Migraine is one of the most frequent disabling neurological conditions with a major impact on the patients’ quality of life. To give evidence-based or expert recommendations for the different drug treatment procedures of the different migraine syndromes based on a literature search and an consensus in an expert panel. All available medical reference systems were screened for all kinds of clinical studies on migraine with and without aura and on migraine-like syndromes. The findings in these studies were evaluated according to the recommendations of the EFNS resulting in level A, B, or C recommendations and good practice points. For the acute treatment of migraine attacks, oral non-steroidal anti-inflammatory drugs (NSAIDs) and triptans are recommended. The administration should follow the concept of stratified treatment. Before intake of NSAIDs and triptans, oral metoclopramide or domperidon is recommended. In very severe attacks, intravenous acetylsalicylic acid or subcutaneous sumatriptan are drugs of first choice. A status migrainosus can probably be treated by steroids. For the prophylaxis of migraine, betablockers (propranolol and metoprolol), flunarizine, valproic acid, and topiramate are drugs of first choice. Drugs of second choice for migraine prophylaxis are amitriptyline, naproxen, petasites, and bisoprolol.

**Objectives**

These guidelines aim to give evidence-based recommendations for the drug treatment of migraine attacks and of migraine prophylaxis. The non-drug management (e.g. behavioral therapy) will not be included, although it is regarded as an important part of migraine treatment. Specific rare migraine syndromes will be considered as well as specific situations such as pregnancy and childhood. A brief clinical description of the headache disorders is included. The definitions follow the diagnostic criteria of the International Headache Society (IHS).

**Background**

The second edition of the classification of the IHS provided a new subclassification of different migraine syndromes [1]. The basic criteria for migraine attacks remained unchanged as compared with the first edition (except one semantic change). The different migraine syndromes with specific aura features, however, have been classified in a new system.

The purpose of this paper is to give evidence-based treatment recommendations for migraine attacks and for migraine prophylaxis. The recommendations are based on the scientific evidence from clinical trials and on the expert consensus by the respective task force of the EFNS. The legal aspects of drug prescription and drug availability in the different European countries will not be considered. The definitions of the recommendation levels follow the EFNS criteria [2].

**Search strategy**

A literature search was performed using the reference databases MedLine, Science Citation Index, and the Cochrane Library; the key words used were ‘migraine’ and ‘aura’ (last search in January 2005). All papers published in English, German, or French were considered when they described a controlled trial or a case series on the treatment of at least five patients. In addition, a review book [3] and the German treatment recommendations for migraine [4] were considered.
Method for reaching consensus

All authors performed an independent literature search. The first draft of the manuscript was written by the chairman of the task force. All other members of the task force read the first draft and discussed changes by e-mail. A second draft was then written by the chairman which was again discussed by e-mail. All recommendations had to be agreed to by all members of the task force unanimously. The background of the research strategy and of reaching consensus and the definitions of the recommendation levels used in this paper have been described in the EFNS recommendations [2].

Clinical aspects

Migraine is an idiopathic headache disorder which is characterized by moderate to severe, often unilateral and pulsating headache attacks aggravated by physical activity and accompanied by vegetative symptoms such as nausea, vomiting, photophobia, and phonophobia. The diagnostic criteria for migraine attacks and the migraine aura are given in (Table 1). The duration of attacks is 4–72 h, at least five attacks must have occurred before the diagnosis can be established. Most of the patients suffer from migraine attacks without aura. However, there are several migraine syndromes with specific aura features and migraine syndromes with uncommon courses or complications. These syndromes have their own diagnostic criteria, the subclassification of these syndromes is given in (Table 2) [1]. The diagnostic criteria for these migraine syndromes have been published on the homepage of the IHS (http://www.i-hs.org).

In children, migraine attacks can be shorter (even only 1–2 h) and the accompanying symptoms can be more prominent including syndromes such as abdominal migraine or periodic syndromes in childhood [5–7].

Table 1 Diagnostic criteria of migraine of the IHS classification (2004)

A. At least five attacks fulfilling criteria B–D
B. Headache lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not attributed to another disorder

Epidemiology

Migraine is one of the most frequent headache disorders. About 6–8% of males and 12–14% of females suffer from migraine [8–11]. The life-time prevalence of females might be even higher up to 25%. Before puberty, the prevalence of migraine is about 5% both in boys and girls. The highest incidence of migraine attacks is in the age between 35 and 45 years with a female preponderance of 3–1. The median duration of untreated migraine attacks is 18 h, the median attack frequency is one per month.

Diagnosis

The diagnosis of migraine is based on the typical patient’s history and a normal neurological examination. Apparative investigations, in particular brain imaging, is necessary if secondary headache is suspected (e.g. the headache characteristics are untypical), if the course of headache attacks changes, or if persistent neurological or psychopathological abnormalities are present [12]. In particular, magnetic resonance imaging (MRI) [and not computed tomography (CT) imaging with its inferior sensitivity to detect vascular abnormalities and lesions] of the brain in migraine is recommended when

• the neurological examination is not normal;
• typical migraine attacks occur for the first time after the age of 40 years;

Table 2 Subclassification of migraine according to the IHS classification (2004)

1.1 Migraine without aura
1.2 Migraine with aura
   1.2.1 Typical aura with migraine headache
   1.2.2 Typical aura with non-migraine headache
   1.2.3 Typical aura without headache
   1.2.4 Familial hemiplegic migraine
   1.2.5 Sporadic hemiplegic migraine
   1.2.6 Basilar-type migraine
1.3 Childhood periodic syndromes that are commonly precursors of migraine
   1.3.1 Cyclical vomiting
   1.3.2 Abdominal migraine
   1.3.3 Benign paroxysmal vertigo of childhood
1.4 Retinal migraine
1.5 Complications of migraine
   1.5.1 Chronic migraine
   1.5.2 Status migrainosus
   1.5.3 Persistent aura without infarction
   1.5.4 Migrainous infarction
   1.5.5 Migraine-triggered seizure
1.6 Probable migraine
   1.6.1 Probable migraine without aura
   1.6.2 Probable migraine with aura
   1.6.3 Probable chronic migraine
• frequency or intensity of migraine attacks continuously increase;
• the accompanying symptoms of migraine attacks change;
• new psychiatric symptoms occur in relation to the attacks.

Drug treatment of migraine attacks

Several large randomized, placebo-controlled trials have been published to establish the best drugs for the acute management of migraine. In most of these trials, successful treatment of migraine attacks was defined as one or a combination of the following criteria:
• pain free after 2 h;
• improvement of headache from moderate or severe to mild or none after 2 h [13];
• consistent efficacy in two of three attacks;
• no headache recurrence and no further drug intake within 24 h after successful treatment (so-called sustained pain relief or pain free).

Analgesics

Drugs of first choice for mild or moderate migraine attacks are different analgesics. Evidence of efficacy in migraine treatment in at least one placebo-controlled study has been obtained for acetylsalicylic acid (ASA) up to 1000 mg [14–17], for ibuprofen 200–800 mg [15,17–19], for diclofenac 50–100 mg [20–22], for phenazon 1000 mg [23], for metamizol 1000 mg [24], tolfenamic acid 200 mg [25], and for paracetamol 1000 mg [26]. In addition, the fixed combination of ASA, paracetamol, and caffeine is effective in acute migraine treatment and is also more effective than the single substances or combinations without caffeine [27,28]. Intravenous ASA was more effective than subcutaneous ergotamine [29]; intravenous metamizol was superior to placebo in migraine without and with aura [30]. In order to prevent drug overuse headache, the intake of simple analgesics should be restricted to 15 days/month and the intake of combined analgesics to 10 days/month. Coxibs are not recommended for acute migraine treatment because of the undetermined cerebrovascular adverse events. Opioids are of only minor efficacy, no modern controlled trials are available for these substances. Table 3 presents an overview of analgesics with efficacy in acute migraine treatment.

Antiemetics

The use of antiemetics in acute migraine attacks is recommended in order to treat vegetative symptoms, and because it is assumed that these drugs improve the resorption of analgesics [31–33]. However, prospective, placebo-controlled randomized trials to prove this assumption are lacking. Metoclopramide also has a mild analgesic efficacy in migraine [34]. There is no evidence that the fixed combination of an antiemetic with an analgesic or with a triptan is more effective than the analgesic or triptan alone. Metoclopramide 20 mg is recommended for adults and adolescents, in children domperidion 10 mg should be used because of the possible extrapyramidal side effects of metoclopramide. Table 4 presents the antiemetics recommended for the use in migraine attacks.

Ergot alkaloids

There are only a very few randomized, placebo-controlled trials on the efficacy of ergot alkaloids in the acute migraine treatment although these substances have been used for a very long time, very severe events have also been reported [35].

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dose</th>
<th>Level of recommendation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid (ASA)</td>
<td>1000 mg (oral) A</td>
<td>Gastrointestinal side effects, risk of bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 mg (i.v.) A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200–800 mg A</td>
<td></td>
<td>Side effects as for ASA</td>
</tr>
<tr>
<td>Naproxen</td>
<td>500–1000 mg A</td>
<td></td>
<td>Side effects as for ASA</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>50–100 mg A</td>
<td></td>
<td>Including diclofenac-K</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1000 mg (oral) A</td>
<td>Caution in liver and kidney failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 mg (supp.) A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA plus, paracetamol plus and caffeine</td>
<td>250 mg (oral), 200–250 mg and 50 mg A</td>
<td>As for ASA and paracetamol</td>
<td></td>
</tr>
<tr>
<td>Metamizol</td>
<td>1000 mg (oral) B</td>
<td></td>
<td>Risk of agranulocytosis</td>
</tr>
<tr>
<td></td>
<td>1000 mg (i.v.) B</td>
<td></td>
<td>Risk of hypotension</td>
</tr>
<tr>
<td>Phenazon</td>
<td>1000 mg (oral) B</td>
<td></td>
<td>See paracetamol</td>
</tr>
<tr>
<td>Tolfenamic acid</td>
<td>200 mg (oral) B</td>
<td></td>
<td>Side effects as for ASA</td>
</tr>
</tbody>
</table>

Table 3 Analgesics with evidence of efficacy in at least one study on the acute treatment of migraine. The level of recommendation also considers side effects and consistency of the studies.
Triptans showed better efficacy than ergot alkaloids [36–38]. The advantage of ergot alkaloids in some patients is a longer half life time and a lower recurrence rate. Therefore, these substances should be restricted to patients with very long migraine attacks or with regular recurrence. The only compound with sufficient evidence of efficacy is ergotamine tartrate 2 mg (oral or suppositories). Ergot alkaloids can induce drug overuse headache very fast and in very low doses [39]. Therefore, their use must be limited to 10 days/month. Major side effects are nausea, vomiting, paresthesia, and ergotism. Contraindications are cardiovascular and cerebrovascular diseases, Raynaud’s disease, arterial hypertension, renal failure, and pregnancy and lactation.

**Triptans (5-HT**1**B/1D-agonists)**

The 5-HT1B/1D agonists sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan (order in the year of marketing), so-called triptans, are specific migraine medications and should not be applied in other headache disorders except cluster headache. The different triptans for migraine therapy are presented in Table 5. The efficacy of all triptans has been proven in large placebo-controlled trials of which meta-analyses have been published [40,41]. For sumatriptan [16,42] and zolmitriptan [43] comparative studies with ASA and metoclopramide exist. In these comparative studies, the triptans were not or only a little more effective than ASA. In about 60% of non-responders to non-steroidal anti-inflammatory drugs (NSAIDs), triptans are effective [44]. Sumatriptan 6 mg subcutaneously is more effective than intravenous ASA 1000 mg s.c., but has more side effects [45]. Ergotaminetartrate was less effective in comparative studies with sumatriptan [36] and with eletriptan [37]. Triptans can be effective at any time during a migraine attack. However, there is evidence that the earlier triptans are taken the better their efficacy is [46,47]. A strategy of strictly early intake can, however, lead to frequent drug treatment in certain patients. The use of triptans is restricted to maximum 10 days/month. Otherwise, the induction of a drug overuse headache is possible for all triptans [39,48,49]. Therefore, in clinical practice, a reasonable trade-off has to be agreed on between early intake and a reasonable intake frequency.

One typical problem of attack treatment in migraine is headache recurrence. This is defined as a worsening of headache after pain free or mild pain has been achieved with a drug within 24 h [50]. This problem is more eminent in triptans and NSAIDs than in ergotamine.

### Table 4

<table>
<thead>
<tr>
<th>Substances</th>
<th>Dose</th>
<th>Level</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>10–20 mg (oral) 20 mg (suppository)</td>
<td>B</td>
<td>Side effect: dyskinesia; contraindicated in childhood and in pregnancy</td>
</tr>
<tr>
<td></td>
<td>10 mg (intramuscular, intravenous and subcutaneous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domperidon</td>
<td>20–30 mg (oral)</td>
<td>B</td>
<td>Side effects less severe than in metoclopramide; can be given to children</td>
</tr>
</tbody>
</table>

**Table 5**

Different triptans for the treatment of acute migraine attacks (order in the time of marketing). Not all doses or application forms are available in all European countries.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dose</th>
<th>Level</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>25, 50 and 100 mg (oral including rapid-release)</td>
<td>A</td>
<td>100 mg sumatriptan is reference to all triptans</td>
</tr>
<tr>
<td></td>
<td>25 mg (suppository)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 and 20 mg (nasal spray)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mg (subcutaneous)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>2.5 and 5 mg (oral including disintegrating form)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 and 5 mg (nasal spray)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Naratriptan</td>
<td>2.5 mg (oral)</td>
<td>A</td>
<td>Less but longer efficacy than Sumatriptan</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>10 mg (oral including wafer form)</td>
<td>A</td>
<td>5 mg when taking propranolol</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>12.5 mg (oral)</td>
<td>A</td>
<td>Probably less side effects than sumatriptan</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>20 and 40 mg (oral)</td>
<td>A</td>
<td>80 mg allowed if 40 mg not effective</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>2.5 mg (oral)</td>
<td>A</td>
<td>Less but longer efficacy than sumatriptan</td>
</tr>
</tbody>
</table>

General side effects for all triptans: chest symptoms, nausea, distal paresthesia, fatigue.

General contraindications: arterial hypertension (untreated), coronary heart disease, cerebrovascular disease, Raynaud’s disease, pregnancy and lactation, age under 18 (except sumatriptan nasal spray) and age above 65 years, severe liver or kidney failure.
About 15–40% (depending on the primary and the lasting efficacy of the drug) of the patients taking an oral triptan experience recurrence. A second dose of the triptan is effective in most cases [51]. If the first dose of a triptan is not effective, a second dose is useless.

After application of sumatriptan, severe adverse events have been reported such as myocardial infarction, cardiac arrhythmias, and stroke. The incidence of these events was about 1 in 1 000 000 [52,53]. Reports on severe adverse events also exist for other triptans and for ergotamine tritate. However, all of the reported patients had contraindications against triptans or the diagnosis of migraine was wrong. In population-based studies, no increased risk of vascular events could be detected for triptan users as compared with a healthy population [54,55]. Thus, contraindications for the use of triptans are untreated arterial hypertension, coronary heart disease, Raynaud’s disease, history of ischemic stroke, pregnancy, lactation, and severe liver or renal failure.

Due to safety aspects, triptans should not be taken during the aura although no specific severe adverse events have been reported. The best time for application is the very onset of headache. Furthermore, triptans are not efficacious when taken during the aura [56,57].

**Comparison of triptans**

The triptans are a very homogenous group of acute migraine drugs with respect to efficacy, pharmacology, and safety. However, some minor differences exist which will be discussed in order to give a guidance which triptan to use in an individual patient. It is important to notice that a triptan can be efficacious even if another (or more) triptan was not.

Subcutaneous sumatriptan has the fastest onset of efficacy of about 10 min [60]. Oral rizatriptan and eletriptan need about 30 min, oral sumatriptan, almotriptan, and zolmitriptan need about 45–60 min [40], an naratriptan and frovatriptan need up to 4 h for the onset of efficacy [58]. Zolmitriptan nasal spray has a shorter duration until efficacy than oral zolmitriptan [61]. There is no evidence that different oral formulations such as melting tablets, wafer forms, or rapid release forms [59] act earlier than others.

Pain relief after 2 h as the most important efficacy parameter is best in subcutaneous sumatripan with up to 80% responders [60]. Sumatriptan nasal spray has the same efficacy as oral sumatriptan 50 or 100 mg. Twenty-five milligram oral sumatriptan is less effective than the higher doses but has less side effects [40]. Sumatriptan suppositories are about as effective as oral sumatriptan 50 or 100 mg and should be given to patients with vomiting [62–64]. Naratriptan and frovatriptan (2.5 mg) are less effective than sumatriptan 50 or 100 mg but have less side effects. The duration until the onset of efficacy is longer in these two triptans as compared with all others. Rizatriptan 10 mg is a little more effective than sumatriptan 100 mg. Oral zolmitriptan 2.5 or 5 mg, almotriptan 12.5 mg and eletriptan 40 mg show a similar efficacy and similar side effects [65–67]. Eletriptan 80 mg is the most effective oral triptan but also has the most side effects [40].

Headache recurrence is a major problem in clinical practice. The recurrence rate is between 15% and 40%. The highest recurrence rate is observed after subcutaneous sumatriptan. Naratriptan and frovatriptan show the lowest recurrence rates. It might be that triptans with a longer half-life time have a lower recurrence rate [68]. If migraine recurs after successful treatment with a triptan, a second dose of this triptan can be given. Another problem in clinical practice is inconsistency of efficacy. Therefore, efficacy only in two of three attacks is regarded as good.

**Migraine prophylaxis**

Prophylactic drug treatment of migraine is possible with several drugs. Substances with good efficacy and tolerability and evidence of efficacy are betablockers, calcium channel blockers, anti-epileptic drugs, NSAIDs, antidepressants, and miscellaneous drugs. The use of all these drugs, however, is based on empirical data rather than on proven pathophysiological concepts. The decision to introduce a prophylactic treatment has to be discussed with the patient carefully. The efficacy of the drugs, their potential side effects, and their interactions with other drugs have to be considered in the individual patient. There is no commonly accepted indication for starting a prophylactic treatment. In the view of the Task Force, prophylactic drug treatment of migraine should be considered and discussed with the patient when

- the quality of life, business duties, or school attendance are severely impaired;
- frequency of attacks per month is two or higher;
- migraine attacks do not respond to acute drug treatment;
- frequent, very long, or uncomfortable auras occur.

A migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by at least 50% within 3 months. For therapy evaluation, a migraine diary is mandatory. In the following paragraphs, the placebo-controlled trials in migraine prophylaxis are summarized. The recommended drugs of first choice, according to the consensus of the Task Force, are given in Table 6. Tables 7 and 8 present drugs recommended as second or third choice when the
drugs of Table 6 are not effective, contraindicated, or when comorbidity of the patients suggests the respective drug of second or third choice (e.g. amitriptyline for migraine prophylaxis in depressed patients or in patients with sleep disturbances or with tension-type headache).

**Betablockers**

Betablockers are clearly effective in migraine prophylaxis and very well studied in a lot of placebo-controlled, randomized trials. The best evidence has been obtained for the selective betablocker metoprolol [69–73] and for the non-selective betablocker propranolol [69,70,74–80]. Moreover, bisoprolol [73,81], timolol [75,82], and atenolol [83] might be effective, but evidence is less convincing compared with propranolol and metoprolol.

**Calcium channel blockers**

The ‘non-specific’ calcium channel blocker flunarizine has been shown to be effective in migraine prophylaxis in several studies [72,80,84–93]. The dose is 5–10 mg, female patients seem to benefit from lower doses than male patients [94]. Another ‘non-specific’ calcium channel blocker, cyclandelate, has also been studied but with conflicting results [89,95–98]. As the better designed studies were negative, cyclandelate cannot be recommended.

**Antiepileptic drugs**

Valproic acid in a dose of at least 600 mg [99–102] and topiramate in a dose between 25 and 100 mg [103–106] are the two anti-epileptic drugs with evidence of efficacy in more than one placebo-controlled trial. The efficacy rates are comparable with those of metoprolol, propranolol, and flunarizine. Other anti-epileptic drugs studied in migraine prophylaxis are lamotrigine and gabapentin. Lamotrigine did not reduce the frequency of migraine attacks but is probably effective in reducing the frequency of migraine auras [107,108]. Gabapentin showed a significant efficacy in one placebo-controlled trial in doses between 1200 and 1600 mg [109].

**NSAIDs**

In some comparative trials, ASA was equivalent to or worse than a comparator (which had shown efficacy in other trials) but never has achieved a better efficacy than placebo in direct comparison. However, in two large cohort trials, ASA 200–300 mg reduced the frequency of migraine attacks [110,111]. Naproxen 1000 mg was better than placebo in three controlled trials [112–114]. Moreover, tolfenamic acid showed efficacy in two placebo-controlled trials [115,116]. Other NSAIDs studied were ketoprofen, mfenamic acid, indobufen, flurbiprofen, and rofecoxib [117]. However, all studies for the later substances were small and had no sufficient design.

**Antidepressants**

The only antidepressant with consistent efficacy in migraine prophylaxis is amitriptyline in doses between 10 and 150 mg. It has been studied in four older placebo-controlled trials, all with positive results [118–121]. As the studies with amitriptyline were small and showed central side effects, this drug is recommended only with level B. For femoxetine, two small positive placebo-controlled trials have been published [122,123]. Fluoxetine in doses between 10 and 40 mg was effective.

---

**Table 6** Recommended substances (drugs of first choice) for the prophylactic drug treatment of migraine

<table>
<thead>
<tr>
<th>Substances</th>
<th>Daily dose (mg)</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betablockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50–200</td>
<td>A</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40–240</td>
<td>A</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td>5–10</td>
<td>A</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25–100</td>
<td>A</td>
</tr>
<tr>
<td>Antiepileptic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>500–1800</td>
<td>A</td>
</tr>
</tbody>
</table>

**Table 7** Drugs of second choice for migraine prophylaxis (evidence of efficacy, but less effective or more side effects than drugs of Table 6)

<table>
<thead>
<tr>
<th>Substances</th>
<th>Daily dose (mg)</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>50–150</td>
<td>B</td>
</tr>
<tr>
<td>Naproxen</td>
<td>2 × 250–500</td>
<td>B</td>
</tr>
<tr>
<td>Petasites</td>
<td>2 × 75</td>
<td>B</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>5–10</td>
<td>B</td>
</tr>
</tbody>
</table>

**Table 8** Drugs of third choice for migraine prophylaxis (only probable efficacy)

<table>
<thead>
<tr>
<th>Substances</th>
<th>Daily dose</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>300 mg</td>
<td>C</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1200–1600</td>
<td>C</td>
</tr>
<tr>
<td>Magnesium</td>
<td>24 mmol</td>
<td>C</td>
</tr>
<tr>
<td>Tanacetum parthenium</td>
<td>3 × 6.25</td>
<td>C</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>400 mg</td>
<td>C</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>300 mg</td>
<td>C</td>
</tr>
<tr>
<td>Candesartan</td>
<td>16 mg</td>
<td>C</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>20 mg</td>
<td>C</td>
</tr>
<tr>
<td>Methysergide</td>
<td>4–12 mg</td>
<td>C</td>
</tr>
</tbody>
</table>
in three [124–126] and not effective in one placebo-controlled trial [127].

Other antidepressants not effective in placebo-controlled trials were clomipramine and sertraline; for several further antidepressants, only open or not placebo-controlled trials are available [117].

Miscellaneous drugs

The antihypertensive drugs lisinopril [128] and candesartan [129] showed efficacy in migraine prophylaxis in one placebo-controlled trial each. However, these results have to be confirmed before the drugs can definitely be recommended. The same is true for high-dose riboflavin (400 mg) and coenzyme Q10 which have shown efficacy in one placebo-controlled trial each [130,131]. For oral magnesium, conflicting studies (one positive, one negative) have been published [132,133]. A herbal drug with evidence of efficacy is butterbur root extract (*Petasites hybridus*). This has been shown for a remedy with 75 mg in two placebo-controlled trials [134,135]. Another herbal remedy, feverfew (*Tanacetum parthenium*), has been studied in several placebo-controlled trials with conflicting results. The most recent and best designed study showed negative results [136], and a Cochrane review resulted in a negative meta-analysis of all controlled studies on tanacetum [137]. However, as there exist positive placebo-controlled trials, Tanacetum can be tried as a third-line drug.

In older studies, clonidin, pizotifen and methysergide have shown efficacy in migraine prophylaxis. The more recent and better designed studies on clonidine, however, did not confirm any efficacy (for review see 117). Methysergide, which is clearly effective, can be recommended for short-term use only (maximum 6 months per treatment period) because of potentially severe side effects [138]; it can be re-established after a wash-out period of 4–6 weeks. Pizotifen is not recommended because the efficacy is not better than in the substances mentioned above and the side effects (dizziness and weight gain) are classified as very severe by the task force and limit the use too much [139]. Ergot alkaloids have also been used in migraine prophylaxis. The evidence for dihydroergotamine is weak as several studies reported both positive and negative results (for review see 117). Dihydroergocryptine has also shown efficacy in one small placebo-controlled study [140].

Botulinum toxin was studied so far in four published placebo-controlled trials [141–144]. Only one study showed an efficacy for the low-dose (but not the high-dose) treatment with botulinum toxin [142]. In another study, only the subgroup of chronic migraine patients without further prophylactic treatment showed benefit from botulinum toxin A [144]. However, this was not the primary end-point of the study.

Finally, those substances with negative modern randomized, placebo-controlled, double-blind trials and which are not mentioned above are listed as follows: no efficacy at all in migraine prophylaxis has been shown for homoeopathic remedies [145–147]; for the antagonist of the cysteiny-l-leukotriene receptor antagonist montelukast [148]; for acetazolamide 500 mg/day [149]; and for the neurokinin-1 receptor antagonist lanepitant [150].

Specific situations

Menstrual migraine

In the recent second edition of IHS diagnostic criteria, the entity of menstrual migraine is to be found in the appendix (and not the main criteria), reflecting a certain degree of uncertainty about the best criteria. Nevertheless, different drug regimes have been studied to treat this condition of quite some importance in clinical practice. On the one hand, acute migraine treatment with triptans has been studied showing the same efficacy of triptans in menstrual migraine attacks as compared with non-menstrual migraine attacks. On the other hand, short-term prophylaxis of menstrual migraine has been studied.

Naproxen sodium (550 mg twice daily) has been shown to reduce pain including headache in the premenstrual syndrome [151]. Its specific effects on menstrual migraine (550 mg twice daily) have also been evaluated [152–154]. In one trial [152], patients reported fewer and less severe headaches during the week before menstruation than patients treated with placebo, but only severity was significantly reduced. In the other two placebo-controlled trials, naproxen sodium, given during 1 week before and 1 week after the start of menstruation, resulted in fewer perimenstrual headaches; in one study, severity was not reduced [153], but in the other both severity and analgesic requirements were decreased [154]. Even triptans have been used as short-term prophylaxis of menstrual migraine. For naratriptan (2 × 1 mg/day for 5 days starting 2 days prior to the expected onset of menses) and for frovatriptan (2 × 2.5 mg given for 6 days perimenstrually), superiority over placebo has been shown [155,156].

Another prophylactic treatment regime of menstrual migraine is estrogen replacement therapy. The best evidence, although not as effective as betablockers or other first line prophylactic drugs, has been achieved for transdermal estradiol (not <100 µg given for 6 days perimenstrually as a gel or a patch) [157–160].
Migraine in pregnancy

There are no specific clinical trials evaluating drug treatment of migraine during pregnancy, most of the migraine drugs are contraindicated. Fortunately, most of the pregnant migraineurs experience less or even no migraine attacks. If migraine occurs during pregnancy, only paracetamol is allowed during the whole period. NSAIDs can be given in the second trimester. These recommendations are based on the advices of the regulatory authorities in most European countries. There might be differences in some respect between different countries (in particular, NSAIDs might be allowed in the first trimester).

Triptans and ergot alkaloids are contraindicated. For sumatriptan, a large pregnancy register has been established with no reports of any adverse events or complications during pregnancy which might be attributed to sumatriptan [3,161,162]. For migraine prophylaxis, only magnesium and metoprolol are recommended during pregnancy (level B recommendation).

Migraine in children and adolescents

The only analgesics with evidence of efficacy for the acute migraine treatment in childhood and adolescents are ibuprofen 10 mg/kg body weight and paracetamol 15 mg/kg body weight [163]. The only antiemetic licensed for the use in children up to 12 years is domperidon. Sumatriptan nasal spray 5–20 mg is the only triptan with positive placebo-controlled trials in the acute migraine treatment of children and adolescents [164–166], the recommended dose for adolescents from the age of 12 is 10 mg. Oral triptans did not show significant efficacy in placebo-controlled childhood and adolescents studies [167–169]. This was, in particular, due to high placebo responses of about 50% in this age group. In post-hoc analyses, however, 2.5–5 mg zolmitriptan were effective in adolescents from the age of 12–17 [170,171]. Ergot alkaloids should not be used in children and adolescents. Moreover, children and adolescents can develop drug-induced headache because of analgesic, ergotamine, or triptan overuse.

For migraine prophylaxis, flunarizine 10 mg and propranolol 40–80 mg/day showed the best evidence of efficacy in children and adolescents [6,168]. Other drugs have not been studied or did not show efficacy in appropriate studies.

Need of update

These recommendations should be updated within 2 years and should be complemented by recommendations for the non-drug treatment of migraine.

Conflicts of interest

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