

# Therapy of Migraine Attacks and Migraine Prophylaxis

## Recommendations of the German Society for Neurology and the German Migraine and Headache Society

### 1. What's new?

#### 1.1 Migraine attacks

- Triptans (5-HT<sub>1B/1D</sub>-agonists) perform better if they are taken at the start of a migraine attack, as long as the headache is of mild or moderate intensity (↑↑). This recommendation to take triptans if the headache is mild only applies for patients who can differentiate migraine attacks from tension headaches.
- The presence of allodynia (touch is perceived as painful) in the area of the face and head during a migraine attack may predict a lower efficacy (↑).
- Zolmitriptan is available as 5 mg nasal spray. This application acts more rapidly than the oral form (↑).
- Sumatriptan is available as a tablet dissolving rapidly in the gastrointestinal tract. Whether efficacy occurs more rapidly than is the case with normal tablets is not known (↔).
- Ergotamine as a monosubstance is available only as a 2 mg tablet.
- The combination of acetylsalicylic acid, paracetamol (acetaminophen) and caffeine is more effective than the combination without caffeine and more effective than the substances given alone (↑↑).
- Acetylsalicylic acid in soluble buffered form (1000 mg) is comparable in effectiveness with 400 mg ibuprofen and 50 mg sumatriptan (↑↑).
- COX-2 inhibitors have a similar effectiveness as ibuprofen or sumatriptan in the therapy of migraine attacks (↑). Up to now none of the COX-2 inhibitors coxibs has been approved for the treatment of migraine attacks. Considering the risk of vascular events in long-term use they can not be recommended for the treatment of migraine attacks.

#### 1.2 Migraine prophylaxis

- Treatment with topiramate is an effective migraine prophylaxis (↑↑). The effective daily dose ranges from 25 to 100 mg. Central side effects restrict the use of topiramate.
- Pizotifen, methysergide and lisuride are no longer approved in Germany for migraine prophylaxis
- Butterburr (↑) and feverfew (↑) may be effective for migraine prophylaxis.
- Cylandelate is probably ineffective (↔).

### 2. An overview of the most important recommendations

- The 5-HT<sub>1B/1D</sub> agonists (in alphabetical order) almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan are the substances with the best efficacy in acute migraine attacks (A).
- Ergotamine is effective against migraine. However, the efficacy has not been confirmed convincingly in prospective studies (B).
- Non-opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are effective in the treatment of migraine (A).
- The effectiveness of non-pharmacological procedures has barely been examined in controlled studies (C).
- With frequent migraine attacks a migraine prophylaxis should be initiated (A).
- First choice migraine prophylactics include the betablockers (A) metoprolol and propranolol, the calcium antagonist flunarizine (A), and the anticonvulsives valproic acid (A) and topiramate (A).
- Second choice migraine prophylactics include the betablocker bisoprolol (B), naproxen (B), acetylsalicylic acid (C), magnesium (C), butterburr (B), feverfew (B) and amitriptyline (B).
- Pharmacotherapy should be complemented by non-pharmacological procedures involving behavioural therapy (A), and by aerobic exercise (B).
- Patients suffering from very frequent migraine (≥3 attacks/month) and a considerable reduction in quality of life should receive psychological therapy (A).

## 1. Introduction

### 1.1. Definition of the health problem

Migraine attacks lead to severe, frequently unilateral pulsating and pounding headaches increasing with physical activity (Olesen et al., 2004). In a third of all patients headache is diffuse. The individual attacks are accompanied by a loss of appetite (almost always), nausea (80 %), vomiting (40-50%), light sensitivity (photophobia, 60 %) noise sensitivity (phonophobia, 50 %) and odour hypersensitivity (10 %). If the headaches are unilateral they can change sides within an attack or from attack to attack. The duration of the attacks depending on the definition of the International Headache Society varies between 4 and 72 hours (Olesen et al., 2004). In children the attacks are shorter and can also occur without headaches only with severe nausea, vomiting and giddiness (Maytal et al., 1997).

### 1.2. Epidemiology

Migraine is one of the most frequent types of headache. About 6-8% of all men and 12-14% of all women suffer from migraine (Lipton et al., 2002, Rasmussen et al., 1991, Scher et al., 1998, Silberstein und Lipton, 1996). The lifetime-prevalence in women is >25%. Before puberty the frequency of migraine is 4-5%. Boys and girls are affected equally. The highest incidence of migraine attacks occurs between the 35th and 45th years of life. During this phase of life women are affected three times more frequently than men.

## 2. Objectives and uses

### 2.2. Definition of the objectives of the guideline

An optimisation of the treatment of acute migraine attacks and the pharmacotherapeutic and non-pharmacological prophylaxis of migraine is the aim of this guideline. The guideline is evidence-based and represents a continuation of the following guidelines and recommendations:

- 1.) Guidelines of the German Neurological Society = DGN (Diener and the Guideline Committee of the German Society of Neurology, 2003)
- 2.) Recommendations of the German Migraine and Headache Society (Diener et al., 2000)
- 3.) Recommendations of the drug committee of the "Deutsche Ärzteschaft" (3rd Edition 2001)
- 4.) Practice Parameters of the American Academy of Neurology (Silberstein and for the US Headache Consortium, 2000)

### 2.2. Definition of uses (target group)

This guideline is primarily targeted at doctors and psychologists who look after patients with migraine either on outpatient basis or in the hospital.

## 3. Summary of the recommendations

### 3.1. Diagnosis:

The diagnosis is based on the typical prior history and normal neurological examination. Additional diagnostics and in particular imaging are only necessary if unusual headaches occur (exclusion of haemorrhage, subarachnoidal bleeding), and if headaches coincide with persistent neurological or psychopathological deficits (**A**) (Quality Standards Subcommittee of the American Academy of Neurology, 1994).

### 3.2. Pharmacotherapy of migraine attacks:

- The 5-HT<sub>1B/1D</sub> agonists (in alphabetical order) almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan are the substances with the best efficacy in acute migraine attacks (**A**).
- Ergotamine is effective in migraine. However, the effectiveness has not been convincingly confirmed in prospective studies (**B**).
- Non-opioid-analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are also effective for the treatment of migraine (**A**).
- The effectiveness of non-pharmacological procedures has barely been examined in controlled studies (**C**)

Success criteria for a successful treatment of a migraine attack in clinical studies include

- 1.) Freedom from headache after 2 hours,
- 2.) Improvement in headaches from severe or moderate to mild or no headache within two hours after intake of a drug (Pilgrim, 1993)
- 3.) Reproducible efficacy in 2 of 3 migraine attacks.

## 4. Procedure and evidence

### 4.1. Pharmacotherapy

#### 5-HT<sub>1B/1D</sub> agonists

The serotonin-5-HT<sub>1B/1D</sub> receptor agonists (Table 1) almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan are specific antimigraine agents which are ineffective in tension-type headache. All triptans have been confirmed to be effective in large placebo-controlled studies (Ferrari et al., 2001, Goadsby et al., 2002). For sumatriptan (Tfelt-Hansen et al., 1995, The Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group, 1992) and zolmitriptan (Geraud et al., 2002) there are comparative studies with oral acetylsalicylic acid (ACE) in combination with metoclopramide. In these comparative studies the triptans were not or only marginally more effective than acetylsalicylic acid. In about 60% of non-responders to non-steroidal anti-inflammatory drugs, triptans are effective (Diamond et al., 2004). Sumatriptan 6 mg s.c. was more effective than 1000 mg acetylsalicylic acid i.v., but showed more side effects (Diener and for the ASASUMAMIG Study Group, 1999). Ergotamine was less effective in comparative studies with sumatriptan (The Multinational Oral Sumatriptan Cafergot Comparative Study Group, 1991) and eletriptan (Diener et al., 2002). Triptans unlike ergotamine tartrate act at every timepoint within an attack, i.e. they do not have to be taken immediately at the start of the attack. They do however act more effectively if they are taken earlier in a migraine attack (Burstein et al., 2004, Dowson et al., 2004). In order to prevent the development of a medication overuse headache an early intake can only be recommended if the attacks are not too frequent (<10 headache days/month) and if the patient can clearly distinguish migraine from tension-type headache.

With longer-lasting migraine attacks the migraine headaches may recur at the end of the pharmacological effect of the antimigraine agent (a so-called "headache recurrence"). Recurrence is defined as a deterioration in headache intensity from headache free or mild headache to moderate or severe headache in a period of 2 to 24 hours after the first effective medication intake (Ferrari, 1999). This problem is more prevalent with triptans than with ergotamine tartrate or acetylsalicylic acid. Recurrence of the headaches occurs in 15-40% of patients after oral intake of triptans, whereby a second application of the substance is then effective again (Ferrari et al., 1994). If the first application of a triptan is ineffective, it is useless to use a second dose for the same migraine attack. All triptans as well as ergotamine can lead to an increase in attack frequency and ultimately to medication overuse headache or chronic migraine if they are taken too frequently (Katsarava et al., 2000, Limmroth et al., 1999). Therefore triptans should not be used on more than 10 days per month.

Life-threatening adverse events (myocardial infarction, severe heart rhythm disorders, stroke) have been observed after use of sumatriptan in a frequency of 1:1,000,000 (O'Quinn et al., 1999, Welch et al., 2000). In almost all patients there were either clear contraindications (e.g. preexisting existing coronary heart disease), or the migraine diagnosis was wrong. For the other triptans no data have yet been published. Since the mode of action of the different triptans is identical, a similar incidence of life-threatening adverse events can be assumed (oral triptans have a lower risk than subcutaneous sumatriptan). For safety reasons in patients who suffer from migraine with aura, triptans should only be applied after the aura fades and when the headache starts. Furthermore, triptans are ineffective when applied during the aura phase (Bates et al., 1994, Olesen et al., 2004). Population-based studies, however, show no raised risk for vascular events when triptans are used compared to analgesics (Hall et al., 2004, Velentgas et al., 2004).

Table 1: Therapy of acute migraine with 5-HT agonists (ordered according to the year of approval of drug registration)

Substances	Dose	Adverse events	Contraindications
Sumatriptan	↑↑ 50 -100 mg p.o. 25 mg suppository 10 - 20 mg nasal spray	Tightness in the chest and neck, parasthesias of the extremities, chills	Hypertension, coronary heart disease, angina pectoris, myocardial infarction , Raynaud's syndrome, peripheral atherosclerotic disease, TIA or stroke, pregnancy, breast-feeding, children (< 12 years), severe hepatic or renal insufficiency, multiple vascular risk factors, simultaneous treatment with ergotamine, within 2 weeks of discontinuation of MAO inhibitors
	6 mg s.c.(auto-injector)	Local reaction at the injection site	
Zolmitriptan	↑↑ 2.5 - 5 mg p. o. 2.5 - 5 mg dissolvable tablet 5 mg nasal spray	as with sumatriptan	as with sumatriptan
Naratriptan	↑↑ 2.5 mg p. o.	a little less than sumatriptan	as with sumatriptan
Rizatriptan	↑↑ 10 mg p. o. or dissolvable tablet	as with sumatriptan	as sumatriptan, 5 mg dose with intake of propranolol
Almotriptan	↑↑ 12.5 mg p. o.	a little less than sumatriptan	as with sumatriptan
Eletriptan*	↑↑ 20, 40 mg p. o.	as with sumatriptan	as with sumatriptan
Frovatriptan	↑↑ 2.5 mg p. o.	a little less than sumatriptan	as with sumatriptan

\* if eletriptan 40 mg is not effective, 80 mg eletriptan can be given.

#### Comparison of the "triptans"

The shortest time to onset of efficacy occurs with subcutaneous sumatriptan (10 minutes) (Tfelt-Hansen, 1993). Oral sumatriptan, almotriptan and zolmitriptan act after 45 to 60 minutes (Ferrari et al., 2001). Rizatriptan and eletriptan are the most rapidly acting oral triptan (after 30 minutes). Naratriptan and frovatriptan require up to 4 hours for their action to take effect (Goadsby, 1997, McDavis et al., 1999). Zolmitriptan 5 mg when given as a nasal spray has a more rapid effect than oral zolmitriptan (Charlesworth et al., 2003). Sumatriptan is available as a tablet dissolves rapidly in the gastrointestinal tract (Dahlöf et al., 2004). Whether a more rapid onset of efficacy occurs than is the case with a normal tablet is not known.

Improvement in headaches after two hours, the most important parameter for clinical studies on the effectiveness of antimigraine agents, is the highest with subcutaneous sumatriptan (70-80%) (The Subcutaneous Sumatriptan International Study Group, 1991). Sumatriptan nasal spray is as effective as sumatriptan tablets. Sumatriptan suppositories can be used for patients who suffer from early vomiting during their migraine attacks (Becker and on behalf of the Study Group, 1995, Ryan et al., 1997, Tepper et al., 1998). 25 mg sumatriptan oral is less effective than 50 and 100 mg (ca. 50-60%), but produces less side effects (Ferrari et al., 2001). Naratriptan and frovatriptan (per 2.5 mg) are less effective than sumatriptan for improving headaches after 2 h, but also have fewer side effects and a lower rate of recurring headache. The onset of effect for naratriptan and frovatriptan is slower compared to that of the other triptans. Moderately effective agents include zolmitriptan in the range 2.5 - 5 mg and almotriptan at 12.5 mg. Rizatriptan at 10 mg is somewhat more effective than 100 mg sumatriptan (Goldstein et al., 1998, Tfelt-Hansen und Ryan, 2000, Tfelt-Hansen et al., 1998). Eletriptan is the most effective oral "triptan" at a dose of 80

mg, but also has the most side effects. Almotriptan has a side effect rate that does not differ from placebo.

The frequency of recurrence of headaches with the different triptans ranges from 15% to 40%. There is evidence that an initial combination of a triptan with a long-acting non-steroidal anti-inflammatory drug (Krymchantowski und Barbosa, 2002, Krymchantowski et al., 1999) can prevent the recurrence of migraine symptoms. Alternatively the non-steroidal anti-inflammatory drug can also be given after a time delay. If one triptan remains ineffective after three consecutively treated attacks, another triptan can still be effective.

#### Ergot alkaloids

Only very few prospective studies on the use of ergot alkaloids against migraine have been published (Tfelt-Hansen et al., 2000). In all studies in which triptans were compared with ergot alkaloids, the former were significantly more effective (Christie et al., 2002, Diener et al., 2002, The Multinational Oral sumatriptan Cafergot Comparative Study Group, 1991). Treatment with ergotamine tartrate should be considered in very long migraine attacks or attacks with multiple "recurrences". Patients who treat their migraine attacks successfully with an ergot alkaloid and who show no side effects and no dose increase can retain this acute therapy. The frequent intake of ergotamine can lead to continuous headaches that can barely be differentiated in their character from migraine headaches (Dichgans et al., 1984, Horton und Peters, 1963). The frequency of intake must therefore be restricted to 10 days/month.

Table 2 Ergotamine for the treatment of acute migraine attack

Substances	Dose	Adverse events	Contraindications
Ergotamine tartrate	↑ 2 mg p. o.	Vomiting, nausea, chills, muscle cramps, continuous headache, ergotism	Pregnancy, breast-feeding, children under 12 years, patients with multiple vascular risk factors, poorly controlled hypertension, coronary heart disease, angina pectoris, myocardial infarction, Raynaud's disease, peripheral atherosclerotic disease, TIA or stroke, severe hepatic or renal insufficiency, multiple vascular risk factors

#### Antiemetics and analgesics

Most patients suffer from gastrointestinal symptoms during the migraine attack. The application of antiemetics such as metoclopramide or domperidone (Table 3) improves not only autonomic disturbances, but also leads in some patients via a restimulation of the inhibited gastric movement at the beginning of the migraine attack to a better absorption and effect of analgesics and triptans (Ross-Lee et al., 1983, Schulman und Dermott, 2003, Waelkens, 1984). Metoclopramide also has a minor analgesic effect in migraine (Ellis et al., 1993). The superiority of a combination of antiemetics with antimigraine agents has not been confirmed up until now in large randomised studies.

Table 3: Antiemetics in migraine therapy

Substances	Dose	Adverse events	Contraindications
Metoclopramide	↑ 10-20 mg p. o. 20 mg rectal ↑ 10 mg i.m., i.v. s.c.	Early dyskinetic syndrome, states of unrest	Children under 14, hyperkinesia, pregnancy, epilepsy, prolactinoma
Domperidone	↔ 20-30 mg p. o.	Rarer than is the case with metoclopramide	Children under 10 years, otherwise see metoclopramide, but less distinct and rarer

Acetylsalicylic acid, ibuprofen, diclofenac-K and paracetamol are the analgesics of first choice for mild and moderately severe migraine headaches (Table 4) (Chabriat et al., 1994, Dahlöf und Björkman, 1993, Havanka-Kanniainen, 1989, Karachalios et al., 1992, Kloster et al., 1992, Limmroth et al., 1999, Nebe et al., 1995, Tfelt-Hansen et al., 1995, The Diclofenac-K/sumatriptan Migraine Study Group, 1999). Metamizole and phenazone are also probably effective (Diener et al., 2004, Tulunay et al., 2004). The older studies on analgesics usually do not fulfill the standards imposed in modern studies. The combination of acetylsalicylic acid, paracetamol and caffeine was examined in the USA and was found to be more effective than placebo (Lipton et al., 1998). A study carried out in Germany showed that the combination of acetylsalicylic acid, paracetamol and caffeine is more effective than the combination without caffeine and more effective than the single substances (Diener et al., 2005). The optimal dose of acetylsalicylic acid or paracetamol is at least 1000 mg with single oral application, while for ibuprofen it is 400-600 mg and for diclofenac K it is 50 to 100 mg. Analgesics should be taken preferably in the form of an effervescent or a chew tablet (for faster resorption). Lysinated acetylsalicylic acid in combination with metoclopramide is almost as effective as sumatriptan (Tfelt-Hansen et al., 1995). Soluble buffered acetylsalicylic acid (1000 mg) is as effective as 400 mg ibuprofen or 50 mg sumatriptan (Diener and Limmroth, 2004, Diener et al., 2004). Paracetamol is absorbed better after rectal compared to oral application (rectal application if there is nausea and vomiting at the start of an attack). Non-steroidal anti-inflammatory drugs such as naproxen and diclofenac-potassium are also effective. Analgesics can also lead to medication overuse headaches with excessively frequent intake. Therefore intake should be restricted to <15 days per month. The COX-2 inhibitors are currently being tested in clinical trials. No approval has been given yet for the treatment of migraine. The question whether episodic intake can lead to an increased frequency of vascular events has not been resolved up to now. The application of these substances for treating migraine attacks can not be recommended.

Opioids and tranquilizers should not be taken for the treatment of migraine attacks. Opioids are of only limited effectiveness, lead frequently to vomiting and are highly addictive.

#### Treatment of migraine attacks in children

Migraine attacks in children are treated with 15 mg/kg paracetamol or 10 mg/kg ibuprofen. In children no Reyes syndrome has ever been observed after treatment of migraine with acetylsalicylic acid. If antiemetics are required, domperidone should be used instead of metoclopramide. Children under 12 years unlike adults do not (yet) seem to benefit from a therapy with triptans. The critical threshold for effectiveness varies between individuals from the 10th to the 13th year of life. Oral triptans, particularly sumatriptan 50-100 mg and rizatriptan 5 mg, are no more effective than placebo in children and adolescents (Hämäläinen et al., 1997, Winner et al., 2002). All these studies suffer, however, from unusually high placebo values (approx. 50 %). Studies with 5, 10 and 20 mg sumatriptan nasal spray in adolescents revealed a statistical superiority compared to placebo (Ahonen et al., 2004, Ueberall und Wenzel, 1999, Winner et al., 1999). Positive results were obtained from post-hoc analyses of studies with oral zolmitriptan at a dose of 2.5-5 mg (Solomon et al., 1997, Tepper et al., 1999) in adults and adolescents (12-17 years). Because of these results, only sumatriptan nasal spray at a dose of 10 mg is currently authorized in Germany for treating adolescents. Ergotamine and oral triptans are not approved for childhood application.

Table 4: Analgesics for treating the migraine attack

Drug (Example)	Dosing	Adverse events	Contraindications
Acetylsalicylic acid	↑↑ 1000 mg	Stomach pains, nausea, coagulation disorders	Gastrointestinal ulcers, hemorrhagic diathesis, pregnancy in months 6-9
Lysinated ASA	↑ 1000 mg i.v.		
Ibuprofen	↑↑ 200-600 mg	as ASA, edema	as AS (reduced tendency to bleed), renal insufficiency, <b>LE</b>
Naproxen	↑↑ 500-1000 mg	as with ibuprofen	as with ibuprofen
Diclofenac-K	↑↑ 50-100 mg	as with ibuprofen	as with ibuprofen
Metamizol	↑ 1000 mg	Allergic reaction, blood count changes	Diseases of the haematopoietic system,
Paracetamol	↑ 1000	Liver damage	Liver damage, renal insufficiency
AS plus paracetamol + caffeine	↑↑ 2x 250 + 200 + 50 mg	See ASA and paracetamol	See ASA and paracetamol

## 4.2. Migraine prophylaxis

### 4.2.1 Recommendation:

- If frequent migraine attacks occur, migraine prophylaxis should be introduced (**A**).
- Migraine prophylactics of the first choice include the betablockers (**A**) metoprolol and propranolol, the calcium antagonist flunarizine (**A**), and the anticonvulsives valproic acid (**A**) (off-label use) and topiramate (**A**).
- Migraine prophylactics of the second choice include the betablocker bisoprolol (**B**), naproxen (**B**), acetylsalicylic acid (**C**), magnesium (**C**), butterburr (**B**), feverfew (**B**) and amitriptyline (**B**).
- Pharmacotherapy should be complemented by the non-pharmacological procedures of behavioural therapy (**A**) and aerobic exercise (**B**).
- Patients suffering from very frequent migraine ( $\geq 3$  attacks/month) and a considerable reduction in quality of life should receive psychological therapy (**A**).

Pharmacological prophylaxis of migraine is indicated if suffering is particularly strong and quality of life is impaired, i.e. if:

- three or more migraine attacks occur per month
- migraine attacks regularly last longer than 72 hours
- attacks do not respond to acute therapy according to the above-mentioned recommendations (including triptans) or if side effects render the acute therapy intolerable,
- if the attack frequency increases and the intake of analgesics or antimigraine agents occurs on more than 10 days per month
- if complicated migraine attacks occur with long lasting auras

The aim of prophylaxis is to reduce the frequency, severity and duration of migraine attacks and to prevent the development of medication overuse headache. Migraine prophylaxis is considered as effective if headache frequency is reduced by at least 50 %. First of all, patients should keep a headache diary over four weeks in order to document headache frequency and success or failure of the appropriate antimigraine medication.

### 4.2.2 Substances for migraine prophylaxis

Agents that are effective for the prophylaxis of migraine include the non-selective betablocker propranolol (Diamond und Medina, 1976, Gawel et al., 1992, Havanka-Kanniainen et al., 1988, Holroyd et al., 1991,

Kangasniemi and Hedman, 1984, Ludin, 1989, Nadelmann et al., 1986, Tfelt-Hansen et al., 1984) and the beta-1-selective betablocker metoprolol (Kangasniemi und Hedman, 1984, Olsson et al., 1984, Sorensen et al., 1991, Steiner et al., 1988, Wörz et al., 1991) (Table 5). Bisoprolol is probably also effective, but has only been examined in a few studies (van de Ven et al., 1997, Wörz et al., 1991). From the group of "calcium antagonists" only flunarizine has been confirmed as effective (Amery et al., 1985, Balkan et al., 1994, Bassi et al., 1992, Bono et al., 1985, Centonze et al., 1985, Diamond and Freitag, 1993, Diamond and Schenbaum, 1983, Freitag et al., 1991, Gawel et al., 1992, Louis, 1981, Sorensen et al., 1991). A dose of 5 mg is probably as effective as 10 mg (Diener et al., 2002). Trial results on cyclandelate are inconsistent (Diener et al., 2001, Diener et al., 1996, Nappi et al., 1987). This substance is probably ineffective.

In several prospective studies the anticonvulsive valproic acid has been shown to be effective (Freitag et al., 2002, Kaniecki, 1997, Klapper and on behalf of the Divalproex Sodium in Migraine Prophylaxis Study Group, 1997, Silberstein et al., 2000) for migraine prophylaxis (Table 5). The daily dose is 500 to 600 mg. Sometimes higher doses are necessary. Valproic acid is not approved in Germany for migraine prophylaxis (off-label use). Topiramate has migraine prophylactic properties confirmed in three large placebo-controlled studies (Brandes et al., 2004, Diener et al., 2004, Silberstein et al., 2004). The effective daily dose is between 25 and 100 mg. the dosing-up phase must be carried out slowly (25 mg/>week). Cognitive side effects restrict the use of topiramate. In 10% of patients loss of weight can occur that sometimes precludes therapy.

Acetylsalicylic acid probably has a minor migraine prophylactic effect (Diener et al., 2001)(Table 6) at a dose of 300 mg/day. Naproxen at doses of 2 x 500 was more effective than placebo. Gastrointestinal side effects during long-term application restrict use here. The serotonin antagonists pizotifen and methysergide are also prophylactically effective, but are no longer available or authorized in Germany. The effectiveness of magnesium is disputed (Peikert et al., 1996, Pfaffenrath et al., 1996). If it is effective at all, the reduction in attack frequency is not very marked.

Amitriptyline is a tricyclic antidepressant. Given alone it is not very effective for migraine prophylaxis (Couch und Hassanein, 1979, Couch et al., 1976, Ziegler et al., 1987). Amitriptyline should be given for prophylaxis if migraine is combined with tension-type headache or if, as is often the case with chronic pain, additional depression exists. The antiepileptic gabapentin had a minor prophylactic effect in a study with a daily dose of between 1200 and 1600 mg (Mathew et al., 2001). Lamotrigine is not effective for reducing the frequency of migraine attacks, but does reduce the frequency of auras (Lampl et al., 1999, Steiner et al., 1997). Of the dopamine agonists, alpha-dihydroergocryptin is probably effective (Bussone et al., 1999). Whether candesartan (Tronvik et al., 2002) or lisinopril (Schrader et al., 2001) are effective can not be judged according to our current state of knowledge. Regarding high-dose vitamin B2, only 2 small monocentre studies have been published indicating possible efficacy (Schoenen et al., 1997, 1998, Schoenen et al., 1994). The substance is not available or authorized in Germany at the daily dose (400 mg) used in clinical trials.

Most placebo-controlled studies showed no migraine prophylactic effect of local injections of botulinum toxin (Evers et al., 2004). This is true both for injections into predefined areas as well as injections at trigger points ("follow the pain"). Two studies revealed effectiveness in a subgroup of patients with chronic migraine. This result must be reproduced in a phase III trial, however, before the therapy can be recommended.

Petadolex (butterbur) has been confirmed to be effective in 2 placebo-controlled studies (Diener et al., 1004). In very rare cases severe liver malfunction can occur. Feverfew (Pfaffenrath et al., 2002) is also effective. The substance is currently undergoing approval (as of 12/2004).

Table 5 Substances used for migraine prophylaxis.

Substances	Dose	Adverse events	Contraindications
Metoprolol	↑↑ 50-200 mg	F: Fatigue, arterial hypotension M: Sleep-disorders, giddiness	A: AV block, bradycardia, cardiac failure, sick-sinus syndrome, asthma
Propranolol	↑↑ 40-240 mg	S: Hypoglycaemia, bronchospasms, bradycardia, gastrointestinal complaints, impotence	R: Diabetes mellitus, orthostatic dysregulation, depression
Bisoprolol	↑ 5-10 mg		
Flunarizin	↑↑ 5 -10 mg	F: Fatigue, weight gain S: Gastrointestinal complaints, depression R: hyperkinesia, tremor, parkinsonsymptoms	A: focal dystonia, pregnancy, breast feeding, depression R: Parkinson's disease in the family
Valproic acid off-label use	↑↑ 500-600 mg	F: Fatigue, giddiness, tremor S: Rash, hair loss, increase in weight, R: Liver malfunctions	A: Liver malfunctions, pregnancy (neural tube defects), alcohol abuse
Topiramate	↑↑ 25-100 mg	F: Fatigue, memory disturbances, weight decrease, parasthesias S: Taste changes, psychosis R: Narrow angle glaucoma	A: Renal insufficiency, kidney stones, narrow angle glaucoma

\* Side effects listed as F: frequent; S: sometimes; R:rare  
Contraindications listed as A: absolute, R: relative

Table 6: Second choice substances for migraine prophylaxis

Substances (Example)	Dose	Adverse events	Contraindications
Amitriptyline	↑↑ 50-150 mg	F: Mouth dryness, fatigue, giddiness, sweating S: bladder disorders, inner unrest, impotence	A: Narrow angle glaucoma, prostate adenoma with urinary retention,
Gabapentin off-label use	↔ 2400 mg	F: Fatigue, giddiness, S: Ataxia, gastrointestinal disturbances	Severe liver or kidney malfunctions
Naproxen	↑ 2 x 250 mg 2 x 500 mg	F: Stomach pains	A: Ulcer, R: bleeding complications, asthma
Butterbur	↑ 2 x 75mg	F: Belching, stomach pains R: Liver malfunctions	A: Pregnancy, breast feeding
Acetylsalicylic acid	↔ 300 mg	S: Stomach pains	A: Ulcer, R: tendency to bleed: bronchial asthma
Magnesium	↔ 2 x 300 mg	F: Diarrhoea with too rapid dosing-up	None
Feverfew	↔ 3 x 6.25 mg	R: Rash	None
Botulinum toxin	↓↓↓	Muscular weakness, ptosis	Myasthenia

Side effects: F: frequent, S: sometimes; R: rare, A: absolute, R: relative; Coronary heart disease KHK =; AVK = arterial occlusive disease

In migraines associated with menstrual periods, a prophylaxis with 2 x 500 naproxen from seven days before until seven days after the period can be attempted (↔) (Sances et al., 1990). Transdermal oestrogen can be used as an alternative for short-term prophylaxis (100 µg) during the phase of hormone drop (↔) (De Lignieres et al., 1986, Dennerstein et al., 1988). Triptans such as 2 x 1 mg naratriptan, 2 x 25 mg sumatriptan or 1 or 2 x 2.5 mg frovatriptan over 5 days are also effective against menstrual migraine (label off; ↑↑↑)(Newman et al., 2001, Newman et al., 1998)

#### 4.2.3 Migraine therapy during pregnancy and breastfeeding

During pregnancy the many therapeutic options that are otherwise available are very restricted. Before any therapy, a careful consideration of the risks and benefits should be carried out and reviewed with the patient. Paracetamol is regarded as a first choice agent for acute therapy in a dose of 1 g p.o. or as a suppository. The use of 1 g acetylsalicylic acid (e.g. as effervescent aspirin) should only be considered as an alternative and only from the 2<sup>nd</sup> trimester. In therapy refractory situations i.v. methylprednisolone can be given (although only after consultation with the gynaecologist). Triptans and ergotamine are not authorised during pregnancy. In this respect it should be mentioned that for the first available triptan, sumatriptan, a pregnancy registry was already established directly after its approval in which all reported cases of triptan intake during pregnancy were recorded. Even though such data does not suffice to allow final conclusions to be drawn, findings until now do not point towards any raised risk of birth deformities or increased complications during pregnancy or birth (Fox et al., 2002, Källen und Lygner, 2001, Olesen et al., 2000). As a prophylaxis, magnesium can be applied at a dose of 2 x 300 mg/d. During pregnancy, a prophylaxis with metoprolol is also possible. Before a planned pregnancy, however, a non-pharmacologically-based prophylaxis should always be applied (e.g. Jacobson training).

During breast-feeding medicines should be used that can not be detected in the mother's milk, or which only appear in very small amounts (Silberstein, 1993). With the use of betablockers it should be considered that the agent does appear in the mother's milk, and that this can cause bradycardia in the babies. Valproic acid has proven itself to be suitable and effective for prophylaxis here.

#### **4.2.4 Migraine prophylaxis in children**

In children and adolescents propranolol at a single dose of 10 mg/kg or flunarizine at a single dose of 5 mg can be given for migraine prophylaxis.

#### **4.3 Behavioural therapy of migraine**

Patients with an episodic or a high-frequency migraine (three and more attacks/month) should undergo psychological therapy as an alternative or supplement to a medication-based treatment (Campbell et al., 2004). The psychological procedures applied in migraine therapy have their foundations mainly in behavioural therapy (BT). For such procedures a sufficient database of information exists to assess the evidence for its effectiveness. Other methods, however, still need to evaluate their concepts. The most important unimodal procedures are thermal biofeedback therapy, EMG-biofeedback therapy and progressive muscle relaxation (PMR). As a multimodal procedure, cognitive-behavioural therapeutic pain management training is employed. The therapeutic procedures in migraine treatment are applied both pain-specifically (e.g. as relaxation procedures with PMR) and pain-unspecifically. Pain-unspecific procedures are based on non-specific dimensions such as 'strengthening of self control' (unimodal) or 'minimisation of impairment and improved pain management' (multimodal).

The best studied relaxation procedure for headaches is progressive muscle relaxation (PMR; also known as Jacobson training) (Bernstein und Borkovec, 1975). The evaluation of the effectiveness of other relaxation procedures used for headache treatment, particularly passive relaxation training, hypnosis, imagination, meditation and yoga, is not yet possible due to a lack of data.

##### *Biofeedback*

Biofeedback allows a patient to precisely and consciously perceive his/her bodily functions and with that to consciously control and change them. A non-specific effect can be achieved by biofeedback-promoted relaxation that can be enabled by measuring muscular tension (electromyographic biofeedback therapy), skin resistance (electrodermal biofeedback therapy) or peripheral body temperature (thermal biofeedback therapy).

Because of the great effort expended in these procedures (e. g. neurofeedback), an insufficient number of scientific studies are available to allow an evidence-based assessment of specific procedures used for the treatment of migraine.

##### *Multimodal behavioural therapy*

Multimodal cognitive behaviour therapy (CBT) is based on the biopsychosocial pain model. CBT is cognitively-behaviourally orientated and considers all components and levels of a human being in which the consequences of pain can be found on an individual basis. The main objective of this procedure is to minimise impairment by pain and improve self-control (Holroyd und Andrasik, 1982). CBT procedures exist for headache patients in well-developed standardized programmes (Frettlöh et al., 1998), and can be carried out in a time and cost-effective (under 10 sessions) manner, being just as effective in group settings as it is in an individual face-to-face setting.

The effectiveness (index from the intensity and frequency of headaches) of the individual therapies and therapeutic combinations are displayed in Tab. 7.

Table 7: Overview of non-medication-based therapeutic procedures (Andrasik, 2003, Campbell et al., 2004)

Therapeutic procedure	Improvement in migraine activity (%)	Effect intensity	Evidence class
Progressive muscle relaxation (PMR)	32 – 37	0.55	↑↑
Thermal finger biofeedback (tBFB)	35 – 37	0.38	↑↑
PMR + tBFB	33 - 50	0.40	↑
PMR + tBFB + propranolol	50 - 70	---	↔
Muscular feedback (EMG-BFB)	40	0.77	↔
Cognitive behavioural therapy (CBT)	35 - 49	0.44	↑↑
CBT + tBFB	38	0.37	↑
Placebo medication	14 - 30	---	---
No treatment	2	---	---
Propranolol	44	---	---

#### *Behavioural therapy of chronic migraine*

Patients suffering almost daily headaches (almost) without medication abuse achieve less success in a behavioural treatment than patients with episodic headaches (13 % vs. 52 % symptom reduction) (Bakal et al., 1981, Blanchard und Andrasik, 1985). Migraine patients taking large amounts of medication (medication overuse headache) also benefit from behavioural-therapeutic approaches alone less than patients with a "normal" use (29 % vs. 52 % symptom reduction) (Michultka et al., 1989).

The combination of behavioural and pharmacological procedures was found to be of value in the treatment of patients undergoing drug withdrawal. Mathew et al. (Mathew et al., 1990) in one study on 200 patients observed a better effectiveness for a combined versus an unimodal pharmaceutically-based treatment (72 % - 86 % versus 58 %). Blanchard et al. (Blanchard et al., 1992) reported a reduction in headache activity of more than 50% that could still be confirmed after a year. Three years after treatment the 61 migraine patients with medication overuse headache in the study of Grazzi et al. (Grazzi et al., 2002) reported fewer headache days, a reduced medication intake and a lower relapse rate when treated with the combination compared to the patients treated with medication alone.

#### *Behavioural therapy of childhood migraine*

Meta-analyses (Hermann et al., 1995) and reviews (Kröner-Herwig und Ehlert, 1992) on the intensity of therapy effects, reported as pre-post changes, revealed that the tBFB- and tBFB/PMR procedures produced the best results. PMR as a single procedure and CBT programmes were less effective for children in the pre-post comparison, but achieved similar effects as prophylactic medications did (5-HT antagonists, calcium blockers, beta blockers). CBT programs have the longest effect duration (up to 10 years; a validated multimodal programme integrating cognitive-behavioural and relaxation elements has been submitted in German form by Denecke and Kröner-Herwig (Denecke und Kröner-Herwig, 2000)). All other procedures used in the treatment of childhood migraine including the migraine-diet that is widely used in Germany (oligoantigenic nutrition) and homeopathy are of unclear value.

### 4.1. Alternative therapies

The effects of aerobic sports (Koseoglu et al., 2003) such as swimming, jogging or cycling has been confirmed scientifically (↑). Physiotherapy alone is not effective, but in combination it can improve the rate at which affected individuals respond to behavioural-therapeutic approaches. For homeopathy, randomised, placebo-controlled studies in adults exist that have shown, however, no effectiveness. (↓↓↓) (Ernst, 1999,

Walach et al., 1997, Walach et al., 2000, Whitmarsh et al., 1997). Acupuncture reduces the frequency of migraine attacks. However, sham acupuncture has the same efficacy as classical acupuncture.

An association exists between patent foramen ovale (PFO) and migraine with aura. There is most probably a common genetic disposition. It is not justified to perform PFO closure as prophylaxis for migraine.

According to the opinion of the consensus group, the following procedures and methods are ineffective: manual therapy, cervical manipulation, chiropractic therapy, local injections into the neck or the skin of the head, neural therapy, hypnosis, classical psychoanalysis, TENS, hyperbaric oxygen therapy, ozone therapy, mandibular correction, bite guard splints, tooth extraction, removal of amalgam fillings, diets, fresh cell therapy, electrical stimulation, magnetic stimulation, psychophonics, tonsillectomy, foot reflex massage, treatment of presumed fungal infections of the intestine, hysterectomy and corrugator surgery.

#### Ineffective medication-based therapies

According to various studies the following are ineffective as pharmacotherapies: bromocriptine, carbamazepine, diphenylhydantoin, primidone, diuretics, clonidine, oestrogens and gestagens, lithium, neuroleptics, proxibarbal, selective serotonin reuptake inhibitors (Steiner et al., 1998), diamox, (Vahedi et al., 2002) clomipramine, montelukast (Brandes et al., 2004) and lanepitant (Goldstein et al., 2001).

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## 4.3. Procedure for consensus finding

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#### Classification of evidence levels

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| <p>↑↑↑ Statement concerning efficacy is based on multiple clinical trials according to modern trial design (randomised controlled trial) or on one or more meta-analyses or systematic reviews.</p> <p>↑↑ Statement concerning efficacy is based on at least one adequate controlled trial</p> <p>↓↓↓ Negative statement is based on multiple clinical trials according to modern trial design (randomised controlled trial) or on one or more meta-analyses or systematic reviews.</p> <p>↔ No data exist about positive or negative effects of this therapy. This is either due to the lack of data from controlled trials or conflicting results from existing trials</p> |
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#### Strength of recommendation

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|----------|---|
| <b>A</b> | High strength of recommendation due to high level of evidence or high relevance for patient care                                  |
| <b>B</b> | Medium level of recommendation due to moderate evidence or in case of weak evidence high evidence level for patient care          |
| <b>C</b> | Low strength of recommendation due to low scientific evidence or weak relevance for patient care in case of higher evidence level |