameters such as migraine-specific quality-of-life questionnaire (MSQ), EuroQol 5-dimension questionnaire (EQ-5D) were also improved at each measurement time point compared to baseline, which was already evident in the interim analyses (p <.001). One fifth of the patients reported mild to moderate adverse effects after BoNT-A treatment.

Further real-world trials have been able to confirm the efficacy and tolerability of BoNT-A treatment for different periods of time: an Italian trial of 172 patients showed that administration of 195 IU versus 155 IU BoNT-A produced significantly better efficacy in terms of mean reduction in headache and migraine days, days of acute medication use, and reduction in Head Impact Test-6 over a two-year period (p <.001). In the cohort, mean days of acute medication use were 20.8 +/- 4.5 (155 IU) versus 21 +/- 5.1 (195 IU) (453). Similar results for a treatment period of two years were seen in studies from Canada (454, 455), the United Kingdom (452), for a treatment period of three years (456, 457) and four years (458). A meta-analysis of the treatment of chronic migraine with onabotulinumtoxinA supports efficacy from real-world data over the past ten years (459).

About a quarter of patients may experience a wearing-off effect after the first administration, typically 2–4 weeks before the follow-up injection. No exact reasons or predictors for this are known. A dose increase showed sustained efficacy of BoNT-A in up to 75% of patients (460, 461). The doses of BoNT-A should be given at three-month intervals for one year of treatment (462). Subsequent stretching of the intervals to four months was possible in about 40% of patients, and about 45% deteriorated under the extended interval, so the three-month intervals were resumed (463). In another prospective trial, 49% of 276 patients showed fewer than five migraine days in two 12-week cycles after completing BoNT-A treatment. At six-month follow-up, 80% of these patients still showed no clinical deterioration (464). It is recommended that, if the interval is successfully stretched to four months and the clinical course is stable, a BoNT-A discontinuation test should be made after at least two four-month intervals (443). NICE in the UK considers at least a 30% reduction in monthly headache days after two cycles of BoNT-A to be necessary to justify continuation of treatment (465). If a 30% reduction in headache days is not achieved after two cycles of BoNT-A (taking into account a dose increase to 195 IU), then treatment with BoNT-A- should be discontinued (443). The indication for BoNT-A treatment should be initiated after at least two to three oral migraine preventive treatments in accordance with treatment guidelines (443), if possible with topiramate based on its evidence base in chronic migraine (305).

A Cochrane review of 28 randomised controlled trials showed a reduction of 3.1 migraine days (95% CI 1.4–4.7) and 1.9 headache days (95% CI 1.0–2.7) at six months for treatment of chronic migraine with BoNT-A (466).

In a randomised, prospective, multicentre FORWARD trial of 282 patients, the treatment arm of patients receiving 155 IU of onabotulinumtoxinA was superior to the treatment arm of 50–100 mg of topiramate at week 32 in the 50% responder rates (40% [56/140] vs. 12% [17/142], OR, 4.9 [95% CI, 2.7–9.1]; p <.001) (467). Two RCTs, each with about 60 patients, showed comparable efficacy of BoNT-A versus topiramate (daily dose 100–200 mg), but with fewer adverse effects in the BoNT-A arm (468, 469). Similar results in the target parameters were seen in the randomised-controlled trial with 250 mg valproate (470) and with 25–50 mg amitriptyline (471). Preclinical data have shown synergistic effects of a combination treatment of BoNT-A and with CGRP-based treatments with respect to clinical target parameters, which has been attributed to the different pathophysiological modes of action (472). To date, there is no prospectively collected data on this combination treatment. There is still no firm data on combination treatments with oral preventive treatments and BoNT-A. In several real-world trials, combination treatments of at least one oral migraine preventive treatment and BoNT-A were established in 50–93% of patients (463, 473). In one study, the oral prophylactic was discontinued after the 3rd BoNT-A administration in 45.2% of cases or the dose was reduced in 13.9% (474).

An Italian study using pooled real-world data from 16 European headache centres observed that an excellent onabotulinumtoxinA response after the 1st dose in chronic migraine was a predictor (defined as ≥ 75% reduction in monthly headache days) of treatment response after the third dose. The rate of excellent percentage-based responders was 10% and the rate of frequency-based responders was 3% after three injection intervals (475).

In a UK study, 56.2% of patients with chronic migraine and overuse of acute medication had a ≥ 30% reduction in monthly headache days, compared with 64.9% of patients with chronic migraine alone, supporting the efficacy of BoNT-A therapy in MO (476). The efficacy of BoNT-A for this subgroup was also confirmed in the large RCT (402) and in a pooled analysis of real-world data from 16 European headache centres (475). In a study from Spain with 115 patients, 61.9% of the patients no longer overused the acute medication under BoNT-A therapy (474).

A systematic review comparing cost-benefit analyses of CGRP-based treatments and onabotulinumtoxinA in chronic migraine showed that the treatment of chronic migraine has a favourable incremental cost-benefit ratio compared with placebo (477). The PREDICT trial identified the benefit of onabotulinumtoxinA treatment for chronic migraine in terms of resource use in the Canadian healthcare system. In the prospective Canadian trial, 123 patients with chronic migraine were treated with seven cycles of onabotulinumtoxinA according to the PREEMPT regimen. Other parameters such as work productivity or frequency of taking acute treatment were significantly improved between baseline and after 2 years of treatment ($p < .001$) (455). The positive effect of onabotulinumtoxinA treatment in chronic migraine on resource use parameters was also seen in other trial populations and health systems, such as the US COMPEL and the European REPOSE trial.

### 4.11.3 OnabotulinumtoxinA for the treatment of episodic migraine

OnabotulinumtoxinA treatment has no evidence of efficacy for the treatment of episodic migraine compared with placebo, as shown in several meta-analyses and reviews (466, 478–480). However, in one small, single-arm, open-label Italian study of 32 patients with high-frequency episodic migraine (8-14 monthly migraine days), there was a significant reduction in monthly headache days of 3.68 migraine days 12 weeks after the 4th course of onabotulinumtoxinA to PREEMPT ($p < .001$) (481). Another trial is currently being conducted to investigate its efficacy in the treatment of episodic migraine (NCT05028569).

## 4.12 Meta-analyses on the efficacy of monoclonal antibodies

**Recommendation**

- Meta-analyses show no differences between the four monoclonal antibodies against CGRP or the CGRP receptor in terms of efficacy, measured as reduction in migraine days per month or the 50% responder rate.

A systematic literature search and meta-analysis in patients with episodic migraine included 13 trials with 7557 patients (482). All trials investigated the difference in migraine days per month between monoclonal antibodies to CGRP (CGRPmAb) (n = 3326) and placebo (n = 2219). Placebo-subtracted data for reduction in monthly migraine days was -1.55 days (95% CI -1.86 to -1.24; $p < 0.001$) in favour of CGRP(R) monoclonal antibody over placebo. The results for topiramate (n = 1032) vs. placebo (n = 543) are based on four trials. Patients treated with topiramate showed a greater reduction in monthly migraine days compared to placebo of -1.11 days (95% CI – 1.62 to -0.59). The rate of adverse effects was significantly higher with topiramate than with CGRPmAb.

Another comparison between CGRPmAb and classic preventive treatments (topiramate, valproate, onabotulinumtoxinA, candesartan, flunarizine, amitriptyline etc.) in chronic and episodic migraine was described by Vandervorst et al (483). After analysing a total of 67 trials (21 for CGRPmAB and 46 for the classical migraine preventive treatments), the reduction in mean migraine days ranged from 0.9 to 2.2, with the highest reduction shown for CGRPmAb. The different population sizes in the individual trials must be critically evaluated here. With regard to the adverse effects rate, the CGRPmAb were superior.

Wang et al. (484) conducted a systematic literature review and network meta-analysis. They analysed 18 randomised trials with 8926 patients treated with monoclonal antibodies against CGRP or the CGRP receptor. The primary endpoint was a change in migraine days per month, with the different doses of monoclonal antibodies pooled for the meta-analysis. The meta-analysis showed an average reduction in migraine days per month compared to placebo of -1.4 to -2.1 (see table 13).

**Table 13: Episodic migraine, reduction in migraine days per month compared to placebo (484). Mean values and 95% confidence intervals**

| Erenumab | Galcanezumab | Fremanezumab | Eptinezumab |
|---|---|---|---|
| -1.43 (-2.40, -0.84) | -2.10 (-2.76, -1.45) | -2.19 (-2.76, -1.45) | -1.43 (-2.59, -0.36) |

Another meta-analysis examined the at least 50% responder rate for CGRPmAB, topiramate and onabotulinumtoxinA in episodic and chronic migraine (301). 32 trials were evaluated. The trials investigating monoclonal antibodies included 13,302 patients and yielded pooled odds ratios for the at least 50% response rate for migraine day reduction of 2.30 (95% CI: 2.11–2.50). See Table 14 for details. Topiramate had an overall effect estimate of 2.70 (95% CI: 1.97–3.69) in 1989 included patients. OnabotulinumtoxinA achieved 1.28 (95% CI: 0.98–1.67) in 2472 included patients. However, it must be taken into account that for onabotulinumtoxinA, trials in episodic migraine were also included in the analysis, although onabotulinumtoxinA was not effective in episodic migraine.

**Table 14: Odds ratio for the at least 50% response rates for episodic and chronic migraine (301)**

| Erenumab | Galcanezumab | Fremanezumab | Eptinezumab |
|---|---|---|---|
| 2.25 (1.69–3.00) | 2.41 (2.11–2.75) | 2.58 (2.26–2.95) | 2.02 (1.71–2.38) |

Similar results were found in four other meta-analyses (485–488).

In summary, the meta-analyses show no differences in the efficacy of the monoclonal antibodies. The average reduction in migraine days per month compared to placebo was between 2.7 and 2.4. The 50% responder rates do not differ, either.

# 5 Prevention treatment – rimegepant

**Recommendations**

- The CGRP receptor blocker rimegepant is effective in preventing episodic migraine and is approved in Germany but not yet available (as of 12/2022).
- Rimegepant is suitable for patients for whom the "classic" migraine preventive treatments are not effective, are not tolerated or if contraindications exist.
- Rimegepant has a good tolerability.

In addition to preventive treatment with monoclonal antibodies against CGRP or the CGRP receptor, gepants also address the CGRP pathway as CGRP receptor blockers. Initially, they were developed to treat acute migraine attacks. Rimegepant has also been studied in migraine preventive treatment and has been approved for preventive treatment in the USA and Europe.

In the EU, the EMA granted market approval for rimegepant on 27 April 2022 for the acute treatment of migraine with or without aura and for the preventive treatment of episodic migraine in adults with at least four migraine attacks per month. This makes rimegepant the first drug to be approved for both acute and preventive treatment of migraine. It is administered every second day. Use is limited in the US to a maximum of 18 doses per month and one dose per day. For preventive treatment, Rimegepant is administered every 2nd day. It is not yet clear when exactly the drug will be launched on the market.

## 5.1 Rimegepant

The efficacy of rimegepant was studied in a multicentre, randomised, double-blind, placebo-controlled trial in the USA (489). The trial lasted a total of 12 weeks. 747 patients with episodic migraine (average 10.1 monthly migraine days) were randomised. After a 4-week baseline phase, 373 patients received 75 mg of rimegepant every other day and 374 patients received placebo. After 9–12 weeks, the number of monthly migraine days was reduced by -4.3 days with rimegepant (95% CI -4.8 to -3.9) and by -3.5 days with placebo (95% CI -4.0, to -3.0; $p < 0.01$). A $\geq$ 50% response (= secondary endpoint) was achieved by 49% (95% CI 44 – 54) of patients on rimegepant and 41% (95% CI 36 to 47) on placebo ($p = 0.044$). The tolerability of rimegepant was similar to that seen in the pivotal trials for acute treatment.

Adverse drug events (ADEs) occurred with equal frequency (36% each) with rimegepant and placebo. Nasopharyngitis and nausea were more common with rimegepant (4% and 3%) than with placebo (2% and 1%). Under rimegepant, 2% (n = 7) and under placebo, 1% (n = 4) of patients discontinued the trial. No serious ADEs occurred. In summary, the study showed that Rimegepant 75 mg every 2nd day had a small effect in the preventive treatment of migraine. However, with an average decrease in monthly migraine days of one day, rimegepant was slightly less effective in indirect comparisons than, for example, anti-CGRP monoclonal antibodies or traditional migraine preventive treatments, but showed a remarkably low rate of ADEs. In an indirect comparison, this was even lower than the rate of ADEs with treatment with monoclonal antibodies.

Health-related quality of life was assessed in a post-hoc analysis of a long-term safety trial in 1800 patients with episodic migraine (490). Based on the monthly migraine days (MMT) in the baseline, three patient groups were formed, which were then assigned to two treatment arms. 1033 patients with 2–8 MMT and 481 patients with 9–14 MMT took 75 mg rimegepant as needed ("PRN" treatment arm), 286 patients with 4–14 MMT took 75 mg rimegepant every two days and as needed ("QOD + PNR" treatment arm). The observation phase lasted 52 weeks in the PRN groups and 12 weeks in the QOD+PNR group. After treatment with rimegepant, the decrease in MTT from baseline was -0.47 (2–8 MMT), -2.94 (9–14 MMT) and -3.31 (4–14 MMT). Health-related quality of life (mapping EQ-5D-3L utility score) improved by +0.09 (2–8 MMT), +0.10 (9–14 MMT) and +0.12 (4–14 MMT). An intake of 75 mg rimegepant thus not only reduced monthly migraine days, but also improved the health-based quality of life of patients with migraine. The greatest effect was observed in patients taking 75 mg of rimegepant every two days and as needed (QOD+PNR treatment arm).

### 5.1.1 Combination of rimegepant and CGRP monoclonal antibodies

A case report of two women who reported a suboptimal response to multiple migraine medications for at least two decades described the addition of erenumab to prior rimegepant treatment (491). Both patients were part of a long-term, multicentre, open-label trial on the safety of rimegepant 75 mg in the acute treatment of migraine (NCT03266588). In both patients, the additional medication taken in the case of attacks (including NSAIDs) was significantly reduced or suspended with the combination treatment. When using rimegepant alone or together with erenumab, both patients reported no associated ADEs. These two case reports suggest that rimegepant 75 mg may be effective and tolerable for acute treatment with concomitant preventive administration of erenumab.

Another trial investigated the safety and tolerability of combination treatment of rimegepant 75 mg and a CGRP monoclonal antibody (mAb) (492). This trial was also part of the multicentre, open-label, long-term safety trial of rimegepant 75 mg for the acute treatment of migraine (NCT03266588). Included were 13 patients treated with a CGRP-mAb (erenumab [n = 7], fremanezumab [n = 4], galcanezumab [n = 2]) who had between two and eight monthly migraine days. For 12 weeks, patients received rimegepant 75 mg for acute treatment as needed, up to one dose per day. A total of 224 doses of rimegepant 75 mg were administered. ADEs occurred in 5 patients, 2/5 had nasopharyngitis. There were no serious ADEs that might have led to discontinuation of treatment.

To what extent the results of these two case series can be generalised is currently unclear. Further trials regarding the safety of combination treatment are needed. No recommendations for a combination treatment can be given at the moment.

## 5.2 Safety aspects of rimegepant

### 5.2.1 Liver function

Rimegepant belongs to the second generation of gepants. Its chemical structure distinguishes it from the first generation gepants that have been associated with hepatotoxicity (493). The clinical trials on hepatic safety to date have shown an increase in alanine aminotransferase or aspartate aminotransferase concentrations of more than three times the upper limit of normal in only a few patients (494–497). None of the trials fulfilled the Hy's criteria (group of findings for serious, substance-related liver damage) (498).

Rimegepant is safe. No serious adverse hepatotoxic events have been reported to date. Rimegepant is not FDA approved for the treatment of migraine patients with severe hepatic impairment (Child-Pugh C) (499, 500).

### 5.2.2 Cardiovascular functions

Rimegepant is not vasoconstrictive but prevents vasodilation by CGRP. Studies have not reported any ischaemic events to date (494, 495, 497, 501). However, patients with many cardiovascular risk factors or patients with manifest cardiovascular disease were excluded from the trials. In addition, a recent animal trial in mice showed that the CGRP receptor antagonists olcegepant and rimegepant increase the risk of stroke, significantly increase infarct volume and significantly worsen functional outcome (502). These effects were mediated via disruption of the pial collaterals. The question of cardio- or cerebrovascular safety has thus not yet been conclusively clarified. Although the FDA and EMA approvals do not list any restrictions in this regard, gepants such as rimegepant should not be used for migraine preventive treatment in patients at high cardiovascular risk or with cardiovascular disease.

# 6 Special situations in migraine prevention treatment

## 6.1 Preventing migraine and comorbid conditions

**Recommendations**

- If migraine is accompanied by comorbid depression, amitriptyline (75-150 mg) should be used as the first-line treatment, alternatively venlafaxine (150-225 mg).
- Amitriptyline or venlafaxine are also used for comorbid anxiety disorder.
- Epilepsy is slightly more common in patients with migraine than without: the drug of choice for preventive treatment is then topiramate. Alternatively, lamotrigine or levetiracetam can be used if migraine and epilepsy are present at the same time.
- In the case of concomitant vascular diseases (stroke, coronary heart disease), the patient's risk profile should be taken into account in the choice of migraine preventive treatment (e.g. candesartan in arterial hypertension).
- Lamotrigine or acetazolamide can be used for hemiplegic migraine.
- In children, primarily non-medication measures should be used for migraine preventive treatment. Migraine preventive treatment with medication remains a reserve due to moderate to low evidence, the only approved drug is propranolol.
- Possible drug preventive treatments in pregnancy are metoprolol, propranolol and amitriptyline.
- Short-term use of triptans or NSAIDs can be used for preventive treatment of menstrual migraine.

### 6.1.1 Psychiatric comorbidity

Population-based trials have shown an increased risk of depression for migraine patients (OR 2.0–5.8) (503–507), with this association being strongest for migraine with aura (505) and most prevalent in women (508). The bidirectional association analyses indicate a familial coaggregation of migraine and depression (509). Comorbid depression is a risk factor for chronicity of migraine (510, 511) and the development of headache due to overuse of analgesics or migraine medications (512). For patients with chronic migraine, MOH is associated with an increased risk of suicidal thoughts and attempts. There is a need for research with regard to a causal relationship and pathophysiology (513). Patients with migraine and depression may also represent a pathophysiologically distinct subgroup. Recent data from 1410 patients with depression showed that the comorbidity of major depression and migraine resulted in significantly higher functional disability and poorer response to antidepressant pharmacotherapy. First-line antidepressant treatment showed a trend towards agomelatine in this cohort.

Migraine patients have an almost fourfold increased risk of generalised anxiety disorder (514, 515) and a significantly increased risk of bipolar disorder (515). Women with migraine show significantly higher anxiety and depression scores than men (516). Patients with menstrual migraine experience significantly greater limitations in health-related quality of life, which correlates with higher depression and suicidal thoughts (513). Furthermore, migraine was a risk factor for anxiety in pregnancy and peripartum depression (517).

Data in 468 patients with migraine show a positive linear correlation between the number of headache days per month and the risk of anxiety ($r = 0.273$; $p < 0.001$) and depression ($r = 0.337$; $p < 0.001$) (518). The risk of anxiety was higher in patients with ≥ 3 headache days per month, patients with ≥ 19 headache days per month have a greater risk of depression. Accordingly, patients with ≥ 3 headache days per month should be examined for the presence of an anxiety disorder.

A longitudinal trial of bipolar disorder type I in 538 patients showed, in connection with comorbid migraine a) greater depressiveness and b) increase in manic symptoms when taking lithium (519). The authors conclude that lithium is contraindicated in bipolar disorder type I and concomitant migraine.

Post-traumatic stress disorder (PTSD) was found about five times more often in patients with chronic migraine than in controls, but also three times more often than in chronic tension headache (520).

A trial of the effects of the SARS-CoV-19 pandemic on patients with migraine showed that depression, anxiety and sleep disturbance increased and correlated with the transition from episodic to chronic migraine (521).

Amitriptyline was particularly suitable for migraine preventive treatment in patients with depression, although the dose must then be in the antidepressant range (75–150 mg/d). Flunarizine is contraindicated in the presence of depression, and topiramate is relatively contraindicated.

SNRIs can be used in patients with an anxiety disorder. There is also evidence for a migraine preventive treatment effect for venlafaxine (329, 330). A recent trial of 80 patients with episodic migraine directly compared amitriptyline 25mg/day and venlafaxine 37.5mg/day in patients with migraine without depression after eight weeks of treatment, showing a comparable effect with significant reduction in monthly migraine days and limitation of daily life in both groups, with a higher adverse effects rate in the amitriptyline arm (331). An analysis of 285 RCTs with a total of 53,533 patients studied does not show depression as a possible adverse effect of betablockers; consequently, depression is not a contraindication for beta-blocker treatment (522). However, the analysis showed an increase in sleep disturbances with beta-blocker treatment, which was why these were considered a relative contraindication (522). Betablockers can, on the other hand, reduce anxiety symptoms and, in patients with panic attacks, dampen the vegetative symptoms that accompany the attacks. There is evidence that preventive treatment with propranolol 160 mg/day in patients with chronic migraine produces equivalent effects to treatment with topiramate 100 mg/day with comparable tolerability (523).

Prophylactic onabotulinumtoxinA treatment of patients with chronic migraine showed a reduction in symptoms of anxiety and depression (524).

In treatment trials with fremanezumab, subgroup analyses in patients with comorbid depression and anxiety disorder showed a significant decrease in the number of patients receiving antidepressants (baseline, 68.6%; follow-up, 56.4%; p = 0.0025) or anxiolytics (baseline, 55.0%; follow-up, 47.2%; p = 0.037) (525). Patients with migraine and accompanying depression showed a reduction in migraine-related limitation of daily life as well as depressive and anxiety symptoms in trials with fremanezumab or galcanezumab (526–528).

Epidemiological trials show a prevalence of up to 48% sleep disturbances in patients with migraine (529). The bidirectional relationship between sleep and migraine also plays a major role in the clinical course of patients (530).

### 6.1.2 Epilepsy

Migraine is weakly but significantly associated with the occurrence of epilepsy (531–534). In addition, there are diseases that are associated with both migraine and epileptic attacks, e.g. mitochondrial diseases (535). The prevalence of epilepsy is about 2–3 times higher in patients who have migraine (536, 537). Children with epilepsy, but also adults with epilepsy, also have a significantly increased risk of developing migraine (536, 538). Comorbidity typically occurs in a special form of childhood epilepsy – idiopathic occipital epilepsy – and the attacks were accompanied by cortical visual disturbance, which was difficult to differentiate from an aura. Migraine aura can be differentiated from epileptic visual disorder based on the duration (migraine aura longer than five minutes), whether it is limited to a hemifield and always on the same side (epileptic disorder) and the centrifugal spread (migraine) (539). In patients with both conditions, topiramate or valproic acid or, in patients with isolated auras, lamotrigine are recommended for migraine preventive treatment. Ictal or postictal migraine headache responds to migraine-specific medication (540). In addition, levetiracetam can be used as an alternative to topiramate in comorbid epilepsy, which in one paper resulted in a 50% reduction in headache frequency (362). Furthermore, perampanel could be used in migraine, which was able to inhibit CGRP in vitro (541, 542).

### 6.1.3 Vascular diseases

There is no indication for the administration of acetylsalicylic acid in women who suffer from migraine with aura and have not yet suffered a cerebrovascular event. Women with frequent migraine attacks with aura and vascular risk factors have a slightly increased absolute risk of ischaemic insults, cerebral haemorrhage and myocardial infarction.

In principle, the risk factors (hypertension, smoking, hyperlipidaemia) must be treated. A large number of epidemiological and case-control trials show an association between migraine with aura in women and vascular events (543–547). As a result, vascular risk factors should be treated in this constellation. However, contraceptives containing oestrogen (548) are not contraindicated in principle, provided that the other risk factors are controlled. In women who suffer from migraine with aura and who have frequent attacks, progestogens should be used as contraceptives. Closure of a patent foramen ovale in migraine does not lead to freedom from attacks, but may reduce the risk of infarction. Patients with metabolic syndrome and migraine should not be treated with valproic acid or amitriptyline for preventive treatment, as these substances can lead to significant weight gain. Topiramate is recommended here. Beta-blockers or sartans are recommended for migraine patients with hypertension. For example, propranolol 160 mg/day can be used, which has been shown to be equivalent to topiramate 100 mg/day in chronic migraine with comparable tolerability (523). It is possible that the combination of simvastatin and vitamin D is effective in preventive treatment (549) and should therefore be discussed in comorbid hyperlipidaemia. In general, a recommendation for regular aerobic endurance sport is particularly appropriate. There is still no human trial data on the CGRP ligand/receptor antibodies and gepants regarding the risk of stroke. To date, only individual case reports have been published, which do not allow any conclusions to be drawn (550). Animal experiments have shown a negative effect of olcegepant (which was not approved in humans) and rimegepant on infarct size in a mouse stroke model (551).

## 6.2 Preventing migraine aura

**Recommendation**

- Lamotrigine, flunarizine or topiramate can be used for preventive treatment of migraine auras.

Lamotrigine is not effective in reducing the frequency of migraine attacks (315), but may reduce the frequency of migraine attacks with aura (312). However, lamotrigine does not have approval for the treatment of migraine auras. Flunarizine causes both a reduction in the frequency of auras and migraine attacks (552). In individual cases, topiramate is also effective (553). For sporadic or familial hemiplegic migraine, an effect of acetazolamide and lamotrigine, also in combination with valproic acid, and of onabotulinumtoxinA has been reported (554–556). Furthermore, a single case trial described a positive effect with non-invasive peripheral stimulation of the vagus nerve (nVNS) for visual and sensory aura (557).

## 6.3 Migraine prevention treatment in children and adolescents

Health insurance data from 56,597 German adolescents aged 15 years showed a 2.1-fold higher risk of developing an additional affective disorder in the next ten years, a 1.8-fold higher risk of neurotic, stress-related and somatoform disorders and a 1.6-fold higher risk of back pain for adolescents with a diagnosis of migraine compared to adolescents without a diagnosis of migraine (558). This underlines the importance of adequate treatment for children and adolescents with migraine. Non-medicinal therapeutic approaches such as education, stress management, relaxation techniques and physical activation should be preferred in migraine preventive treatment in children and adolescents. Group treatment programmes are particularly effective. A recent open-label trial from Germany in 75 children and adolescents with primary headache showed both a significant reduction in headache frequency and an improvement in everyday function after an interdisciplinary multimodal treatment programme (559). A randomised controlled trial showed that cognitive behavioural treatment in addition to drug treatment with amitriptyline is more effective than drug preventive treatment alone in chronic migraine in children aged 10 to 17 years (560). In a retrospective analysis, biofeedback was shown to reduce headache frequency significantly in children aged 8 to 18 years (561).

A meta-analysis of 23 trials (2217 patients) on pharmacological migraine preventive treatment for children and adolescents showed no significant long-term effect in migraine preventive treatment (> six months) for any of the substances studied (topiramate, valproate, amitriptyline, flunarizine, propranolol, nimodipine, coenzyme Q10, riboflavin, L-hydroxytryptophan) compared with placebo. In the short term (<5 months), propranolol and topiramate were significantly more effective than placebo, but the quality of these trials was limited (562).

A pooled analysis of prospective randomised treatment trials of flunarizine in children with migraine found that flunarizine reduced the frequency of headache attacks by 0.4 attacks per four weeks compared with placebo (five trials, 249 participants: difference -0.44; 95% CI -0.61 to – 0.26) (296). The analysis also showed that the efficacy of flunarizine preventive treatment was comparable to that of propranolol (seven trials, 1151 participants, difference -0.08; 95% CI -0.34 to 0.18).

Topiramate was effective in two trials at a dose of 15–100 mg/d and was FDA approved for adolescents with migraine (563, 564). In a large randomised trial in children and adolescents, topiramate and amitriptyline were no more effective than placebo (565). In this trial, however, there was an extremely high placebo effect, so the efficacy of the two substances cannot be conclusively assessed.

A meta-analysis included four controlled trials of topiramate (465 children and adolescents). Of these patients, 329 were assigned to the topiramate group and 136 to the placebo group (566). The meta-analysis showed that, compared with placebo, topiramate did not reduce the number of patients who experienced a relative reduction in headache frequency of ≥ 50% (n = 465, RR = 1.26, 95% CI = 0.94-1.67), did not reduce the number of headache days (n = 465, difference = - 0.77, 95% CI = -2.31-0.76), but did reduce PedMIDAS scores (n = 205, mean difference = -9.02, 95% CI = [-17.34, -0.70], Z = 2.13, p = 0.03). Significantly more adverse effects occurred with topiramate than in the placebo group.

There is some evidence of efficacy for propranolol (567). Valproic acid is not effective in children and adolescents (568). However, a randomised controlled trial of 158 children and adolescents with migraine from Iran showed that cinnarizine and valproate were superior to placebo treatment. Children in this trial were ten years old on average, majority boys (90/158; 57%) and showed a mean of 11 migraine days per month (569). After 12 weeks of treatment, cinnarizine reduced headache frequency by 4.6; 95% CI -5.2 to -4.0, valproate by 4.0; 95% CI -4.8 to -3.3, placebo by 2.6; 95% CI -3.4 to -1.8. Interestingly, the placebo effect was less pronounced in this trial than in other migraine treatment trials involving children. Adverse effects occurred significantly more often in both the cinnarizine and valproate groups than in the placebo group.

A randomised controlled trial of levetiracetam (61 children with migraine; 31 levetiracetam, 30 placebo) showed a significant reduction in migraine frequency and intensity with more frequent adverse effects with levetiracetam (570). 68% of the levetiracetam group and 30% of the placebo group showed at least 50% reduction in migraine days ($p = 0.007$).

Case series as well as a controlled trial show efficacy of botulinum toxin A for chronic migraine in adolescents (571–573) (574). Given the proven benefit in the treatment of paediatric migraine, off-label use should be considered in individual cases. However, further trials are needed to better define the injection regimen, dosage and patient population (574).

In general, there is little evidence for the efficacy of preventive pharmacological treatments for paediatric migraine. Future research is needed to identify factors associated with individual response to pharmacological preventive treatment. In individual cases, drug treatment can also be considered for children and adolescents in cases of high distress and after exhaustion of non-medicinal treatment options. Currently in Germany, only propranolol (0.25–0.5 mg/kg body weight; three to four times daily) is approved for migraine preventive treatment in children.

## 6.4 Migraine prevention treatment during pregnancy

Patients should be informed about the typical course of migraine during pregnancy in order to prevent any anticipatory anxiety: About 50–80% of patients report a decrease in migraine attacks during pregnancy (575). The improvement was particularly marked in the 2nd and 3rd trimesters. However, about 8% experience an increase in headaches during pregnancy. Especially migraine with aura can manifest itself for the first time during pregnancy. In principle, if there is a significant increase or new onset of migraine in pregnancy, it makes sense to carry out a clinical neurological assessment while considering the question of whether diagnostic imaging is needed. Breastfeeding probably has no effect on postpartum headache incidence (576).

Non-pharmacological methods of migraine preventive treatment are considered safe during pregnancy. Patients who are planning a pregnancy should therefore be informed about the individual procedures (relaxation techniques, biofeedback, acupuncture) at an early stage and, if necessary, practise them before the pregnancy begins.

Controlled trials on drug preventive treatment are not available. It is recommended to research the current experience on the use of a substance during pregnancy and lactation on the following website: https://www.embryotox.de. Possible substances for drug preventive treatment in pregnancy are metoprolol (577), propranolol and amitriptyline (578). There is a high to very high level of experience for these substances. It is advisable to cooperate with the gynaecologist in charge so that the pregnancy can be optimally monitored by additional sonographic checks, if necessary. There are currently no indications of teratogenicity in the 1st trimester. If beta-receptor blockers are taken until delivery, bradycardia may occur in the baby. As a result, the lowest possible effective dosage should always be aimed for. Amitriptyline can cause neurological, gastrointestinal and respiratory adjustment disorders in the child due to its anticholinergic effects if taken in high doses until birth. As a result, close clinical monitoring should be done in the first days after birth and the dose should be reduced one to two weeks before the expected date of birth.

Topiramate should be avoided or discontinued for preventive migraine treatment in pregnancy because of the increased risk of developing cleft palate and hypospadias when used in the 1st trimester (579). If used in the 2nd-3rd trimester, low birth weight and adjustment disorders must be expected (580). In addition, the risk of autism is probably increased (581).

There is little experience with flunarizine in pregnancy. Even though there are no indications of teratogenicity so far, the substance should be replaced by a preventive treatment with a higher level of experience as a precaution.

Against the background of a recommended daily intake of 300 mg magnesium during pregnancy, oral administration still seems justifiable, at least in this dose range.

Small case series and individual cases have been reported on the successful use of onabotulinumtoxinA for chronic migraine and repeated nerve blocks with lidocaine (578, 582, 583). The largest case series includes 45 patients with chronic migraine treated with onabotulinumtoxinA within three months prior to conception. Treatment was continued during pregnancy in 32 patients. One miscarriage occurred. All the other children were born on schedule with normal birth weight and without congenital malformations. Botulinum toxin is probably not placenta-compatible, but no recommendation for treatment in pregnancy can be derived on the basis of this limited experience (584)

Monoclonal antibodies against CGRP or the CGRP receptor, rimegepant and lasmiditan must not be used during pregnancy.

## 6.5 Migraine prevention treatment of menstrual migraine

**Recommendations**

- For short-term preventive treatment, naproxen or triptans with a long half-life, starting two days before menstruation, for 5–6 days, can be considered.
- Continuous administration of a combined oral contraceptive (COC) can be considered as a preventive measure.
- For the preventive treatment of menstrual migraine, the administration of desogestrel can also be considered.

Short-term preventive treatment options, assuming a regular cycle, include naproxen or a long half-life triptan starting two days before the expected onset of migraine for a total of 6–7 days. In placebo-controlled trials, the following substances and dosages have been investigated: frovatriptan 2.5 mg 1 x, 2 x or 3 x per day, zolmitriptan 2.5 mg 2 x or 3 x per day, naratriptan 1 mg or 2.5 mg 2 x daily and naproxen 2 x 550 mg per day (585–593). Within these options, the data is best for frovatriptan 2 x daily 2.5 mg according to an evidence-based review (594). Alternatively, naratriptan 2 x 1 mg or naproxen 2 x 500 mg may be considered. The risk of developing medication-overuse headache from short-term preventive treatment is likely to be low if no or few acute medications are taken in the remaining time interval. Nevertheless, the risk should be kept in mind. For this purpose, it is advisable to document the number of days on which acute medication is taken in a headache calendar.

The previously propagated strategy of percutaneous oestrogen administration cannot be recommended, as this only leads to a postponement of migraine attacks until after the oestrogen has been discontinued (595). However, percutaneous oestrogen gel substitution may be considered if other established preventive measures fail. A regular cycle or monitoring of the cycle are, in a sense, conditions to determine the time for application (596). Percutaneous oestrogen administration in the pill-free interval cannot be recommended as migraine preventive treatment due to a lack of evidence related to the indication (596).

As a preventive measure, the continuous administration of a combined oral contraceptive (COC) can be considered; this should be done in consultation with the attending gynaecologist. The rationale behind this approach is to reduce the number of cycles and the number of migraine attacks triggered by them. The continuous use of COCs is generally considered safe for a period of up to two years (597, 598). However, the effect on the occurrence of headaches and non-menstruation-associated migraine attacks has so far only been investigated in open trials (599, 600). However, as COCs significantly increase the risk of stroke and since migraine, especially with aura, is itself a risk factor for stroke, the individual vascular risk profile of patients

must be taken into account. Of least concern is the continued use of COCs in patients with migraine without aura and without other cardiovascular risk factors. Of least concern is the continued use of COCs in patients with migraine without aura and without other cardiovascular risk factors. As a general rule, preference should be given to low oestrogen-content contraceptives (548, 601). Highly active migraine with aura in a patient with an elevated vascular risk profile is considered a contraindication to the administration of COCs.

A pooled analysis of four trials showed that desogestrel 75 µg/day in migraine preventive treatment significantly but slightly reduced the number of migraine attacks and migraine days. Reduced intensity and duration of attacks, reduced use of analgesics and triptans, and improved headache-related quality of life are observed (602).

# 7 Practical aspects of migraine prevention treatment using medication

## 7.1 Real-world trials of conventional migraine prevention treatments and monoclonal antibodies

Compared to the real-world trials on the efficacy and safety of CGRP-(R) MABs, far fewer real-world trials on those two characteristics of conventional oral migraine preventive treatments have been published, despite the much longer approval period. Several real-world trials exist on onabotulinumtoxinA, which was approved in 2011 for the preventive treatment of chronic migraine.

Using the PubMed search "Real world trial AND migraine AND [substance]", no real world trials on migraine preventive treatment with metoprolol, propranolol and flunarizine are found.

Across all substance classes, there is low six-month adherence (26–29%) and persistence (25%) to conventional oral migraine preventive treatments. The most common reasons for discontinuing treatment are adverse effects or lack of efficacy (603–606).
However, this data is largely based on database analyses and web-based surveys, so bias cannot be ruled out.

### 7.1.1 Valproic acid

A trial from Brazil compared the efficacy of topiramate and valproic acid in 120 patients with episodic migraine and found a reduction in monthly headache frequency >50% in 51% of patients treated with valproic acid after three months. Weight gain, hair loss and gastrointestinal symptoms were reported by 24% of each patient group (607).

### 7.1.2 Topiramate

The trial mentioned under valproic acid found a 50% reduction in monthly headache frequency in 58% of patients with episodic migraine treated with topiramate (607). The most common adverse effects were weight loss (50%), paresthesias (48%) and cognitive disorders (20%). The same group showed similar results in an earlier trial of 134 patients, but here even more patients (78.4%) had a weight loss of 3.4 kg on average (608).

### 7.1.3 OnabotulinumtoxinA

Following the approval of onabotulinumtoxinA for the treatment of chronic migraine, many trials have investigated the treatment in a real-life setting. In a COMPEL trial, 715 patients with chronic migraine in the USA, Australia and South Korea showed similar results to the PREEMPT trials, with a sustained treatment effect and a significant reduction in monthly headache days of -10.7 days (baseline 22 days) after two years (451). In the European REPOSE trial, 633 patients with chronic migraine had a reduction in headache frequency from 20.6 to 7.4 days after two years of onabotulinumtoxinA treatment. However, the treatment providers in this trial were not bound by the doses and administration regimen of PREEMPT (609). These real-world trials were confirmed by other, mainly Italian and English, trials with similar results with a trial duration of up to eight years (453, 476, 610–614). Similarly, as in the PREEMPT trials, an equivalent treatment effect was also shown for concomitant medication-overuse headache in the real-world trials (453, 612, 615).

In terms of safety, in a pooled analysis of all real-life trials involving 6558 patients, treatment-related adverse effects (mostly mild to moderate) occurred in 13.6% of patients. The most common adverse effects were neck pain (5.4%), ptosis (4.5%) worsening of migraine (2.1%) and pain at the injection site (2.2%). Dysphagia occurred in 0.1% (616).

In summary, several real-life trials can thus confirm the results of the randomised double-blind trials regarding the efficacy and safety of onabotulinumtoxinA.

### 7.1.4 Monoclonal antibodies against calcitonin gene-related peptides (CGRP) or the CGRP receptor

Most trials report data on real-world use of erenumab (five trials). Studies on fremanezumab (411) and galcanezumab (528) are also available. The efficacy data regarding the endpoint of a 50% reduction in MMT at three months are comparable to those of the phase III trials. For episodic migraine (EM), response rates of approximately 50–60% have been reported in real-world conditions (423, 617, 618). However, the patients studied here suffered from refractory migraine with failure of at least four previous attempts at preventive treatment. Real-world data on patients with fewer prior treatments report a slightly higher 50% response rate of up to 77% (MKT) (411). In chronic migraine (CM), similar effects of treatment history are seen, such that in refractory courses with chronic daily headache (30/30 days per month; CDH), response rates of only 13% are reported in two trials (617, 618). However, patients without a nominal response to MMT showed improvement in headache intensity and attack duration (617). Treatment-refractory courses of CM without CDH responded significantly better and about 40% of cases achieved a 50% reduction in MMT (619, 620). When cases of CM with fewer prior treatments and no CDH are treated with CGRP-(R) MABs, response rates of up to 58% are possible in real-world use (411). In addition, in this trial, 75% of patients with CM converted to an episodic course, and 68% of patients with medication-overuse headache (MOH) no longer had overuse. When the threshold of treatment response is adjusted to a 30% reduction in MMT, the efficacy of CGRP-(R) MABs in CM increases up to 70% (621).

A Dutch trial specifically investigated the course of treatment response over a period of six months during treatment with erenumab (622). Here, the 50-unit response rate for patients with EM ranged from 29% to 61% and with CM from 11% to 28% when considering the individual months of treatment. About 80% of patients with CM and 45% of patients with EM achieved a 50% reduction in MMT in at least one month. For at least three of the six months, about 50% of patients with EM and 25% of patients with CM still achieved a halving of MMT.

With regard to safety, no adverse effects were reported in the real-world applications that were not already known from the pivotal trials. Only in terms of frequency were there some clear discrepancies. For example, a Dutch trial reported up to 93% adverse events (ADEs), with constipation occurring in 65% of cases under erenumab (other agents were not investigated in the trial) (622). The authors attribute this unexpectedly high frequency of adverse events to the targeted questions about specific ADEs in the prospective observation. A Belgian trial also reported 48% ADEs with 20% constipation, with treatment discontinuation due to ADEs in only 4% of cases within three months (618). In a Danish trial with an observation period of 12 months, 14% of patients discontinued treatment with erenumab due to an ADE (621). In an Italian prospective multicentre analysis, only 6% treatment-related ADEs were documented among CGRP-(R) MABs.

In summary, real-world data confirm the efficacy of CGRP-(R) MABs from the pivotal trials, even in refractory courses. Similarly, the efficacy is confirmed in patients with MOH. With regard to a treatment response for each individual month of treatment, it shows that a deterioration in individual months should not be confused with a general treatment failure. This observation is explained by the established cyclical variation in attack frequency (623). The presence of a CDH appears to be a negative predictor of treatment response to CGRP-(R) MABs. The increased occurrence of ADEs could be due to information bias. The dropout rate due to ADEs is ultimately no higher than in the pivotal trials.

## 7.2 Further practical aspects of migraine prevention treatment using medication

### 7.2.1 Communication

The primary goal of any preventive treatment is to halve the number of headache days. Secondary goals are to relieve attacks, improve response to acute medication and reduce the number of days requiring acute medication. Adherence to and compliance with preventive treatment can be improved by communicating realistic treatment goals and explaining the delayed onset of action. Experience has shown that it is also helpful to point out the limited duration of treatment. Relevant adverse effects should be addressed. For many patients, it is important to know that adverse effects are not automatic, that the severity of adverse effects usually decreases with the duration of use and that there are no permanent adverse effects to worry about. Furthermore, in the case of non-specific substances for preventive treatment, it is advisable to point out their other indication(s) and their significance for the current treatment. Information sheets from the DMKG, which can be downloaded from the website https://www.attacke-kopfschmerzen.de/infomaterial are useful.

### 7.2.2 Specific vs. non-specific drugs for preventive treatment

The exact mechanism of action of non-specific substances for preventive treatment is not known. However, their migraine preventive treatment effect has been confirmed by controlled trials. It may be advantageous that they have other effects that can be used to treat concomitant diseases such as depression, sleep disorders or arterial hypertension. Another advantage is the long experience with the substances.

Migraine-specific substances (antibodies) for preventive treatment block CGRP-mediated steps in the generation of migraine attacks and are generally very well tolerated. However, they have no other known mechanisms for treating concomitant diseases.

### 7.2.3 Combination of drug and non-drug treatment

Many patients wish for a non-medication treatment, but do not find the time to practise basic measures such as relaxation techniques and endurance sports on a regular basis. Taking a drug is more convenient, especially if a drug-based preventive treatment is well tolerated. However, it has been shown that a better therapeutic effect is achieved by combining non-pharmacological and pharmacological procedures than with one procedure alone (624). Non-medicinal methods can also have a positive influence on lifestyle factors that favour the occurrence of attacks (for an overview, see: (625)).

### 7.2.4 Combination of two prophylactic or therapeutic substances

To date, there are few trials investigating the effects of drug combination preventive treatment. In chronic migraine, a prospective, randomised trial showed that the addition of propranolol to a treatment with topiramate did not have a stronger preventive treatment effect than topiramate as a monotherapy (626). In an older trial, the effect of flunarizine and topiramate in monotherapy was compared with the combination of flunarizine with topiramate prospectively over one year. There was improvement in migraine in all three arms of the trial. The reduction in migraine days was slightly higher with combination treatment, but did not achieve statistical significance. The tolerability of the monotherapy and the combination was comparable.

For the combination of onabotulinumtoxinA with a CGRP (receptor) antibody in chronic migraine, there are some retrospective evaluations and case series that report a beneficial effect of combination treatment with a further decrease in migraine headache days and reduction in pain intensity with good tolerability (627–633). However, controlled prospective studies are lacking, so that sufficient evidence for this combination treatment cannot yet be assumed.

The data situation for episodic migraine is even worse. In a small prospective placebo-controlled trial, patients who had not achieved a 50% reduction in the frequency of migraine attacks within eight weeks with 100 mg of topiramate or 30 mg of nortriptyline were either treated with the combination of both substances or placebo was added to the ongoing monotherapy (308). Headache frequency decreased somewhat more significantly with combination treatment (mean 4.6 vs. 3.6 days, $p < 0.05$). However, tolerability was worse. Adverse effects occurred in 65.9% of patients on combination treatment, 41.2% on topiramate and 36.8% on nortriptyline.

In summary, the present trials do not provide sufficient evidence for the superiority of drug combination treatment over monotherapy. However, comorbidity (high blood pressure, depression, anxiety) can certainly be a reason for combination treatment even in migraine patients.

### 7.2.5 Ineffectiveness of preventive treatment

If preventive treatment procedures do not work, there is either insufficient compliance, concomitant overuse of acute medication, misdiagnosis or true resistance to treatment. To improve compliance, it may be necessary to dose poorly tolerated substances more slowly than usual in order to keep adverse effects as low as possible and still achieve an effective preventive dose. In addition, realistic treatment goals should be formulated and information about the risks of chronification through medication overuse should be provided. If drug-based preventive treatment is ineffective for continued overuse of medications, a break should be taken from acute medications (headache due to overuse of analgesics or migraine medications = MOH, S1 Guideline. In: German Society for Neurology https://dgn.org/leitlinien)

If various preventive treatment substances continue to show no effect, the clinical diagnosis should be critically reconsidered. If the diagnosis of migraine is confirmed, non-effective substances prescribed for preventive treatment should be discontinued. Treatment must then focus on non-medicinal procedures, with particular emphasis on pain and disease management procedures and treatment of relevant comorbidities.

# 8 Medicines that are probably ineffective in preventing migraine

A large number of other substances have been investigated for their efficacy in migraine preventive treatment. Often, individual substances showed efficacy in initially published case series and open trials, but this could not be proven in subsequent randomised, placebo-controlled trials with an appropriate primary endpoint (634). In addition, there are substances with contradictory data from placebo-controlled trials for which no proven efficacy can be derived, either. This guideline only lists drugs whose efficacy has been proven in randomised controlled trials, or meta-analyses in the case of contradictory data. Below, selected drugs whose preventive treatment efficacy could not be proven on the basis of the criteria mentioned are presented. Food supplements such as coenzyme Q10, riboflavin or vitamin D3 are not included.

Conflicting data are available on the preventive treatment effect of melatonin. On the one hand, taking 3 mg of melatonin showed a superior reduction in monthly headache frequency of 2.7 days vs. 1.1 days with placebo (both groups: 7.3 headache days/month in baseline) (635). However, in another trial, 2 mg melatonin was not shown to be superior to placebo (636). Due to its good tolerability and safety, melatonin would certainly be an interesting substance, but current trials do not allow a clear conclusion on its preventive treatment efficacy.

Due to comorbid affective disorders and the efficacy of tricyclic antidepressants, there is a positive expectation in clinical routine regarding the efficacy of selective serotonin (SSRI) or serotonin-norepinephrine (SNRI) reuptake inhibitors in migraine preventive treatment. However, an efficacy of SSRIs superior to that of placebo could not be demonstrated (637). Venlafaxine at 150 mg but not 75 mg was significantly more effective in a placebo-controlled trial (330). However, that trial was exploratory and preventive efficacy was not the primary endpoint. In addition, a large number of positive open trials exist for other SNRIs (including milnacipran, duloxetine) (323). However, there is no proof of efficacy according to the criteria mentioned above, and it remains unclear to what extent antidepressant effects act as a mediator.

# 9 Interventional procedures for migraine treatment

**Recommendation**

- The use of occipital nerve block has shown moderate effects in short-term (<3 months) treatment of chronic migraine in a few trials. In view of the minor adverse effects, its use can be considered in individual cases, although it was unclear whether local anaesthetics, steroids or both were most effective. Acute effects on migraine attacks have not been sufficiently studied.

### Occipital nerve block in acute migraine treatment

Three randomised controlled trials investigated the efficacy of occipital nerve blocks in the emergency department (A&E). In a randomised, placebo-controlled trial in acute migraine patients who had not responded to intravenous metoclopramide in the emergency department, 13 patients received bilateral injections near the greater occipital nerve (GON) with a total of 6 ml bupivacaine 0.5% (= 15 mg per side) and 15 patients received bilateral intradermal scalp injections with a total of 1 ml bupivacaine 0.5% (= 0.5 mg per side, placebo group). After 30 minutes, 4/15 (= 31%) of the patients in the bupivacaine group and 0/15 (= 0%) in the placebo group were free of headaches. After 48 hours (= secondary endpoint), 3/15 (= 23%) of the patients in the bupivacaine group and 0/15 (= 0%) in the placebo group were headache-free. However, the trial was terminated before the required sample size was reached (638).

In another randomised, placebo-controlled trial in acute migraine patients in A&E, bupivacaine was found to be superior to placebo and non-inferior to classical treatment with a non-steroidal anti-inflammatory and anti-emetic. Twenty patients in each group received either GON injections with 0.5 ml bupivacaine 0.5% (= 2.5 mg) or NaCl or intravenous infusions with 50 mg dexketoprofen and 10 mg metoclopramide as initial medication in the emergency situation. There was a significant decrease in headache 30 minutes and 45 minutes after intervention in all three groups compared to pre-treatment. The bupivacaine group (from NRS 9 to 3, 1 at 30 minutes, 45 minutes) was as effective as the dexketoprofen/metoclopramide group (from NRS 8 to 1, 1 at 30 minutes, 45 minutes). Both groups were superior to placebo (from NRS 8 to 4, 3 at 30 minutes, 45 minutes) ($p = 0.03$ and $p = 0.03$, respectively) (639).

Similar results regarding non-inferiority of bupivacaine-0.5% GON injections versus classical treatment with intravenous metoclopramide were found in a randomised, double-blind, double-dummy non-inferiority trial (640). 51 patients with acute migraine attacks received bilateral GON injections with a total of 6 ml bupivacaine 0.5% (= 15 mg per side) and 100 ml NaCl intravenously, 48 patients received bilateral GON injections with a total of 6 ml NaCl and 10 mg metoclopramide intravenously. 1 hour after intervention, pain intensity (NRS) had decreased by an average of 6.1 points (95% CI: 5.2 - 6.9) in the metoclopramide group and by an average of 5 points (95% CI: 4.1 - 5.8) in the bupivacaine group (95% CI for group difference of - 1.1: -2.3 - 0.1) compared with pre-treatment. However, in the exploratory data analysis, the efficacy of GON injections was comparable to intravenous metoclopramide when the intervention was performed by experienced clinicians (previously > 7 occipital nerve blocks) (640).

In a small case series (n = 18) in patients with visual and/or sensory auras, some of which are prolonged for two hours to one week, occipital injection of bupivacaine within 30 minutes resulted in marked improvement in 85% of cases and complete regression in 60% of cases with concomitant improvement of headache in 80% of cases (641).

### Occipital nerve block in migraine preventive treatment

In migraine prevention, the efficacy of occipital nerve blocks has mostly been studied in the short-term course of chronic migraine. Studies on long-term efficacy are lacking.

Three randomised, double-blind, placebo-controlled trials in patients with chronic migraine showed a positive effect of occipital nerve block. A small monocentric trial investigated the short-term efficacy of a single occipital nerve block. Patients were injected with 2 ml of bupivacaine 0.5% (= 10 mg) or NaCl near the greater occipital nerve (GON). In the week following the injection, the bupivacaine group had a greater reduction in the number of moderate-to-severe headache days than the placebo group (-2, 95% CI -2.7 to – 1.3 vs -0.4, 95% CI -1.4 to 0.5, p = 0.027) (642).

In another multicentre trial, patients received either a GON injection with 1.5 ml bupivacaine 0.5% (= 7.5 mg) or NaCl weekly for four weeks. After four weeks, the blinding was removed and both groups of patients received bupivacaine once a month for another two months. After the first month, the number of headache days decreased more in the bupivacaine group (from 18.1 ± 5.3 to 8.8 ± 4.8 days) than in the placebo group (16.9 ± 5.7 to 13.2 ± 6.7; p = 0.004, between groups). In the 2nd and 3rd months, i.e. after switching from placebo to bupivacaine, both groups showed a similar decrease in headache days (643).

Another monocentric trial showed a similar trial design, in which patients also received a weekly GON injection with 1.5 ml bupivacaine 0.5% (= 7.5 mg) or NaCl for the first four weeks. This study also extended over three months, but blinding was maintained and patients were followed up at month 2 and 3 without injections. The number of headache days decreased similarly in both groups compared to baseline in the first month (bupivacaine group: from 21.0 ± 4.4 to 10.9 ± 7.1 days (p <0.001), placebo group: from 20.9 ± 5.0 to 15.5 ± 7.3 days (p <0.001). There was no difference between the groups until then (p = 0.097). However, after 3 months, headache days continued to decrease in the bupivacaine group (to 6.3 ± 1.9 days), but increased in the placebo group (to 19.1 ± 6.3 days), making the comparison between the groups significant (p <0.001) (644).

### Efficacy of steroids in occipital nerve blocks

A randomised, double-blind, placebo-controlled trial investigated the efficacy of a single GON injection of 2.5 ml bupivacaine 0.5% (= 12.5 mg) plus 20 mg methylprednisolone versus placebo (NaCl plus 0.25 ml 1% lidocaine) in patients with episodic and chronic migraine. No significant effect of occipital nerve blockade was found; in both the verum and placebo groups, there was at least a 50% reduction in moderate to severe migraine days four weeks after injection in 30% of patients in each group (645).

Similarly, in a well-designed 24-week, randomised, double-blind, placebo-controlled cross-over trial at a tertiary headache centre, there was no significant difference in the decrease in monthly migraine days between GON injections of 0.1 ml lidocaine 4% (= 4 mg) plus betamethasone 7 mg (verum) or placebo (NaCl plus 0.1 ml lidocaine 4%). The efficacy is studied in adults with chronic migraine in whom two or more previous preventive treatments had been unsuccessful. Bilateral GON injections with verum or placebo are administered on day one of the two eight-week double-blind phases, with a four-week wash-out phase between the cross-over periods. Due to slow recruitment, the trial was terminated before reaching the a priori sample size; a total of 10 patients were included with a mean number of monthly migraine days of 22.9 (range 14–30). The number of monthly migraine days averaged between 23 and 24 after verum treatment and between 22 and 23 after placebo treatment. Both groups were not significantly different (p = 0.147, 95% CI -0.6 – 3.7 days). The trial concluded that treatment with lidocaine plus betamethasone was not beneficial for difficult-to-treat patients with chronic migraine compared with placebo (646).

In a randomised, double-blind, placebo-controlled trial in patients with episodic migraine without aura, there was also no significant difference in the reduction of headache attacks between GON injections with a corticosteroid and local anaesthetic versus local anaesthetic alone. The trial examined four groups of patients with an average of 8 to 10 monthly migraine attacks who received either 40 mg triamcinolone, 40 mg triamcinolone plus 2 ml lidocaine 2% (= 40 mg), 2 ml lidocaine 2% (= 40 mg) or NaCL-GON injections at baseline and after 1, 2 and 4 weeks. Only the patient group with 40 mg triamcinolone plus 2 ml lidocaine 2% and the patient group with 2 ml lidocaine 2% showed a significant decrease in the number of headache attacks after four weeks compared with pre-treatment (combination group: -5.69 (95% CI: -1.11 to -10.27), p = 0.019; lidocaine group: -5.81 (95% CI: -2.52 to – 9.09), p = 0.002). The two groups did not differ significantly from each other. However, the trial had too few cases, as the desired sample size calculated a priori was not reached in each group (647).

### Significance of the localisation of the occipital nerve blockade

Ultrasound-guided occipital nerve blocks offer the advantage of visualisation of the nerve, targeted application of the injection material at the target site and reduction of the risk of anaesthesia of adjacent structures or injection into vessels, such as the occipital artery. The therapeutic benefit and superiority of this technique over the conventional landmark-guided approach, which is based solely on superficial bone-based anatomical landmarks along the nuchal line, is not proven.

A four-week prospective, randomised, placebo-controlled, double-blind trial is conducted to evaluate the efficacy of a single ultrasound-guided GON injection of 1.5 ml bupivacaine 0.5% (= 7.5 mg) or NaCl in 23 patients with refractory chronic migraine. Headache intensity, measured by the VAS score, decreased significantly (p = 0.003) on the injection side in the bupivacaine group compared to pre-treatment, but not in the placebo group (p = 0.110). However, when comparing the two groups, the VAS scores did not differ (p = 0.095). There were no changes (p = 0.625 between groups) in the analysis of VAS scores on the side that had not received injections (648).

In a multicentre, prospective, randomised control trial, two different localisations of occipital nerve block with 1 ml bupivacaine 0.5% (= 5 mg) plus 40 mg methylprednisolone were investigated in chronic migraine patients. In one group of patients, infiltration was performed at the distal site at the level of the superior nuchal line (2–3 cm lateral to the occipital protuberance), in the other group of patients at the proximal site between the spinous process of C2 and the transverse process of C1. A significant decrease in headache intensity (NRS score) compared to pre-treatment was observed in both the distal and proximal groups at 24 hours and 1 week; at 1 and 3 months, significance was only observed in the proximal group (NRS decrease from baseline at 1 month (primary endpoint): proximal group: mean value: -1.85, 95% CI; -3.29 to -0.42; p = 0.014; distal group: mean value: 1.00, 95% CI: -2.03 to 0.03; p = 0.056). At no time were the two groups significantly different from each other (649).

The value of occipital nerve blockade in the long-term preventive treatment of migraine cannot be assessed with certainty. There seems to be efficacy in short-term preventive treatment.
The methodological variability of the trials is problematic with regard to injection sites (including injection site, unilateral or bilateral injection), injection frequency (single, weekly), medication used (local anaesthetics, corticosteroids or combination), technique used (landmarks, ultrasound-guided), experience of the practitioners and trial endpoints. In addition, the small number of cases in most trials is problematic (mostly <100 subjects) and the lack of information on blinding (the hypaesthesia caused by the local anaesthetic makes blinding difficult). Serious adverse effects were not reported. The three most common adverse events were local pain at the injection site, vasovagal syncope and dizziness (650). Case reports of local alopecia and cutaneous atrophy have been reported with the use of corticosteroids, but these appear to be reversible (647, 651, 652).

## 9.1 Invasive and neuromodulating procedures for treating migraine

**Recommendations**

- Given their good tolerability, non-invasive stimulation procedures can be used in patients who refuse migraine prevention treatment with medication. At this point in time, only electrical stimulation of the supraorbital nerve is of practical importance in migraine treatment.
- Invasive neurostimulation procedures such as bilateral stimulation of the greater occipital nerve or implanting an electrode in the sphenopalatine ganglion are not recommended for migraine preventive treatment.
- Surgical transection of the corrugator muscle and other pericranial muscles is not recommended.
- Closure of a patent foramen ovale is not recommended.

## 9.2 Invasive neurostimulation

An invasive neuromodulatory procedure should only be considered in migraine treatment if the criteria of chronic migraine with additional resistance to treatment are met. In addition, these procedures should only be used within prospective trials of established interdisciplinary and specialised care structures. Postoperative care and continuing care must be ensured. Before invasive interventions, a structured catalogue of established diagnostic measures, including a psychiatric evaluation, should be completed (653). In the case of pathological findings, the indication for intervention should be examined very critically. In addition, there is the purely practical problem that the implantable systems in question are either no longer available (stimulation of the sphenopalatine ganglion) or have no approval (stimulation of the greater occipital nerve).

Limited efficacy of chronic stimulation of the greater occipital nerve (ONS) for chronic migraine with or without additional medication-overuse headache has been demonstrated in two controlled trials (654, 655) and other smaller uncontrolled trials and case series (656, 657). However, due to the limited trial quality (problems with blinding) and especially the frequent complications (breakage or dislocation of the electrode) and adverse effects (658), ONS cannot currently be recommended for the treatment of chronic migraine, or only in exceptional cases (see above) (659). From 2011 to 2014, a neurostimulator had been approved for the stimulation of the n. occipitalis major in the "chronic migraine" indication, but this was withdrawn again due to the unfavourable efficacy/adverse effect profile. For other invasive stimulation procedures such as high cervical spinal cord stimulation, sphenopalatine ganglion stimulation and combined occipital and frontal (supra- or infraorbital) nerve stimulation, there is currently a lack of both larger trials and long-term experience, so that the use of these procedures for the treatment of chronic migraine cannot be recommended at present (660).

## 9.3 Non-invasive neuromodulation

Non-invasive neuromodulation can be divided into procedures that primarily stimulate transcutaneous nerves in the area of the neck or head or those that stimulate the brain transcranially. In transcutaneous procedures, a distinction is made between stimulation of the trigeminal nerve, the greater occipital nerve and the vagus nerve. There is also transcranial magnetic stimulation of the visual cortex for the treatment of attacks of migraine with aura (661).

### 9.3.1 Neurostimulation for the preventive treatment of migraine

A trial on the preventive treatment of episodic migraine with n.supraorbitalis stimulation by Cefaly® included 67 patients. The nerve was stimulated for 20 minutes daily for three months. There was a significant superiority in the change in monthly migraine days and in the 50% responder rate in the verum group (-2.06 days and 38.1%) compared with the control group (+0.34 days, 12.1%) (662). The treatment was tolerated without serious adverse effects. A register evaluation showed that of a total of 2313 patients, 53.4% were satisfied with the effect experienced and purchased the device, while 46.6% were not satisfied. Serious adverse effects were not reported (663). In an open-label trial of patients with chronic migraine, 50% of patients achieved a significant reduction in the number of days on acute medication (664).

A trial at three Chinese centres compared the efficacy of supraorbital stimulation (20 minutes daily) with retroauricular stimulation in the area of the mastoid (40 minutes daily) in 90 patients with episodic migraine. Both stimulation methods were comparably effective and reduced monthly migraine days by a mean of about three days (-2.85, 95% CI -4.55 to -0.17, and -3.5, 95% CI -4.74 to -0.47) (665). Problematically, the number of headache days at baseline was unbalanced (4.7 ± 2.06 to 6.5 ± 2.07 days).

The controlled, double-blind, randomised PREMIUM-I and PREMIUM-II trials were conducted on the effect of transcutaneous vagus nerve stimulation in the lateral neck region in preventing migraine. In the PREMIUM I trial, a four-week baseline phase was followed by a 12-week double-blind phase and then a 24-week open-label follow-up phase (666). Patients with episodic migraine stimulated themselves bilaterally in the neck area three times a day for 2 x 120 seconds. A total of 332 patients were included in the analysis. Compared with the four-week baseline (nVNS 7.9 ± 2.2 days, Sham 8.1 ± 2.0 days), there was no significant difference in the reduction in monthly migraine days between the two groups (nVNS -2.26 versus sham: 1.80, p = 0.15). In a post-hoc analysis, patients who performed more than 67% of the stimulations showed a significant difference (-2.27 days to -1.53 days; p = 0.042), with the caveat that the difference was due to the greater reduction in the sham group.

The Premium II trial was a further development of the Premium I trial and was designed to address some of the limitations of the PREMIUM I trial, while providing additional data to support and complement the trial results (667). A modified inactive sham device was used, since the sham device used in the PREMIUM-I trial had produced some degree of vagal activation, so that an active therapeutic effect could not be ruled out (668). Episodic (EM) and chronic (CM) migraine patients were included to increase treatment adherence. The 3 x daily nVNS stimulation with 2 x 120 seconds was only performed unilaterally, ipsilateral to the predominant headache side. The trial included a four-week baseline and a 12-week double-blind phase. A total of 113 patients are included (nVNS, n = 56, 23 EM, Sham, n = 57, 23 CM). The trial population was 60% smaller than the statistical target for full efficacy because the trial was terminated early due to the COVID 19 pandemic. Compared to the four-week baseline (nVNS 9.2 ± 4.6 days, sham 9.9 ± 3.5 days), there was no significant difference in the reduction of monthly migraine days (= primary endpoint) between the two groups (-3.12 to -2.29, p = 0.23). The 50% reduction in monthly migraine days (= secondary endpoint) was significantly higher in the nVNS group (44.87%) than in the sham group (26.81%; p = 0.0481). Finally, it should be mentioned that in this trial, too, a high effect was observed in the sham group, which points to the problem of correct blinding in neuromodulation trials (669, 670).

In PREMIUM I and II as well as in other controlled-randomised trials on cluster and migraine treatment, transcutaneous n.vagus stimulation in the area of the lateral neck was shown to be tolerable and safe. The most common adverse effects were local irritation, redness, mild pain, muscle twitching, tingling paraesthesia as well as dizziness and headache (in total <5%). No serious adverse events were observed (671).

Another procedure for stimulating the vagus nerve is electrical stimulation of the auricular sensitive branch of the vagus nerve in the area of the concha of the auricle with the NEMOS® system. In a monocentric, controlled, randomised trial, four-hour daily stimulation with 25 Hz or 1 Hz was investigated in 46 patients with chronic migraine (19). 40 patients completed the trial (four weeks baseline and 12 weeks stimulation). Surprisingly, a significant difference was found in favour of the 1 Hz stimulation group (19.1 days minus 7.0 days) compared to the 25 Hz stimulation group (19.2 days minus 3.3 days). The number of patients with a 50% responder rate was also higher in the 1 Hz group than in the 25 Hz group (29.4% to 13.3%). There were no serious adverse effects, although there were isolated cases of skin irritation in the area of the concha. The findings were confirmed by an fMRI trial by Zhang et al. who described a significant reduction in migraine days in the 1 Hz group compared to a Sham group (verum vs. sham: --2.5 to --0.7) (672).

In addition, a number of mostly uncontrolled case series reported on the preventive treatment effect of transcranial magnetic stimulation or transcranial direct current stimulation. An open trial investigated the clinical effect of a daily dose of two-times stimulation with four single pulses each over 12 weeks in 132 patients on the frequency of migraine. Overall, there was an average reduction of 2.75 days. No control group was studied (673). Regarding repetitive serial stimulation, there are a number of mostly uncontrolled smaller studies (review in: Jürgens and Rimmle 2019 (674)). The majority of these trials reported improvement in migraine, although the risk of outcome bias is generally considered high.

Recently, the results of a monocentric open observational trial were also published (675), reporting the results of 153 patients with high-frequency or chronic migraine. Patients stimulated with occipital TMS six times daily and could also use TMS for attack treatment (two stimuli every 15 minutes for up to two hours). 45% of patients reported a sustained effect 12 months after initiation. 60% of the patients were classified as responders. The median reduction in headache days was five days (from 18.0 to 13.0) at three months and the HIT-6 score also reduced significantly.

Transcranial direct current stimulation over the visual cortex was investigated in a combined trial to evaluate the excitability of the visual cortex and the effect of twelve 20-minutes sessions of stimulation over four weeks (676). A total of 19 patients with episodic migraine with or without aura are randomised and asked about migraine frequency for a period of 90 days. Stimulation is carried out with a battery-operated stimulator with 2 mA over the occipital cortex. Both the verum group and the placebo group showed a reduction in migraine days over time, with pain intensity remaining unchanged. The authors evaluated the result as an indication for a positive effect of inhibitory tDCS over the visual cortex. In addition to cathodal stimulation of the occipital cortex, some other trials have also investigated anodal stimulation of the motor cortex. Here, too, a positive effect was seen in four trials. A systematic review that included a total of 16 randomised trials concludes that there is sufficient evidence to suggest that cathodal occipital and anodal stimulation of the motor cortex is likely to be effective (677).

In summary, the results of the above trials show little evidence for the use of non-invasive neurostimulators (674, 678). The evaluation and comparability of the trials are complicated by the small number of cases, the methodological variability (different stimulation sites, stimulation parameters) and the difficulties in blinding. One practical problem is the lack of availability of many stimulators on the German market (e.g. combined supraorbital and occipital nerve stimulation, auricular vagus nerve stimulation, TMS single stimulation of the visual cortex) as well as the lack of cost coverage by health insurance companies.

### 9.3.2 Other surgical procedures

The efficacy of transection of the corrugator muscle or other pericranial muscles for the preventive treatment of migraine has not been scientifically proven and is therefore not indicated in preventing migraine (679).

### 9.3.3 Closure of a patent foramen ovale (PFO) as a preventive treatment for migraine

In most case series and also in case-control trials, a PFO is found more frequently among patients with migraine, especially migraine with aura, than in the general population, with frequencies of 64% and 90%, respectively (680, 681). In contrast, two population-based trials found no increased likelihood of PFO in migraine patients (682, 683). The extent to which there is a pathophysiological connection between migraine and PFO, or whether this is merely an ontogenetic phenomenon, has not yet been clarified. Numerous open trials show therapeutic effects of PFO closure for the most part, although the quality of these trials is mostly low (680). The prospective randomised MIST (Migraine Intervention with STARFlex Technology) trial was not able to confirm the efficacy of this procedure for the endpoint of freedom from migraine attacks (684). In a PRIMA trial, which investigated the efficacy of PFO closure in patients with migraine with aura, all patients received clopidogrel 75 mg for three months and ASA 100 mg for six months (685). 54 patients were treated with medication only, and 53 patients also underwent PFO closure using an Amplatzer PFO occluder. After 12 months, there were no statistically significant differences in the primary endpoint (number of days with migraine with and without aura) and most of the secondary endpoints (number of monthly migraine attacks, number of days taking pain medication, headache-specific impairment) between patients treated with medication only and those treated with medication and interventions. Only the rate of patients with at least a 50% reduction in migraine days/month was higher in the group with PFO closure. Another randomised controlled trial of PFO closure (PREMIUM trial) also showed no advantage of PFO closure over a "conservative" approach (686). Patients with migraine with and without aura were studied. All the patients received clopidogrel 75mg for one month and acetylsalicylic acid 325 mg for six months. After 12 months, 38.5% (47/117) patients in the PFO group and 32% (33/103) patients in the control group showed a $\geq$ 50% reduction in monthly migraine days (= primary endpoint, p = 0.32). The differences for the secondary endpoints such as number of monthly migraine attacks (PFO group 3.4, control group 2.0, p = 0.03) and freedom from migraine at 12 months (PFO group ten patients (= 8.5%), control group one patient (= 1%), p = 0.01) were statistically significant between the two groups. In a secondary prevention trial in patients with cryptogenic stroke and PFO comparing PFO closure with antiplatelet treatment or oral anticoagulation, patients were also asked at baseline if they suffered from migraine (687). Of the 473 patients randomised to either the PFO closure group or the antiplatelet group, 145 patients had migraine (75 migraine with aura, 70 migraine without aura). 67 of the patients received PFO closure and 78 patients received antiplatelet treatment. During the five-year follow-up period, there was no difference in the number of annual migraine attacks (= primary endpoint). In patients with migraine with aura, an average of 9.2 migraine attacks per year occurred after PFO closure and an average of 12 occurred with antiplatelet treatment (p = 0.81). Patients with migraine without aura had an average of 12.1 and 11.8 migraine attacks per year, respectively (p = 1). There were also no significant differences in the secondary endpoints of freedom from migraine, migraine-related disability at two years (HIT-6 score ≥ 56) and use of acute migraine medication.

The results of the three randomised trials and the CLOSE trial contradict published meta-analyses (688–692). However, the results must be critically assessed, as they are derived from the retrospective pooling of patient cohorts, different trial methods and outcome measures. In summary, there is no evidence at this time for the benefit of PFO closure in migraine preventive treatment. The procedure is therefore not recommended (693, 694).

# 10 Psychological procedures for preventing migraine

**Recommendations**

- Prevention treatment using medication should generally be accompanied by psychological procedures such as education, self-observation, self-management, cognitive behavioural treatment, social skills training, relaxation procedures, mindfulness, biofeedback and others.
- In patients with pronounced migraine-related impairment and/or psychological comorbidity, psychological pain treatment methods should always be used.
- Relaxation methods, cognitive behavioural treatment methods and biofeedback can also be used instead of medication prevention treatment.
- In a multimodal approach, both medication and psychological prevention treatment can be combined.
- Psychological methods were equally effective compared to conventional medication-based prevention treatment (this does not apply to monoclonal antibodies) and can be used instead.

Migraine is multidimensional in its development, i.e. genetic, psychosocial, physiological and biochemical predispositions in combination with dysfunctional habitual stress processing can have an effect on a migraine attack and influence its course (695). Migraine can be considered an adaptive response that occurs in genetically predisposed individuals in whom there is a mismatch between the brain's energy reserves and the neuronal mental and physical workload (696). It follows that migraine can be influenced by psychological strategies with modification of experience and behaviour.

Among the psychological methods, behavioural therapy (BT) has been empirically proven to be suitable for effectively performing these tasks and to be combinable with medical measures (so-called multimodal/multidisciplinary approach) (697, 698), so that the focus of treatment evaluation also lies in this area. Psychodynamic and other approaches have so far failed to provide evidence of procedure-specific efficacy in preventing migraine. BT interventions emphasise migraine prevention measures in terms of reducing attack frequency and headache-related affective and behavioural impairment. BT interventions teach the patient skills and abilities to influence the course of migraine through the modification of cognitive, affective and social experience and behavioural factors. A variety of effective psychological procedures and strategies are available today for the psychological treatment of migraine (695).

Formally, psychological procedures can be divided into simple (education, self-observation, self-management, relaxation, biofeedback) and combined (cognitive-behavioural) procedures. Cognitive-behavioural therapy (CBT) is particularly indicated for patients with high-frequency or chronic headaches, as they usually suffer from a high degree of psychological comorbidity. Intensified application of combined psychological treatment methods should be used under certain conditions (e.g. also (699):

- Impairment of quality of life, ability to work and/or attend school
- Failure of unimodal treatments
- Medication misuse or overuse
- Accompanying mental illness that causes pain
- Somatic concomitant disease complicating pain treatment

In recent years, reviews have shown that the three behavioural treatment methods (relaxation, biofeedback, cognitive behavioural treatment) hardly differ in their efficacy. More recent reviews emphasise the great heterogeneity of the trials and result in smaller effect sizes compared to older trials and cite methodological limitations (e.g. small groups, lack of randomisation) (cf. (698)). A Cochrane analysis initially reported no clear evidence for psychological interventions in adults with migraine in 2019 (700), for a discussion of the effects of psychotherapy trials see (701). The authors of the Cochrane trial saw a major limitation in the strict inclusion criteria of their trial, which restricted the significance. In an extended analysis of relevant trials, they concluded in 2022 that adults with headache benefit from psychological interventions and that effect sizes are in the small to medium range (702). Bae et al. come to similar conclusions regarding CBT in a recent review and meta-analysis (703). A major problem, however, is the varying quality of the included trials; the number of high-quality trials is low. Another problem, besides these more methodological aspects, seems to be the actual implementation of the approaches in standard clinical treatment (704).

## 10.1 Education

**Recommendation**

- Educational approaches are recommended for behavioural preventive treatment of migraine.

Educational approaches (i.e. counselling and education on diagnosis, pathomechanisms and treatment options) should always be essential first steps in the treatment of migraine. Their contents serve primarily to convey information. Education is a vaguely defined, relatively broad therapeutic category consisting of elements such as information, bibliotherapy, low-threshold offers of cognitive behavioural treatment (e.g. trigger analysis through headache diaries, physical exercises/endurance sports, improvement of sleep hygiene) and typically education about causes, typical symptoms and therapeutic options. Education can also contain elements that are counted as relaxation or cognitive behavioural treatment or stress management.

In the guideline "Relaxation methods and behavioural treatment interventions for the treatment of migraine" (705), counselling is rated as clearly superior to placebo treatment or control. The trials and meta-analyses included in the evaluation (706–708) comprised randomised-controlled approaches and included various counselling elements; internet-based approaches are common here (see section on apps). Counselling approaches can be delivered by therapeutic assistant staff (709) or digital applications (710, 711).

In a small, uncontrolled trial of US veterans, a one-day workshop (Acceptance and Commitment Therapy (ACT) plus education) reduced anxiety and depression scores and headache-related impairment.

In the case of education, the content of the approach is relevant. For example, an education group (eight two-hour sessions with migraine-specific information) and a meditation group with various exercise elements of comparable duration are able to reduce migraine days in the same way. However, when influencing the secondary outcome measures, education alone performed worse (712).

One area of application can be the workplace, where offers are provided via training or the internet/intranet that affected employees can use. This can lead to productivity gains (713). An online programme of this kind consisting of webinars, educational videos and other internet-based offerings led to a significant improvement in migraine (frequency and severity) and a reduction in productivity losses in a sample of 79 employees (714); similar effects are found in another trial (715). Due to the high prevalence of headache in childhood and adolescence, education should also be provided in this group (716).

## 10.2 Relaxation

**Recommendation**

- Relaxation techniques are recommended for the preventive treatment of migraine. They can be used instead of or in combination with drug preventive treatment.

Relaxation techniques include various skills that all aim to reduce tension and achieve relaxation. These include, among others: autogenic training, progressive muscle relaxation, breathing techniques, biofeedback methods or hypnosis.

Relaxation procedures are intended to redress the imbalance between the brain's energy reserves and the neuronal mental and physical workload and to reduce the general level of activation. The background is that, in addition to a general relaxing effect, a central stabilising regulation and dampening of information processing should also be achieved (717). However, relaxation not only causes a reduction in hypervigilance and attention, it also reduces anxiety, which in turn increases pain tolerance and at least reduces the subjective pain reported. Relaxation techniques are often said to have a prophylactic function in preventing pain; however, patients also report abortive properties of relaxation in acute pain states. The procedure of progressive muscle relaxation (PMR) consists of a gradual tensing and relaxing of various muscle groups. It is important to practise regularly and not only on a pain-contingent basis, and to ensure that it becomes part of one’s everyday life. Hypnosis seems to be comparable in its effect with other relaxation methods (718). Among the relaxation methods, PMR is superior to autogenic training for untrained people because successes are achieved more quickly and motivation remains high. There are few trials so far that explicitly investigate the use of PMR for migraine. Trautmann and Kröner-Herwig, among others, used PMR to treat headaches in children (719). They found significant results, which increased further in the follow-up survey. However, no differentiation was made here between different types of headache, which limits the significance. Similar to biofeedback (see above), relaxation techniques (mostly PMR) achieve an average reduction in migraine frequency of 35–45% (720, 721), which is in the range reported for propranolol. The treatment methods are used in migraine treatment both pain-specifically (e.g. in PMR) and non-pain-specifically. In addition to clinical efficacy, a change in cortical attention allocation can also be demonstrated in the contingent negative variation (CNV) measure. Previously elevated contingent negative variation (CNV) normalises with regular use of PMR in migraine patients (722).

Flynn was able to show in a review that hypnosis had significant effects on pain activity in migraine, based on assessment of randomised controlled trials (723).

The effects of relaxation techniques are comparable in size to those of biofeedback or cognitive-behavioural treatment (724). For relaxation methods, there are also corresponding apps that offer exercises for PMR, for example (725).

## 10.3 Mindfulness

**Recommendation**

- Mindfulness can be recommended for the preventive treatment of migraine in terms of improving quality of life.

Conceived as stress management training (mindfulness-based stress reduction, MBSR) by Jon Kabat-Zinn in 1979, mindfulness-based approaches are now used in many ways in psychotherapy, combined with other techniques (acceptance and commitment treatment, ACT; dialectical-behavioural treatment, DBT), further developed (mindfulness-based cognitive treatment, MBCT) and increasingly integrated into pain management (726). In MBSR, content is offered in a group setting, usually in 8–12 sessions over a period of 8–10 weeks, often supplemented by a mindfulness day (retreat). In principle, mindfulness can be used at any time in everyday life and is thus a low-threshold form of preventive treatment in any life situation. In addition, good compliance is reported (727). As shown in randomised controlled trials, mindfulness meditation can achieve a reduction in migraine days per month and is comparably effective to education (712), n = 89 or a combination of education and PMR (727), n = 62. Quantitative sensory testing (QST) showed a reduction in pain perception through mindfulness practice (712). However, with regard to the effects on pain (intensity, frequency), there are still inconsistent results, partly no significant improvement is reported (728, 729). Other parameters such as impairment, quality of life, self-efficacy, depressive symptomatology and catastrophising thinking are described in randomised controlled trials as being favourably influenced by mindfulness, even when migraine is not significantly reduced. Medium to strong effects are achieved (712, 727). Effects on quality of life and pain experience as well as pain acceptance have also been documented from other pain disorders and primary headaches in general (726, 728). The stress-reducing effect of mindfulness also addresses one of the most common migraine triggers. Especially patients with episodic migraine compared to chronic migraine benefited from mindfulness-based approaches in the randomised controlled trial by Seng et al (729).

## 10.4 Biofeedback

**Recommendations**

- Biofeedback procedures are recommended for the preventive treatment of migraine. They can be used instead of or in combination with drug preventive treatment.
- Vasoconstriction training is suitable for the treatment of acute migraine attacks (see Chapter 3.6).

Biofeedback is a therapeutic intervention for conditioning physiological functions, especially autonomic functions. Affected persons learn in several sessions to regulate via feedback of their own bodily signals (e.g. auditory, visual) and thereby gain control over functions that are normally not consciously registered (257). Usually the sessions are conducted in an outpatient setting and require special biofeedback equipment. In the preventive treatment application, signals of tension in particular are fed back, so patients learn to relax. The control of physiological functions (specifically in terms of relaxation) and the conviction of symptom control (non-specific) are discussed as mechanisms of action of biofeedback. It is unclear to what extent, for example, stress reduction through biofeedback is directly responsible for causing a reduction in attack frequency (730).

In a meta-analysis, which is now almost 15 years old, almost 100 clinical trials were included and biofeedback was shown to be effective. The weighted mean effect sizes are between 0.4 and 0.6 (for the use of EEG biofeedback, skin temperature biofeedback, EMG biofeedback or the combination of temperature and EMG biofeedback) for the preventive treatment of a migraine attack (259, 731) (for acute treatment see Chapter 3.5). Meta-analyses thus come to the unanimous conclusion that both relaxation methods (mostly PMR) and various biofeedback methods achieve an average reduction in migraine frequency of 35–45% (731–733). The extent of the effect of these procedures is therefore in the range reported for propranolol (698, 734); in the long term, the relapse rate appears to be greater with propranolol (735). The effects of biofeedback techniques are comparable in size to those of relaxation procedures or cognitive-behavioural treatment procedures (724). A recent randomised controlled trial conducted in an outpatient setting found comparable effects to those available in the literature, with as few as 8 to 11 sessions being sufficient. The effects on self-efficacy appear to be more pronounced than on headache characteristics (736). Newer biofeedback approaches include smartphone applications, which have the potential to be used independently of therapists (730, 737); however, many questions regarding adherence still need to be clarified.

## 10.5 Cognitive behavioural therapy

**Recommendation**

- Cognitive behavioural therapy is strongly recommended for the preventive treatment of migraine. It can be used instead of or in combination with drug preventive treatment.

Cognitive behavioural therapy (CBT) is based on the assumption that experiences and learned attitudes throughout the course of one's life, in interaction with genetic and physical factors, influence health and can be relearned if necessary. Therapeutic approaches for headache include the individual interaction of biological, psychological and social factors in the development and maintenance of complaints and include cognitive-behavioural treatment strategies that are essentially intended to improve the patient's self-efficacy and control beliefs (738). Behavioural therapy strategies also provide patients with techniques to analyse and improve their own handling of stressful events and can change expectations (739). CBT methods are available for migraine patients in well-developed standardised programmes and can be economically implemented both as individual and group treatment with equal efficacy (740–742). The CBT includes the following building blocks: psychoeducation, self-observation, self-management, improvement of self-perception, modification of pain-related cognitions, modification of social impairment, modification of migraine-specific dysfunctional lifestyles (detailed description of treatment modules at (741, 743)).

Newer approaches also focus on disease acceptance and active, quality-of-life and value-oriented rather than avoidant strategies of coping with disease (acceptance and commitment treatment, ACT; trigger management). Acceptance and commitment treatment for primary headache achieved improvements in quality of life, impairment in daily life and depressive symptoms that were still detectable one year after treatment (744); RCT, n = 94; 87.35% migraine patients. In another randomised controlled trial, the effects of a day course of ACT (promoting openness and coping with painful and unpleasant experiences) combined with education on migraine are shown to be superior to a supportive intervention (PMR) and education in the group: in migraine patients with depression, this was reduced or remitted even after six months compared to the supportive group. Similarly, anxiety and headache-related impairment were improved (745), n = 103. The approach "learning to cope with triggers" (LCT), in which a differentiated, active rather than avoidant approach to migraine triggers is learned, was also studied in 2014 (746), RCT, n = 127. Compared to the waiting-list group, trigger avoidance group and CT + avoidance, the LCT group was significantly superior in terms of headache frequency and medication use. In a three-arm randomised controlled design, Klan et al. (255), n = 121, investigated the efficacy of a programme combining trigger management and anxiety coping strategies with education.

It was shown to be equally effective as PMR and more effective than the waiting-list group in terms of self-efficacy in dealing with headache. At 12-month follow-up, the treatment groups also showed improvements in headache frequency, emotional distress and migraine interference compared to the waiting-list group.

## 10.6 Combined pharmacological and psychological treatment

**Recommendation**

- Drug treatment should be accompanied with behavioural therapy methods (such as education, self-observation, self-management, cognitive behavioural therapy, social skills training, relaxation methods, biofeedback, etc.).

Combined pharmacological and psychological therapy is an important component of treatment in a multimodal setting. Studies that examined the effects of such a combination (705) are available on this topic. For example, Grazzi et al. combined behavioural therapy strategies (initially PMR, later additionally EMG biofeedback) with medication preventive treatment in patients with transformed migraine with medication overuse during an inpatient medication break. After treatment and after one year, the effects of both groups were comparable; after three years, the group with the combination showed better results (fewer headache days and less analgesic use) and had fewer relapses in terms of headaches. Medication overuse (747). An important placebo-controlled combination trial for migraine preventive treatment compared the effect of the beta-blocker propranolol with a behavioural therapy programme (PMR, trigger identification and management, stress management, partly also temperature biofeedback) as well as with a combination of both treatments in a total of 232 migraine patients with at least three migraine days per month (624). At the same time, the acute drug treatment was optimised in all participating patients. Only the combination treatment led to an improvement compared to optimising acute treatment alone. Recent work also points to benefits of combined treatment (748, 749).

## 10.7 Endurance sports

**Recommendation**

- Regular aerobic endurance sports are recommended for the preventive treatment of migraine.

Regular endurance exercise is often recommended for the preventive treatment of migraine and is included in most multimodal treatment programmes for headache patients. It is unclear whether endurance sports achieve rather unspecific effects, i.e. represent "a special relaxation procedure", or whether they are actually specific effects that are achieved through an improvement in physical performance.

Further effects could be achieved by weight reduction achieved with exercise, as obesity seems to be associated with higher headache frequency (750). These questions are crucial in order to be able to make statements about the recommended training frequency, training duration and training intensity for migraine preventive treatment. A review of trials published up to 2008 concluded that there are a number of trials that support the possible efficacy of exercise in migraine preventive treatment, but none of the trials are large enough actually to provide statistical evidence of efficacy (751). A recent review comes to similar conclusions; the results are promising, but the individual specific contribution has not been investigated so far (752). A pilot trial showed positive effects of endurance exercise on migraine frequency (753). Overath et al. (754) were able to show in a pre-post trial with 33 patients that aerobic endurance training over a period of 10 weeks improved or normalised both clinical symptoms (number of migraine days per month) and areas of executive functions as well as amplitudes and habituation of the contingent negative variation (CNV). Regular endurance exercise was compared with the effect of topiramate up to the maximum individually tolerated dose and relaxation training in a three-arm trial. There was no significant difference between the treatment arms, but the number of headache attacks was reduced by less than one attack per month in all three arms. Adverse effects were only reported from the treatment arm with topiramate (755). In a quantitative meta-analysis (756) including six RCT trials with a total of 168 patients in sports programmes (and 172 controls), there was a moderate effect for aerobic training. A prospective cohort trial (757) with 94 patients found a more pronounced effect of moderate to vigorous endurance training on at least three days a week in migraine patients on medication preventive treatment compared to patients without medication preventive treatment, with the recommendation to use endurance exercise as an adjunct to medication preventive treatment. An RCT trial with a total of 52 migraine patients who also had tension-type headache and neck pain (758) found improvements in tension-type headache and neck pain in addition to improvements in migraine parameters. Eslami et al (759) found no difference between moderate and vigorous endurance training on headache frequency, intensity and duration in migraine-affected women. In a cross-sectional trial with a student sample with affinity for sports, with and without migraine (760), the positive effect of sport (of various kinds) seems to be more pronounced in women than in men.

In general, exercise seems to be associated with positive effects, sufferers can benefit from low impact exercises (e.g. yoga) if more strenuous exercises are not tolerated. Exercise and endurance sports are now considered evidence-based recommendations. Therapeutic discussion about, and motivation for, exercise and endurance sports can lead sufferers to experience more self-directed control over their headaches. These measures, in combination with other preventive treatment measures, may provide additional benefits (761, 762).

## 10.8 Acupuncture

**Recommendation**

- The superiority of classical acupuncture over sham acupuncture in preventing migraine is contradictory according to current trials. Overall, there are moderate, non-specific effects.

Acupuncture as a treatment option for episodic migraine has been increasingly studied since the early 2000s (763). The resulting systematic reviews, meta-analyses and Cochrane evaluations now allow statements about efficacy. An important factor is the choice of placebo condition, with sham acupuncture being the best choice here. With this active placebo, needling is carried out on parts of the body that are not counted as classical acupuncture points.

While a Cochrane trial from 2009 was not able to show any superiority over sham acupuncture (764), the 2016 re-evaluation showed evidence of a small superiority of classical acupuncture over sham acupuncture. The trials reviewed in it suggest a similar efficacy of treatment as with drug preventive treatment (765). Fan et al. came to the same conclusion in a recent meta-analysis (766), which also showed a superiority over sham acupuncture in the reduction of migraine attacks after treatment, but also in follow-up surveys; the responder rate no longer showed a difference in follow-up surveys. The effect of acupuncture was comparable to medication preventive treatment. In terms of the occurrence of adverse events, acupuncture was significantly better than drug preventive treatment. A meta-analysis of trials from 2010 to 2019 (767) showed an effect over no treatment and over Western medicine (pharmacotherapy), but not over sham acupuncture. The meta-analysis by Yang et al. came to a comparable conclusion. With regard to menstrual migraine, there is no convincing evidence (768).

However, the low quality of the trials in the review by Ni et al. (three quarters with "risk of bias") is a limiting factor for clear conclusions. Similar statements about effective headache reduction, but also about limiting factors, can be found in the published reviews of recent years (254, 769–773).

An interesting aspect was brought into play by Liao et al. (774) who found lower medical expenses (775) and lower anxiety and depression in about 2000 patients who underwent acupuncture compared to an equal number of comparable patients who did not. The effect on anxiety and depression was observed over a period of about 10 years.

For chronic migraine, there is a meta-analysis comparing acupuncture, topiramate and botulinum toxin (776). Acupuncture and topiramate showed numerical superiority over botulinum toxin, but this was not significant. Topiramate had the most adverse events and dropouts.

## 10.9 Cold applications

Cold stimuli can be perceived by patients both as a trigger of migraine attacks and as pain relieving. In acute treatment, local cooling of the head and forehead is found to be positive in various trials (777). However, placebo-controlled efficacy can hardly be methodically tested. However, a randomised controlled trial compared the cooling effect of menthol oils, which also activate the transmembrane cold receptors TRPM8, on the forehead and temples at different concentrations and was able to show a superiority of the higher concentration compared to the lower placebo concentration (778, 779).

## 10.10 Drinks to treat migraine

**Recommen**

- Sufficient fluid intake of at least 1.5 litres/day is recommended.
- Dehydration should be avoided.

Too little fluid intake should be avoided to prevent dehydration headache. Increased fluid intake is often popularly advised as a home remedy for headaches. However, a randomised controlled trial failed to demonstrate any changes in headache frequency in migraine patients with regular, increased fluid intake (780). Caffeinated beverages have been described as both a trigger and a therapeutic option for acute headache attacks. There is positive evidence for the efficacy of caffeine and analgesics in particular, although migraine patients should be careful to limit caffeine to 200 mg daily to avoid chronicising effects (781).

## 10.11 Procedures with no effect

There are a number of other approaches for which no effect could be proven or, even in the case of isolated positive findings, the length of the trial is unclear because, for example, large-scale and methodologically high-quality trials are lacking. These are briefly listed here for the sake of completeness.

### 10.11.1 Piercing

In recent years, so-called daith piercings have been advertised as a treatment for migraine, especially on social media platforms. This involves placing a piercing in the area of the ear cartilage (tragus), comparable to one of the acupuncture points used for migraine treatment.

There is no comprehensible pathophysiological basis; meaningful randomised controlled trials are not available. Due to possible health risks such as local infections (perichondritis), the use of ear piercings in migraine treatment is not recommended given the current data.

### 10.11.2 Homeopathy

A therapeutic effect of homeopathy for migraine could not be proven in previous trials. There are no effects beyond the placebo effect (782, 783). From a health business point of view, it should be critically noted in this context that the treatment costs for homeopathy clearly exceed those for conventional medical care (784, 785).

## 11 Diets and dietary supplements

**Recommendations**

- Dietary supplements and probiotics are not effective in preventing migraine.
- Low-sugar, low-fat or ketogenic diets may be effective.

### 11.1 Dietary supplements

Apart from riboflavin, magnesium and Q10, other smaller trials have also been conducted with natural substances. However, the efficacy is less clearly assured. With vitamin B12, an open trial was conducted with 20 patients (786). 1 mg hydroxycobalamin was administered intranasally for three months. A reduction in migraine attack frequency of >50% was observed in 10 out of 19 patients (53% responders). However, the open trial design is not suitable to prove the efficacy of vitamin B12 and the number of patients is too small. Vitamin D was studied together with simvastatin in a placebo-controlled, randomised, double-blind trial in 57 adults with episodic migraine (549). Participants received 20 mg simvastatin twice daily plus 1000 IU vitamin D3 twice daily for 24 weeks. Compared with placebo, simvastatin plus vitamin D3 showed a greater reduction in the number of migraine days from baseline to intervention weeks 1 to 12: a change of -8.0 days in the active treatment group versus +1.0 days in the placebo group, $p < 0.001$. The potential effect of vitamin D3 alone on migraine cannot be assessed because of the combination with simvastatin. However, the results of this trial could not be confirmed in clinical practice. A monocentric, randomised, triple-blind, placebo-controlled cross-over trial was conducted with acetyl-1-carnitine in episodic migraine (787). For 12 weeks, 3 g acetyl-1-carnitine or placebo was administered.

In this trial, no differences in headache outcomes are found between acetyl-l-carnitine and placebo. Wagner describes a trial with polyunsaturated fatty acids in 168 patients over a period of six months in an open uncontrolled trial (788). In 129 patients available for the trial, 86% showed a reduction in the severity, frequency and duration of migraine attacks. In a controlled double-blind trial from Brazil, 60 patients with chronic migraine were treated with amitriptyline and omega-3 fatty acids or amitriptyline and placebo for 60 days as a preventive treatment (789). In 67% (18/27) of patients taking amitriptyline + omega-3 fatty acids, the number of days with headache decreased by more than 80.0% per month, while in the control group the same improvement occurred in 33.3% (8/24) of patients ($p = 0.036$). In a double-blind trial, 196 patients received placebo or 6 g of omega-3 fatty acids per day for 16 weeks (790). The primary endpoint, the number of migraine attacks per month, was not different between verum and placebo.

## 11.2 Probiotics

The importance of the microbiome for health and its physiological role in a variety of diseases and dysfunctions is currently being intensively researched (791). Probiotics have also been studied for migraine preventive treatment. However, the number of trials is very small and two recent reviews found no evidence for their efficacy. In the first review, it was only possible to analyse two trials. Due to methodological differences, a meta-analysis was not possible. One trial found no significant change in migraine frequency and intensity, while the second trial found highly significant improvements (792). The other review included three randomised controlled trials involving 179 patients. Probiotic supplementation had no significant effect on the frequency and severity of migraine attacks with significant heterogeneity between trials ($I2 = 98\%$, $p < 0.001$) (793).

## 11.3 Diets

In the trials on the influence of food on migraine, a distinction must be made between avoiding identified or perceived triggers of migraine attacks and changing the diet. Most patients for whom certain drinks or foods play a role as migraine triggers have already identified them and usually avoid them. A systematic literature review identified 43 trials that investigated the role of diet and nutrition in migraine (794). There were 20 trials on trigger factors of migraine. The most important is alcohol and especially red wine.

12 Studies looked at specific diets. In these trials, a positive effect on various parameters of migraine was found for diets low in sugar, diets low in lipids, a vegan diet low in fat, the ketogenic diet and the DASH diet high in fruits, vegetables, poultry, fish and nuts. A total of four trials investigated diets which eliminated putative allergens in the diet, based on an IgG elimination diet. However, the German Nutrition Society (Deutsche Gesellschaft für Ernährung e.V.) sees no scientific basis for this approach (795).

Table 15: Studies on diets in migraine preventive treatment

| Quantity | Refer-ence | Intervention and design | Result |
|---|---|---|---|
| n = 350 | (796) | Low-sugar diet versus migraine preventive treatment with medication, RCT | Reduction of attack frequency in both treatment groups by 3–4 days per month |
| n = 83 | (797) | Low-fat diet versus normal diet, cross-over | Significant reduction in migraine days per month<br>(-6.8 versus -2.9) |
| n = 42 | (798) | Vegan diet, low fat versus placebo, cross-over | No effect on headache days |
| n = 96 | (799) | Ketogenic diet versus low-calorie diet, cross-over | After six months, no difference in attack frequency and headache days |
| n = 35 | (800) | Ketogenic diet versus control in overweight women, RCT | Significant reduction in migraine days |

RCT = randomised controlled trial

Overall, the scientific evidence for special diets or nutrition for migraine preventive treatment is weak (794, 801).

# 12 Smartphone applications (apps) and telemedicine services for migraine

**Recommendations**

- Smartphone applications and telemedicine services can support the diagnosis and treatment of migraine.
- They can document the course of migraine and headache and thus support the monitoring of progress and success.
- Information tools can provide knowledge and behavioural treatment options.
- Internet-based services and apps can be helpful when time or location constraints (e.g. pandemic, rural areas, long waiting times) make face-to-face care difficult.
- For the selection of apps in migraine and headache treatment, minimum criteria should be met.
- Results from randomised controlled trials on clinical efficacy or improvement of the quality of care are currently not available.

Internet-based services and digitally supported services for the diagnosis and treatment of migraine have been used and scientifically studied since the 1990s (698, 710, 802).

With the introduction of the operating systems iOS in 2007 and Android in 2008, extensive computer functionalities and connectivity also became possible on mobile devices. For these systems, a variety of smartphone applications (apps) have been developed for the health sector in general as well as for the pain and headache sector in particular (710, 803). They offer many new possibilities for those affected and those treating them. They can document the course of migraine and headache and thus support progress and outcome monitoring (710, 711, 804–807). Information tools can provide knowledge and behavioural therapy options (705, 710, 802, 808). A particularly interesting function for research is the digital collection of data in anonymised form, which can be used for scientific analyses (710, 807). Apps also allow innovative elements of digitisation such as chatbots, social networking e.g. through digital support groups or psychoeducation through videos and animations (710, 711, 802, 807, 808). Internet-based services and apps can be helpful when time or location constraints (e.g. pandemic, rural areas, long waiting times) make face-to-face care difficult (806, 809).

Mobile software applications are used early on to monitor progress and success in the context of pain and headache treatment (810–813). They have a number of advantages over paper documentation. People tend to carry their smartphone with them at all times. It is the central communication device for over 88% of the population. Documentation of headache phenotype and headache course over time can be done prospectively and directly. Algorithms can classify headache attacks based on the International Headache Society criteria (814). Historical parameters can be entered and evaluated directly in the app. Current information on environmental variables such as air temperature, air pressure and location can be added digitally. The smartphone can generate clear evaluations and reports from this diverse data. In medical consultation, these can be used directly to support treatment decisions. Medication overuse, the efficacy of preventive medication, attack treatment and other progression patterns can be directly evaluated and used as a basis for further treatment (815). Monitoring progress and success with smartphone applications has proven to be more reliable than paper diaries in scientific trials. They show higher compliance compared to paper diaries (816), the compliance rate for electronic diaries is 94%, while for paper diaries it is only 11% (817).

Internet-based services and apps are companion media to aggregate diagnostic information and support therapeutic elements (705), however, they cannot replace contact with therapeutic professionals (818). A particular challenge, however, is the large number of apps available, some of which are of low quality and not in line with guidelines. Access to app stores is not professionally regulated for medical content providers. The applications can also be made available in the app stores without medical expertise. According to the Digital Health Care Act (DVG), the statutory health insurance companies cover the costs of digital health applications if they are listed in the DiGA directory of the BfARM and are prescribed by a doctor. This requires data protection, information security, efficacy and/or a positive effect on patient care to be confirmed. However, this does not mean that apps not listed in the DiGa directory (e.g. by scientific societies) do not fulfil these requirements.

A uniform catalogue of criteria was drawn up for Switzerland (819) to support users in the usage decision-making process (statement of 20.11.2019). Nine overarching criteria are derived as the basis for a self-declaration of health apps: I. Transparency, II. Expediency, III. Risk adequacy, IV. Ethical harmlessness, V. Legal conformity, VI. Content validity, VII. Technical adequacy, VIII. Fitness for use and IX. Resource efficiency. Currently, there are no standards for the evaluation and selection of apps in migraine and headache treatment. The following is a list of minimum criteria that the authors believe the apps should continue to fulfil.

- The app should have been developed with clinical and/or scientific headache expertise. The author team should be scientifically proven in the treatment of headache.
- The app's therapeutic recommendations should be guided by published scientific guidelines.
- The interest of the providers in the development of the app should be declared.
- The bearing of development costs should be transparent.
- The requirements of the General Data Protection Regulation should be met.
- The headache parameters collected should be based on the current classification of the International Headache Society.
- The app should be evaluated according to scientific criteria with regard to its efficacy and/or improvement of the quality of care.

Many apps are designed as digital headache diaries. However, there are also offers that additionally include therapeutic approaches (i.e. education, relaxation, elements of cognitive behavioural therapy). Such an approach is investigated, for example, by Sorbi and colleagues (820, 821) in a randomised controlled trial of 368 patients with frequent episodic migraine. Although no immediate improvement in headache frequency could be demonstrated in the experimental group compared to the control group, the intervention did lead to an improvement in patients' self-efficacy and attack management.

Further conclusions can be drawn from several smaller randomised controlled trials and feasibility trials – at least for the scientifically developed apps (cf.also Table 16). Studies indicate that more frequent use of the respective app is associated with better effects (710, 711, 725), which should be taken into account especially with regard to adherence. Larger randomised controlled trials are needed to evaluate headache apps with therapeutic modules (822) and are being conducted (805, 823).

There is now a whole range of apps (e.g. from America "N1-Headache" [Curelator] and "Migraine Buddy"), although in the German-speaking area the following apps are particularly popular: "Migraine App" and the "M-sense Migraine" app (804). The "Migraine App" documents the course of migraine and headache with active data entry. It reports back aggregated information from the data set and thus supports patients and attending physicians in monitoring progress and success, in adhering to treatment rules as well as in adjusting treatment. The "Migraine App" contains reporting, information, treatment and self-help tools. The "Migraine App" is contractually integrated into medical treatment and treatment within the framework of statutory health insurance via a care contract according to Section 140a et seq SGB V for integrated care of migraine and headache (824–826). Göbel et al. (710) investigated the use of the "Migraine App" in the care of 1464 migraine and headache patients in a standardised survey. The integration of the "Migraine App" into the active care process showed a promotion of treatment adherence and a reduction of complications such as medication overuse headache. Compared to the time before using the app, there is a significant reduction in monthly headache days (from 13.3 to 10.0) and acute medication days (from 7.6 to 6.8).

The "M-sense Migraine" app combines a digital, interactive headache diary with non-medicinal treatment methods such as relaxation techniques, endurance sports programmes, physiotherapeutic exercises and patient education. In addition, a trigger analysis helps to identify possible triggers for migraine attacks. A data analysis of over 1500 patients showed that the use of the basic functions (diary function and trigger analysis) is associated with a significant reduction in monthly headache days (from 9.4 to 6.4) and medication days (5.4 to 4.3) (827). "M-sense" was listed in the DiGA directory of the BfArM, but the manufacturer withdrew the app from the directory in May 2022, so it can no longer be prescribed. The results of the two randomised controlled trials (EMMA and SMARTGEM) that investigated the efficacy of the app in different constellations had not yet been published at the time of writing this guideline.

On the initiative of the German Migraine and Headache Society, an app for monitoring the course of migraine has been developed and made available for Android and Apple users. The DMKG app is based on the DMKG Headache Calendar, which collects and compiles relevant information for the practitioner in a clear format (807). There is the option of a digital link to the DMKG registry trial, which patients can agree to independently of app use. Via an online interface, the contents of the app calendar are transferred directly to the digital patient file of the participating headache centres, thus simplifying the transfer of information to the treating physician.

At present, no results of randomised controlled trials have been published on these apps, so no conclusive statement on the level of evidence can be made.
In the future, it will also be relevant to consider whether digital applications, in addition to a possible clinical efficacy, can also lead to an improvement in structures and procedures and thus contribute to an improvement in the quality of care.

### Further digital treatment options and telemedicine

Many of the trials mentioned in the guideline "Relaxation methods and behavioural therapy interventions for the treatment of migraine" (705) under the item "Education/counselling" are online-based offers. These are assessed with a high level of evidence, which means that online-based offers can be provided and used in a low-threshold manner, especially in the field of education. Thakur et al. (828), for example, showed in 95 people with migraine and comorbid depression that a short one-hour online educational video could contribute to increased knowledge about migraine and better self-management, while also positively influencing depressive symptoms.

Especially in the context of the COVID 19 pandemic, online-based formats in patient care have recently received increased attention. Telemedicine seems particularly suitable for the long-term management of migraine because of the importance of anamnestic information in the evaluation of the course of the disease in headache patients. It allows greater flexibility for patients to keep appointments and is particularly suitable for rural regions or in pandemic situations. A smaller randomised controlled trial found no difference in disease outcomes for migraine patients with telemedicine treatment monitoring versus on-site appointments. However, the convenience of telemedical appointments is rated more highly by patients, and it was also possible to shorten visit times (829).

**Table 16: Overview of randomised-controlled trials of app- or online-based relaxation techniques for migraine since 2018**

| Trial | Sample | Result |
|---|---|---|
| (725) | Migraine (n = 139), 77 received the "RELAXaHEAD" app with the PMR module, 62 without the PMR module | The group with the PMR module showed a greater, though not statistically significant, decrease in MIDAS score (-8.7 vs. -22.7, p = .10, Cohen's d = 0.38) |
| (737) | Migraine (n = 52), 26 received heart rate variability biofeedback (app "HeartMath"), 26 in waiting-list control group | No difference in quality of life between groups; users with frequent use showed significantly better change in quality of life, users with low use did not |
| (830) | Migraine (n = 40), 22 received hypnosis MP3s as part of online-based hypnotherapy, 18 in waiting-list control group. | Hypnosis MP3s group showed a significantly greater decrease in pain catastrophising, headache-related impairment and migraine attack duration compared to the waiting group. |

# 13 Special cases for Austria and Switzerland

## 13.1 Special cases for Austria, prophylactic treatments for migraine

The monoclonal CGRP antibodies eptinezumab, erenumab, fremanezumab and galcanezumab are approved in Austria and in the green box with regard to reimbursement, which means that they can be prescribed freely, but with certain conditions:

- The first prescription must be issued by a specialist in neurology.
- Patients must have at least four migraine days per month.
- Patients must have taken at least three of the conventional preventive treatment substances that either had an insufficient effect or for which treatment had to be discontinued due to adverse effects, or there were contraindications or warnings against the prescription; there is no prescribed duration of treatment or dosage.
- After three months, the success of the treatment must be evaluated by a neurological specialist, while continuous documentation in the form of a headache diary must be verifiable and further controls should be carried out at regular intervals.
- After 12 months of treatment, discontinuation/pause may be considered.
- A restart is possible in line with the conditions according to the rule text, as is a change to another monoclonal CGRP antibody after a break in treatment.

Eptinezumab is approved in Austria, but there are currently no regulations for reimbursement.

**Ditans:**

Lasmiditan, as a representative of the 5-HT-1F receptor agonists, has been approved in Austria since 18.08.2022 under the trade name Rayvow ®, however, there is no reimbursement by the Austrian health insurance companies for the prescription, but the substance can be prescribed by obtaining a chief physician's authorisation or self-payment.

**Gepants:**

Rimegepant is now approved in Austria, but there is no reimbursement by the Austrian health insurance companies.

Phenazone is not available in Austria.

## 13.2 Special cases for Switzerland

For the treatment of episodic and chronic migraine, non-migraine-specific preventive treatments are approved in Switzerland: amitriptyline (tricyclic antidepressant), topiramate (anticonvulsant), metoprolol and propranolol (beta blockers) and flunarizine (calcium antagonist).

OnabotolinumtoxinA is not approved for the treatment of chronic migraine, but is at least partially reimbursed by many health insurance companies.

The monoclonal antibodies against CGRP or the CGRP receptor erenumab, galcanezumab, fremanezumab and eptinezumab are approved as migraine-specific drugs. According to a decision by the Swiss Federal Office of Public Health (FOPH), their use is subject to strict limitations, among other things there must be an average number of monthly migraine days of at least 8 and it must be proven that the patients have responded inadequately to at least 2 preventive treatments with a beta blocker, calcium antagonist or anticonvulsant, that these are not tolerated or that there are contraindications or warnings against their use (details can be found in the treatment recommendations of the Swiss Headache Society, available at https://www.headache.ch/, or in the FOPH list of specialities https://www.spezialitaetenliste.ch/). Gepants and ditans are not approved in Switzerland. Lasmiditan manufacturer Eli Lilly submitted a marketing approval application to the Swiss regulatory authority for medicinal products and medical devices (Swissmedic) in January 2021, which is still pending (as of June 2022).

Among the non-invasive stimulation methods, the Cefaly device (Cefaly® Technology Sprl, Herstal, Belgium) is approved for acute and preventive treatment of migraine.

# 14 Funding of the guidelines

This guideline has been developed without third-party funding.

# 15 Methodology of the guideline development

The DGN and the DMKG nominated the authors for the guideline. Each of the authors was responsible for updating an assigned section of the guideline. For this purpose, a search of the literature of the last four years was carried out in each case.

The first complete version was then sent to all authors a total of four times in an iterative Delphi process with the request for corrections and additions. The recommendations were voted on in two ZOOM conferences in September 2022.

The final version of the guideline was adopted by the participating authors in November 2022.

This guideline was adopted by the Guidelines Commission of the German Neurological Society (DGN), the German Migraine and Headache Society (DMKG) and the boards of the participating specialist societies.

# 16 Declaration of interests and dealing with conflicts of interest

All the contributors to the guideline submitted their completed declarations of interest (AWMF form, version dated 2018, for declaration of interests in the context of guideline projects) to the coordinator (HCD) or to the Editorial Office Guidelines of the DGN prior to the start of text preparation. The assessment of the declarations of interest for thematic relevance to the guideline was carried out by the coordinators Prof Dr Hans-Christoph Diener, PD Dr Stefanie Förderreuther and Prof Dr Peter Kropp, whose interests were assessed by an anonymous, independent and expert conflict of interest officer of the DGN.

The information was reviewed with regard to a present thematic reference, thematic relevance, type and intensity of the relationship as well as the amount of the payments.

A *minor* conflict of interest is assessed as: Lecturing and authoring activities on products of the pharmaceutical industry or third-party funding from government sources, which are recommended in the guideline.

A *moderate* conflict of interest is assessed as: Ad board, consultant and expert interests on pharmaceutical industry products discussed in the guideline. Furthermore, third party industrial funding in a responsible position, which is recommended in the guideline.

A *major* conflict of interest is assessed as: Ownership interests; ownership of business shares; patent ownership from processes or products related to the guideline; family ties to a company marketing a product covered by the guideline. This was not the case with any of the contributors.

### Findings

The editorial committee comprises 28 members, including three lead authors.

Of the total group, 11 members are free of conflicts of interest (CIs) or have only minor thematically relevant conflicts of interest.

17 Members received personal grants related to the guideline regarding monoclonal antibodies against CGRP or the CGRP receptor and drug treatment (onabotulinumtoxinA, triptans, sumatriptan, fremanezumab, lasmiditan). This was assessed as "moderate". These authors did not work on the topic in question and abstained from the subject matter in the final Delphi round. Three of the authors were not directly involved in the preparation of the guideline text and undertook the correction and editorial revision of the final version.

Coordinator Ms Förderreuther (moderate CIs) was offset by two coordinators with only low CIs (Diener, Kropp).

In order to comply with the 50% rule of the DGN, a balance of interests was ensured by balancing authors chapter-wise with moderate CIs with contributors with no or only low CIs. This concerns the chapters on monoclonal antibodies and on onabotulinumtoxinA.

For reasons of transparency, the interests of the stakeholders as well as their assessment are listed in the tabular summary (see appendix).

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# Appendix: Declaration of interests – tabular summary

The original fully completed declarations of interests have been lodged with the guideline coordinators at the Guideline Editorial Office.
The authors' declarations of interests are shown below in a standardised tabular form with the results of the conflict of interests assessments. The table only lists those details that are considered thematically applicable in the context of this guideline. The guideline group declarations were reviewed and assessed by H.-C. Diener, S. Förderreuther and P. Kropp and their declarations as coordinators were, in turn, reviewed and assessed by anonymous, independent, conflict-of-interest DGN officers with knowledge of the subject matter.

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Hans-Christoph Diener (Coordinator for DGN)** | no | no | Teva (fremanezumab), Lilly (galcanezumab), Lundbeck (eptinezumab), Biohaven (rimegepant) | Lundbeck (eptinezumab), Lilly (galcanezumab), Teva (fremanezumab), Weber und Weber (Petasides) | DFG (Preventive treatment of MOH; without industrial involvement) | no | Press Officer for DGN, DMKG, EHF, IHS, AAN, EAN<br><br>Scientific activities:<br>Headaches<br><br>Lead participation:<br>Information on neurology & psychiatry, Medscape, Neurodiem<br><br>Department for neuro-epidemiology, IMIBE<br>University of Duisburg-Essen | Talks, author activities<br><br>low,<br><br>none |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Stefanie Förderreuther (coordinator for DMKG)** | no | Novartis (erenumab), Sanofi (thomapyrin tensioduo), Hormosan (sumatriptan), Lundbeck (eptinezumab), TEVA (migraine preventive treatment), Lilly (migraine preventive treatment), Novartis (erenumab) | TEVA<br>Novartis<br>Allergan | no | no | no | DMKG<br>Scientific activities:<br>Headaches, IHA diagnostic methods<br><br>Clinical activities:<br>Pain therapy, determining brain death<br><br>Neurological Clinic and Polyclinic at the LMU in Munich | AdBoards, presentations<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding monoclonal antibodies against CGRP or the CGRP receptor |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Peter Kropp (Coordinator for DMKG)** | Novartis (psychological factors relating to headache treatment)<br><br>TEVA (non-drug headache treatment) | Novartis (monoclonal antibodies)<br><br>Lilly (monoclonal antibodies) | no | no | no | no | DGMP, DMKG<br><br>Scientific activities: Pathophysiology of headaches and migraine<br><br>Clinical activities: Non-drug headache treatment, behavioural therapy<br><br>Lead participation: DGVT, DGPSF, ISM, OPK<br><br>Institute for Medical Psychology and Medical Sociology, Rostock University Clinic | Consulting, AdBoards<br><br>low, because no contact with medications (all activities related to non-drug treatments)<br><br>none |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Thomas Dresler (author)** | no | no | Hormosan (psychology and headaches, digital approaches and aspects of the pandemic)<br><br>TEVA (coping day to day with migraine) | Hogrefe Verlag publishers, Springer (but both without industrial involvement) | no | no | DMKG, DGPA, Society for fNIRS, MCLS, DGPs, ADHS-network in Tübingen<br><br>Scientific activities: Research, junior research group leader, publications neuroscience and education, headaches<br><br>University Hospital for Psychiatry and Psychotherapy Tübingen, LEAD Graduate School & Research Network Tübingen | Presentations<br><br>low,<br><br>none |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Robert Fleischmann (author)** | no | Novartis (erenumab)<br><br>TEVA (fremanezumab) | Novartis, TEVA (treatment of migraine) | no | Novartis (erenumab, APOLLON)<br><br>TEVA (fremanezumab, migraine) | no | DMKG<br><br>Scientific activities: Pathophysiological fundamentals and migraine care<br><br>Clinical activities: Headache centre, university outpatient clinic, day-care and inpatient headache treatment<br><br>Clinic for Neurology, University Clinic Greifswald | AdBoards, presentations, research<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding monoclonal antibodies |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Charly Gaul (author)** | Allergan Pharma/Abbvie (botulinum toxin) | Lilly (lasmiditan, galcanezumab), Teva (fremanezumab), Novartis (erenumab), Lundbeck (eptinezumab) | Lilly (lasmiditan, galcanezumab), Lundbeck (eptinezumab), Grünenthal (zolmitriptan), Novartis (erenumab), Teva (fremanezumab), Hormosan (sumatriptan), Allergan Pharma/Abbvie (botulinumtoxin) | Novartis (erenumab) | no | no | DMKG, DGN, DGNB, Deutsche Schmerzgesellschaft, DGS, IHS, IASP, Migräne-Liga e.V., CSG e.V.<br><br>scientific and clinic activities Headache disorders<br><br>Independent, Headache Centre Frankfurt | Consulting, AdBoards, presentations, author<br><br>moderate<br><br>Only involved in formal final editorial stage (corrections and editorial review of the final version) |
| **Florian Giese (author)** | no | no | no | no | no | no | University Hospital in Halle | none |
| **Carl Göbel (author)** | no | no | no | no | no | no | Pain Clinic, Kiel and Clinic for Neurology, UKSH Lübeck | none |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Hartmut Göbel (author)** | Organon Austria (rizatriptan) | Grünenthal (zolmitriptan)<br><br>Lilly (galcanezumab)<br><br>Novartis (erenumab)<br><br>TEVA (fremanezumab) | Allergan GmbH (onabotulinum toxin) | Springer Verlag (headaches; without industrial involvement) | no | no | DGN, DGS, DMKG, DSG<br><br>Scientific activities:<br>Neurological pain therapy, headaches<br>neuropathic pain<br><br>Clinical activities:<br>Neurological pain therapy, migraine Headaches, neuropathic pain<br><br>Pain Clinic, Kiel | Consulting, AdBoards, instruction<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding triptans & monoclonal antibodies |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Gudrun Gossrau (author)** | no | Novartis (erenumab)<br><br>Lilly (galcanezumab)<br><br>TEVA (fremanezumab) | Novartis (erenumab)<br><br>Lilly (galcanezumab)<br><br>TEVA (fremanezumab) | no | no | no | DMKG, Deutsche Schmerzgesellschaft, IHS, DGN<br><br>scientific activities: Migraine, headaches, pain, olfactory, sensor technology<br><br>Clinical activities: Headaches, neuropathic pains<br><br>Lead participation: Medical faculty at TU Dresden<br><br>University Pain Centre, University Clinic, Dresden | AdBoards, presentations<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding monoclonal antibodies |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Anna-Lena Guth (author)** | TEVA/ Ratiopharm (pain, pain memory, pain management strategies)<br><br>Sanofi Aventis (psychotherap eutic methods for headaches) | Novartis (future outlook for migraine treatments) | Novartis (psychotherapy and psych. Comorbidity with migraine, the role of the psychotherapist in headache treatment)<br><br>TEVA (migraine, relaxation procedures)<br><br>Allergan/Abbvie (headache disorders)<br><br>Lundbeck (psyche and headaches) | Kohlhammer (headaches)<br><br>ABW Scientific publishers (patient advice on migraine and headaches)<br><br>Elsevier (headaches, Uexküll, psychosomatic medicine)<br><br>Hormosan (acute treatment of migraine and blood-injection-injury phobia) | no | no | DMKG, DGPSF, Psychotherapists' Chamber, Hesse<br><br>Scientific activities: Psychotherapy for headache disorders, cognitive behavioural therapy, interdisciplinary multimodal pain therapy<br><br>Clinical activities: Psychotherapy for headache disorders, cognitive behavioural therapy, relaxation treatments<br><br>Headache Centre Frankfurt | consulting, AdBoards, author (Hormosan), presentations on psychological topics<br><br>moderate<br><br>Involvement only in non-medical |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Till Hamann (author)** | no | no | no | Springer Verlag (GRP antibodies in preventive treatment for migraine; without industrial involvement) | no | no | DGN, DMKG, Hartmannbund<br><br>Clinic and Polyclinic for Neurology, Rostock University Clinic | none |
| **Simon Heintz (author)** | no | no | TEVA (CGRP methods in preventive treatment for migraine) | no | no | no | DMKG<br><br>Clinical activities: Neurological A&E Integrated care Headaches, headache A&E<br><br>Clinic for Neurology, University Clinic in Halle (Saale) | Presentation<br><br>low,<br><br>none |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Dagny Holle-Lee (author)** | no | TEVA (fremanezumab)<br><br>Lilly (galcanezumab)<br><br>Novartis (erenumab)<br><br>Lundbeck (eptinezumab)<br><br>Hormosan (sumatriptan s.c) | Allergan/Abbvie (onabotulinum toxin A)<br><br>Lilly/Zuellig PHARMA (galcanezumab)<br><br>Novartis (erenumab)<br><br>Lundbeck (eptinezumab)<br><br>Hormosan (sumatriptan s.c) | no | no | no | DMKG, DGN<br><br>scientific<br><br>activities: Clinic and pathophysiology<br><br>Headache disorders<br><br>Clinical activities:<br><br>Manager of West German Headache Centre<br><br>West German Headache and Vertigo Centre<br><br>for neurology,<br>University Clinic, Essen | AdBoards, presentations<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding sumatriptan, onabotulinumtoxinA & monoclonal antibodies |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Tim Jürgens (author)** | Assessment Federal Joint Committee (G-BA) (benefit assessment of botulinum toxin, fremanezumab, erenumab) | Allergan (botox), TEVA (fremanezumab), Novartis (erenumab), Lilly (galcanezumab), lasmiditan), Hormosan (sumatriptan), Lundbeck (eptinezumab) | Allergan (botox), TEVA (fremanezumab), Novartis (erenumab), Lilly (galcanezumab), lasmiditan), Hormosan (sumatriptan), Lundbeck (eptinezumab) | no | Federal Joint Committee (G-BA) (Evaluation of Migraine App) | no | DMKG, DGN Further Training Academy, pain congress, IHS, Chair Special Interest Group Emerging Therapies<br><br>Scientific activities: Neurophysiology and pain, neuromodulation for pain, autonomic nervous system and pain, Neuropsychology and pain<br><br>Clinical activities: Headaches and facial pains, Neuropathic pain, neurogeriatrics, palliative care, mobility disorders, peripheral neurology:<br><br>Clinic for Neurology, KMG Clinic Güstrow | AdBoards and presentations (expert opinions & evaluation Federal Joint Committee (G-BA), not industry-led)<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding monoclonal antibodies, onabotulinumtoxinA and lasmiditan |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Katharina Kamm (author)** | no | Novartis (migraine ) | Novartis (primary and secondary headaches/ menstrual migraine)<br><br>Lundbeck (migraine)<br><br>TEVA (photophobia and migraine)<br><br>Lilly (cluster headaches) | no | Novartis (migraine) | no | DMKG<br><br>Scientific activities: Migraine, cluster headaches<br><br>Clinical activities: Neurology:<br><br>LMU Clinic, Munich | AdBoards, presentations, research<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding monoclonal antibodies |
| **Doris Lieba-Samal (author)** | no | no | Lilly (Migraine therapy) | no | no | no | ÖKSG, ÖGUM<br><br>Lead participation: Sonocampus GmbH (Neuromuscular ultrasound) | Presentations low<br><br>none |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Arne May (author)** | no | no | no | no | no | no | DGN, DMKG, ISASP, IHS<br><br>Scientific activities: Headaches, pathophysiology, neuroimaging<br><br>Clinical activities: Neurology, pain medicine, headaches, facial pain<br><br>Lead participation: Cephalalgia and cephalalgia report<br><br>Institute of Systems Neuroscience, University Clinic Hamburg Eppendorf, (UKE) | none<br><br>as publisher of cephalalgia with no connection to industry<br><br>none, only involved in formal final editorial stage (corrections and editorial review of the final version) |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Steffen Nägel (author)** | no | TEVA (fremanezumab)<br><br>Lilly (galcanezumab)<br><br>Novartis (erenumab)<br><br>Lundbeck (eptinezumab)<br><br>Hormosan (sumatriptan s.c) | Allergan (onabotulinum toxin A)<br><br>Lilly (galcanezumab)<br><br>Novartis (erenumab)<br><br>TEVA (fremanezumab)<br><br>Hormosan (sumatriptan s.c, eletriptan) | Hormosan (sumatriptan s.c, eletriptan) | no | no | DMKG, DGN, INS, MN, EAN<br><br>Scientific activities: Clinic and pathophysiology of headaches and vertigo disorders<br><br>Clinical activities: Manager of University and Headache A&E<br><br>University A&E, Headache A&E, Clinic and Polyclinic for Neurology, Martin-Luther University Halle-Wittenberg | AdBoards, presentations, author<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding monoclonal antibodies |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Lars Neeb (author)** | TEVA (fremanezumab /ajovy) | Novartis (erenumab/ sumatriptan s.c.) | Novartis (erenumab)<br><br>Lilly (galcanezumab)<br><br>TEVA (fremanezumab)<br><br>Pharm Allergan (botox) | Springer Medicine Verlag GmbH (migraine and dementia; no industrial involvement) | Deutsches Zentrum Für Luft- Und Raumfahrt e.V. (Smartphone-assisted migraine therapy "eHealth")<br><br>TEVA (fremanezumab)<br><br>Lilly (galcanezumab)<br><br>Allergan/ Abbvie (atogepant) | no | DGN, DMKG, IHS<br><br>Scientific activities: Migraine, cluster headaches, stroke<br><br>Clinical activities: Headache, epilepsy, stroke<br><br>Clinic and University A&E for neurology, Charité University Clinic, Berlin | Consulting, AdBoards, presentations, research<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding monoclonal antibodies |
| **Uwe Niederberger (author)** | no | no | Memomed e.V./ DGVT/ISM (Psychological pain therapy) | no | no | no | DGPSF, DMKG<br><br>Institute for Medical Psychology, UKSH, Campus Kiel | Presentations without industrial involvement.<br><br>none |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Antonella Palla (author)** | no | Lundbeck (Switzerland) AG (eptinezumab)<br><br>Novartis (Interview und Steering Committee MÜKS topics) | TEVA (CGRP antibodies and three-country expert meeting on migraine) | IFAK DATA (Headaches) | no | no | MigraineAction<br><br>Scientific activities: Neuro-otology, dizziness<br><br>Clinical activities: Neuro-otology, dizziness, headaches, concussion<br><br>Lead participation: Medical Faculty of the University of Zurich (headaches, clinical neurology, neurology)<br><br>Neurology, Swiss Concussion Centre, Schultheiss Clinic | AdBoards, presentations, author<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding monoclonal antibodies |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Uwe Reuter (author)** | Pfizer (rimegepant)<br><br>Lundbeck (eptinezumab) | Amgen, Novartis (erenumab)<br><br>Abbvie/Allergan (botox/onabotulinum toxin)<br><br>Lilly (galcanezumab, lasmiditan)<br><br>TEVA (fremanezumab)<br><br>Lundbeck (eptinezumab) | Amgen, Novartis (erenumab)<br><br>Abbvie/Allergan (botox/onabotulinum toxin)<br><br>Lilly (galcanezumab, lasmiditan), Medscape (CGRP mABs)<br><br>Springer (lasmiditan, rimegepant, monoclonal antibody)<br><br>StreaMedUp (CGRP mABs) | Amgen, Novartis (erenumab)<br><br>Abbvie/Allergan (botox, atogepant)<br><br>Lilly (galcanezumab, lasmiditan)<br><br>TEVA (fremanezumab) | Novartis (erenumab)<br><br>Abbvie/Allergan (botox, atogepant)<br><br>Lilly (galcanezumab, lasmiditan)<br><br>TEVA (fremanezumab)<br><br>Lundbeck/ Alder (eptinezumb) | no | DMKG, DGN, EHF<br><br>Scientific activities: Headaches / migraines<br><br>Clinical activities: Headaches<br><br>University Clinic Greifswald, Charité University Clinic Berlin | Consulting, AdBoards, presentations, author, research<br><br>moderate<br><br>Only involved in formal final editorial stage (corrections to bibliography references and tables) |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Victoria Ruschil (author)** | no | no | no | no | no | no | DMKG<br><br>Scientific activities: Headaches, genetics, polyneuropathy<br><br>Clinical activities: Headaches<br><br>Department for Neurology, focussing on epileptology, University Clinic Tübingen | none |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Christoph Schankin (author)** | TEVA (fremanezumab) | Almirall (almotriptan)<br><br>Lilly (galcanezumab)<br><br>Lundbeck (eptinezumab)<br><br>Novartis (erenumab)<br><br>TEVA (fremanezumab) | Grünenthal (zolmitriptan)<br><br>Lilly (galcanezumab)<br><br>Novartis (erenumab)<br><br>TEVA (fremanezumab) | no | TEVA (fremanezumab)<br><br>Novartis (erenumab) | no | SNS, SKG, EAN, AAN, AHS, IHS, DMKG<br><br>Scientific activities: Headache, migraine, headache as an emergency, aura, visual snow,<br>Secondary headaches<br><br>Clinical activities: Management of university headache consultation sessions<br><br>Neurological Clinic, Inselspital, University Hospital Bern | Consulting, AdBoards, presentations, research<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding monoclonal antibodies |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Andreas Straube (author)** | Sanofi (thomapyrin) | Allergan (botox)<br>Novartis (aimovig)<br>Lilly (emgalitiy)<br>TEVA (Ajavy) | Allergan<br>Novartis<br>Lilly<br>TEVA | Novartis (data from a survey at headache centres) | no | no | Scientific activities: Headaches, oculomotor dysfunction, oncology<br>Clinical activities: Head of the Headache A&E<br>Lead participation: Munich Pain Congress<br>Neurology, University Clinic Grosshadern, Munich | Consulting, AdBoards, presentations, author<br>moderate<br>Involvement in non-invasive neuromodulation |

| | Activity as a consultant or expert | Involvement in a scientific advisory board | Activity as a speaker or instructor | Activity as an author or co-author | Research work / running clinical trials | Owner interests in the health system | Indirect interests | Thematic link to the guideline/ thematic relevance<br>Assessment of conflicts of interests<br>Consequence |
|---|---|---|---|---|---|---|---|---|
| **Sonja-Maria Tesar (author)** | no | Abbvie, Novartis, Teva, Lilly, Ratiopharm, Pfizer, Stada (onabotulinum toxin A, erenumab, glacanezumab, fremanezumab, eletriptan, zolmitriptan) | Abbvie, Novartis, Teva, Lilly, Ratiopharm, Pfizer, Stada (onabotulinum toxin A, erenumab, glacanezumab, fremanezumab, eletriptan, zolmitriptan) | no | n/a | no | ÖKSG<br><br>Scientific activities: Headache and pain therapy<br><br>Clinical activities: Special pain therapy, general neurology<br><br>KABEG: Klinikum Klagenfurt am Wörthersee and Wolfsberg (Klagenfurt: headache and facial pain A&E) | AdBoards, presentations<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding onabotulinumtoxinA & monoclonal antibodies |
| **Cem Thunstedt (author)** | no | TEVA (migraine) | TEVA (Migraine in family medicine, DGSS presentation) | no | no | Not relevant to guideline | DMKG<br><br>scientific and clinic activities CGRP, Chiari malformation, migraine, IIH<br><br>University Clinic Grosshadern, Munich, (LMU) | AdBoards, presentations<br><br>moderate<br><br>no involvement and abstention (in Delphi rounds) regarding fremanezumab |

# Legal notice



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