

EFNS TASK FORCE ARTICLE

EFNS guideline on the drug treatment of migraine – report of an EFNS task force

Members of the task force: S. Evers^a, J. Áfra^b, A. Frese^a, P. J. Goadsby^c, M. Linde^d, A. May^e and P. S. Sándor^f

^aDepartment of Neurology, University of Münster, Münster, Germany; ^bNational Institute of Neurosurgery, Budapest, Hungary; ^cHeadache Group, Institute of Neurology, The National Hospital for Neurology and Neurosurgery, London, UK; ^dCephalea Pain Center, Lärarhuset Södra vägen, Gothenburg, Gothenburg, Sweden; ^eDepartment of Neurology, University of Hamburg, Hamburg, Germany; and ^fDepartment of Neurology, University of Zurich, Zurich, Switzerland

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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.

Correspondence: Stefan Evers, Department of Neurology, University of Münster, Albert-Schweitzer-Str. 33, 48129 Münster, Germany (tel.: +49-251-8348196; fax: +49-251-8348181; e-mail: everss@uni-muenster.de).

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-h-s.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)

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- 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
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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 atypical), 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)

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- 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
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- 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 sub-

cutaneous 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 domperidon 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]. In comparative trials,

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

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

Table 4 Antiemetics recommended for the acute treatment of migraine attacks

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

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_{1B/1D}-agonists)

The 5-HT_{1B/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 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

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

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 tartrate. 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 sumatriptan 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

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

Substances	Daily dose	Level
Betablockers		
Metoprolol	50–200 mg	A
Propranolol	40–240 mg	A
Calcium channel blockers		
Flunarizine	5–10 mg	A
Antiepileptic drugs		
Valproic acid	500–1800 mg	A
Topiramate	25–100 mg	A

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

Substances	Daily dose (mg)	Level
Amitriptyline	50–150	B
Naproxen	2 × 250–500	B
Petasites	2 × 75	B
Bisoprolol	5–10	B

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

Substances	Daily dose	Level
Acetylsalicylic acid	300 mg	C
Gabapentin	1200–1600 mg	C
Magnesium	24 mmol	C
Tanacetum parthenium	3 × 6.25 mg	C
Riboflavin	400 mg	C
Coenzyme Q10	300 mg	C
Candesartan	16 mg	C
Lisinopril	20 mg	C
Methysergide	4–12 mg	C

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, mefenamic 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

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, clonidine, 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 cysteinyl-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 $<100 \mu\text{g}$ 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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References

1. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 2nd edn. *Cephalalgia* 2004; **24**(Suppl. 1): 1–160.
2. Brainin M, Barnes M, Baron JC, *et al.* Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *European journal of neurology* 2004; **11**: 577–581.
3. Olesen C, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J. Pregnancy outcome following prescription for sumatriptan. *Headache* 2000; **40**: 20–24.
4. Diener HC (ed.). Therapie der Migräneattacke und Migräneprophylaxe. Leitlinie der Deutschen Gesellschaft für Neurologie und der Deutschen Migräne- und Kopfschmerzgesellschaft. Stuttgart, Thieme 2005.
5. Maytal J, Young M, Shechter A, Lipton RB. Pediatric migraine and the International Headache Society (IHS) criteria. *Neurology* 1997; **48**: 602–607.
6. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. American Academy of Neurology Quality Standards Subcommittee; Practice Committee of the Child Neurology Society. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology* 2004; **63**: 2215–2224.

7. Lewis DW. Toward the definition of childhood migraine. *Current Opinion in Pediatrics* 2004; **16**: 628–636.
8. Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population – a prevalence study. *Journal of Clinical Epidemiology* 1991; **44**: 1147–1157.
9. Scher A, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. *Headache* 1998; **38**: 497–506.
10. Rasmussen BK. Epidemiology of headache. *Cephalalgia* 2001; **21**: 774–777.
11. Lipton R, Scher A, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. *Neurology* 2002; **58**: 885–894.
12. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: the utility of neuroimaging in the evaluation of headache in patients with normal neurologic examinations. *Neurology* 1994; **44**: 1353–1354.
13. Pilgrim AJ. The methods used in clinical trials of sumatriptan in migraine. *Headache* 1993; **33**: 280–293.
14. Chabriat H, Joire JE, Danchot J, Gripon P, Bousser MG. Combined oral lysine acetylsalicylate and metoclopramide in the acute treatment of migraine: a multicentre double-blind placebo-controlled study. *Cephalalgia* 1994; **14**: 297–300.
15. Nebe J, Heier M, Diener HC. Low-dose ibuprofen in self-medication of mild to moderate headache: a comparison with acetylsalicylic acid and placebo. *Cephalalgia* 1995; **15**: 531–535.
16. Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaert RG, Schoenen J, Chazot G. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; **346**: 923–926.
17. Diener HC, Bussone G, de Liano H, *et al.* Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalalgia* 2004; **24**: 947–954.
18. Havanka-Kannianen H. Treatment of acute migraine attack: ibuprofen and placebo compared. *Headache* 1989; **29**: 507–509.
19. Kloster R, Nestvold K, Vilming ST. A double-blind study of ibuprofen versus placebo in the treatment of acute migraine attacks. *Cephalalgia* 1992; **12**: 169–171.
20. Karachalios GN, Fotiadou A, Chrisikos N, Karabetsos A, Kehagioglou K. Treatment of acute migraine attack with diclofenac sodium: a double-blind study. *Headache* 1992; **32**: 98–100.
21. Dahlöf C, Björkman R. Diclofenac-K (50 and 100 mg) and placebo in the acute treatment of migraine. *Cephalalgia* 1993; **13**: 117–123.
22. The Diclofenac-K/Sumatriptan Migraine Study Group. Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal antiinflammatory drug, diclofenac-potassium, in comparison to oral sumatriptan and placebo. *Cephalalgia* 1999; **19**: 232–240.
23. Göbel H, Heinze A, Niederberger U, Witt T, Zumbroich V. Efficacy of phenazone in the treatment of acute migraine attacks: a double-blind, placebo-controlled, randomized study. *Cephalalgia* 2004; **24**: 888–893.
24. Tulunay FC, Ergun H, Gulmez SE, *et al.* The efficacy and safety of dipyron (Novalgin) tablets in the treatment of acute migraine attacks: a double-blind, cross-over, randomized, placebo-controlled, multi-center study. *Functional Neurology* 2004; **19**: 197–202.
25. Myllylä VV, Havanka H, Herrala L, *et al.* Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: comparable effect in a double-blind, randomized, controlled, parallel-group study. *Headache* 1998; **38**: 201–207.
26. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Archives of Internal Medicine* 2000; **160**: 3486–3492.
27. Lipton RB, Stewart WF, Ryan RE, Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain - Three double-blind, randomized, placebo-controlled trials. *Archives of Neurology* 1998; **55**: 210–217.
28. Diener H, Pfaffenrath V, Pageler L. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 2005; **25**: 776–787.
29. Limmroth V, May A, Diener HC. Lysine-acetylsalicylic acid in acute migraine attacks. *European Neurology* 1999; **41**: 88–93.
30. Bigal ME, Bordini CA, Tepper SJ, Speciali JG. Intravenous dipyron in the acute treatment of migraine without aura and migraine with aura: a randomized, double blind, placebo controlled study. *Headache* 2002; **42**: 862–871.
31. Ross-Lee LM, Eadie MJ, Heazlewood V, Bochner F, Tyrer JH. Aspirin pharmacokinetics in migraine. The effect of metoclopramide. *European Journal of Clinical Pharmacology* 1983; **24**: 777–785.
32. Waelkens J. Dopamine blockade with domperidone: bridge between prophylactic and abortive treatment of migraine? A dose-finding study. *Cephalalgia* 1984; **4**: 85–90.
33. Schulman E, Dermott K. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache* 2003; **43**: 729–733.
34. Ellis GL, Delaney J, DeHart DA, Owens A. The efficacy of metoclopramide in the treatment of migraine headache. *Annals of Emergency Medicine* 1993; **22**: 191–195.
35. Tfelt-Hansen P, Saxena PR, Dahlöf C, *et al.* Ergotamine in the acute treatment of migraine. A review and European consensus. *Brain* 2000; **123**: 9–18.
36. The Multinational Oral Sumatriptan Cafergot Comparative Study Group. A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine. *European Neurology* 1991; **31**: 314–322.
37. Diener HC, Reches A, Pascual J, Pascual J, Pitei D, Steiner TJ. Eletriptan and Cafergot Comparative Study Group. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison. *European neurology* 2002; **47**: 99–107.
38. Christie S, Göbel H, Mateos V, Allen C, Vrijens F, Shivaprakash M, Rizatriptan-Ergotamine/Caffeine

- Preference Study Group. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine. *European Neurology* 2003; **49**: 20–29.
39. Evers S, Gralow I, Bauer B, *et al.* Sumatriptan and ergotamine overuse and drug-induced headache: a clinicoepidmiologic study. *Clinical Neuropharmacology* 1999; **22**: 201–206.
 40. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT_{1B/1D} agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; **358**: 1668–1675.
 41. Goadsby PB, Lipton RB, Ferrai MD. Migraine: current understanding and management. *New England Journal of Medicine* 2002; **346**: 257–270.
 42. The Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. A study to compare oral sumatriptan with oral aspirin plus oral metoclopramide in the acute treatment of migraine. *European Neurology* 1992; **32**: 177–184.
 43. Geraud G, Compagnon A, Rossi A. Zolmitriptan versus a combination of acetylsalicylic acid and metoclopramide in the acute oral treatment of migraine: a double-blind, randomised, three-attack study. *European Neurology* 2002; **47**: 88–98.
 44. Diamond M, Hettiarachchi J, Hilliard B, Sands G, Nett R. Effectiveness of eletriptan in acute migraine: primary care for excedrin nonresponders. *Headache* 2004; **44**: 209–216.
 45. Diener HC, for the ASASUMAMIG Study Group. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. *Cephalalgia* 1999; **19**: 581–588.
 46. Burstein R, Collins B, Jakubowski M. Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. *Annals of Neurology* 2004; **55**: 19–26.
 47. Dowson A, Massiou H, Lainez J, Cabarrocas X. Almotriptan improves response rates when treatment is within 1 hour of migraine onset. *Headache* 2004; **44**: 318–322.
 48. Limmroth V, Kazarawa S, Fritsche G, Diener HC. Headache after frequent use of new serotonin agonists zolmitriptan and naratriptan. *Lancet* 1999; **353**: 378.
 49. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001; **57**: 1694–1698.
 50. Ferrari MD. How to assess and compare drugs in the management of migraine: success rates in terms of response and recurrence. *Cephalalgia* 1999; **19**(Suppl. 23): 2–8.
 51. Ferrari MD, James MH, Bates D, *et al.* Oral sumatriptan: effect of a second dose, and incidence and treatment of headache recurrences. *Cephalalgia* 1994; **14**: 330–338.
 52. O'Quinn S, Davis RL, Guttermann DL, *et al.* Prospective large-scale study of the tolerability of subcutaneous sumatriptan injection for the acute treatment of migraine. *Cephalalgia* 1999; **19**: 223–231.
 53. Welch KMA, Mathew NT, Stone P, Rosamond W, Saiers J, Guttermann D. Tolerability of sumatriptan: clinical trials and post-marketing experience. *Cephalalgia* 2000; **20**: 687–695.
 54. Hall G, Brown M, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; **62**: 563–568.
 55. Velentgas P, Cole JA, Mo J, Sikes CR, Walker AM. Severe vascular events in migraine patients. *Headache* 2004; **44**: 642–651.
 56. Bates D, Ashford E, Dawson R, *et al.* Subcutaneous sumatriptan during the migraine aura. *Neurology* 1994; **44**: 1587–1592.
 57. Olesen J, Diener HC, Schoenen J, Hettiarachchi J. No effect of eletriptan administration during the aura phase of migraine. *European journal of neurology* 2004; **11**: 671–677.
 58. Goadsby PJ. Role of naratriptan in clinical practice. *Cephalalgia* 1997; **17**: 472–473.
 59. Dahlöf C, Cady R, Poole AC. Speed of onset and efficacy of sumatriptan fast-disintegrating/rapid release tablets: results of two replicate randomised, placebo-controlled studies. *Headache Care* 2004; **1**: 277–280.
 60. The Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. *New England Journal of Medicine* 1991; **325**: 316–321.
 61. Charlesworth BR, Dowson AJ, Purdy A, Becker WJ, Boes-Hansen S, Farkkila G. Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine. *CNS Drugs* 2003; **17**: 653–667.
 62. Becker WJ, on behalf of the Study Group. A placebo-controlled, dose-defining study of sumatriptan nasal spray in the acute treatment of migraine. *Cephalalgia* 1995; **15**(Suppl. 14): 271–276.
 63. Ryan R, Elkind A, Baker CC, Mullican W, DeBussey S, Asgharnejad M. Sumatriptan nasal spray for the acute treatment of migraine. *Neurology* 1997; **49**: 1225–1230.
 64. Tepper SJ, Cochran A, Hobbs S, Woessner M. Sumatriptan suppositories for the acute treatment of migraine. *International journal of clinical practice* 1998; **52**: 31–35.
 65. Goldstein J, Ryan R, Jiang K, *et al.* Crossover comparison of rizatriptan 5 mg and 10 mg versus sumatriptan 25 and 50 mg in migraine. *Headache* 1998; **38**: 737–747.
 66. Tfelt-Hansen P, Teall J, Rodriguez F, *et al.* Oral rizatriptan versus oral sumatriptan: a direct comparative study in the acute treatment of migraine. *Headache* 1998; **38**: 748–755.
 67. Tfelt-Hansen P, Ryan RE. Oral therapy for migraine: comparisons between rizatriptan and sumatriptan. A review of four randomized, double-blind clinical trials. *Neurology* 2000; **55**(Suppl. 2): S19–S24.
 68. Geraud G, Keywood C, Senard JM. Migraine headache recurrence: relationship to clinical, pharmacological, and pharmacokinetic properties of triptans. *Headache* 2003; **43**: 376–388.
 69. Kangasniemi P, Hedman C. Metoprolol and propranolol in the prophylactic treatment of classical and common migraine. A double-blind study. *Cephalalgia* 1984; **4**: 91–96.
 70. Olsson JE, Behring HC, Forssman B, *et al.* Metoprolol and propranolol in migraine prophylaxis: a double-blind multicenter study. *Acta Neurologica Scandinavica* 1984; **70**: 160–168.
 71. Steiner TJ, Joseph R, Hedman C, Rose FC. Metoprolol in the prophylaxis of migraine: parallel group comparison with placebo and dose-ranging follow-up. *Headache* 1988; **28**: 15–23.
 72. Sorensen PS, Larsen BH, Rasmussen MJK, *et al.* Flunarizine versus metoprolol in migraine prophylaxis: a

- double-blind, randomized parallel group study of efficacy and tolerability. *Headache* 1991; **31**: 650–657.
73. Wörz R, Reinhardt-Benmalek B, Grottemeyer KH. Bisoprolol and metoprolol in the prophylactic treatment of migraine with and without aura - a randomized double-blind cross-over multicenter study. *Cephalalgia* 1991; **11**(Suppl. 11): 152–153.
 74. Diamond S, Medina JL. Double blind study of propranolol for migraine prophylaxis. *Headache* 1976; **16**: 24–27.
 75. Tfelt-Hansen P, Standnes B, Kangasniemi P, Hakkarainen H, Olesen J. Timolol vs. propranolol vs. placebo in common migraine prophylaxis: a double-blind multicenter trial. *Acta Neurologica Scandinavica* 1984; **69**: 1–8.
 76. Nadelmann JW, Stevens J, Saper JR. Propranolol in the prophylaxis of migraine. *Headache* 1986; **26**: 175–182.
 77. Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Long acting propranolol in the prophylaxis of migraine. Comparison of the daily doses of 80 mg and 160 mg. *Headache* 1988; **28**: 607–611.
 78. Ludin H-P. Flunarizine and propranolol in the treatment of migraine. *Headache* 1989; **29**: 218–223.
 79. Holroyd KA, Penzien DB, Cordingley GE. Propranolol in the management of recurrent migraine: a meta-analytic review. *Headache* 1991; **31**: 333–340.
 80. Gawel MJ, Kreeft J, Nelson RF, Simard D, Arnott WS. Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. *Canadian Journal of Neurological Sciences* 1992; **19**: 340–345.
 81. van de Ven LLM, Franke CL, Koehler PJ. Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. *Cephalalgia* 1997; **17**: 596–599.
 82. Stellar S, Ahrens SP, Meibohm AR, Reines SA. Migraine prevention with timolol. A double-blind crossover study. *JAMA* 1984; **252**: 2576–2580.
 83. Johannsson V, Nilsson LR, Widelius T, *et al.* Atenolol in migraine prophylaxis a double-blind cross-over multicentre study. *Headache* 1987; **27**: 372–374.
 84. Louis P. A double-blind placebo-controlled prophylactic study of flunarizine in migraine. *Headache* 1981; **21**: 235–239.
 85. Diamond S, Schenbaum H. Flunarizine, a calcium channel blocker, in the prophylactic treatment of migraine. *Headache* 1983; **23**: 39–42.
 86. Amery WK, Caers LI, Aerts TJL. Flunarizine, a calcium entry blocker in migraine prophylaxis. *Headache* 1985; **25**: 249–254.
 87. Bono G, Manzoni GC, Martucci N, *et al.* Flunarizine in common migraine: Italian cooperative trial. II. Long-term follow-up. *Cephalalgia* 1985; **5**(Suppl. 2): 155–158.
 88. Centonze V, Tesaro P, Magrone D, *et al.* Efficacy and tolerability of flunarizine in the prophylaxis of migraine. *Cephalalgia* 1985; **5**(Suppl. 2): 163–168.
 89. Nappi G, Sandrini G, Savoini G, Cavallini A, de Rysky C, Micieli G. Comparative efficacy of cyclandelate versus flunarizine in the prophylactic treatment of migraine. *Drugs* 1987; **33**(Suppl. 2): 103–109.
 90. Freitag FG, Diamond S, Diamond M. A placebo controlled trial of flunarizine in migraine prophylaxis. *Cephalalgia* 1991; **11**(Suppl. 11): 157–158.
 91. Bassi P, Brunati L, Rapuzzi B, Alberti E, Mangoni A. Low dose flunarizine in the prophylaxis of migraine. *Headache* 1992; **32**: 390–392.
 92. Diamond S, Freitag FG. A double blind trial of flunarizine in migraine prophylaxis. *Headache Quarterly* 1993; **4**: 169–172.
 93. Balkan S, Aktekin B, Önal Z. Efficacy of flunarizine in the prophylactic treatment of migraine. *Gazi Medical Journal* 1994; **5**: 81–84.
 94. Diener H, Matias-Guiu J, Hartung E, *et al.* Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia* 2002; **22**: 209–221.
 95. Gerber WD, Schellenberg R, Thom M, *et al.* Cyclandelate versus propranolol in the prophylaxis of migraine – a double-blind placebo-controlled study. *Functional Neurology* 1995; **10**: 27–35.
 96. Diener HC, Föh M, Iaccarino C, *et al.* Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. *Cephalalgia* 1996; **16**: 441–447.
 97. Siniatchkin M, Gerber WD, Vein A. Clinical efficacy and central mechanisms of cyclandelate in migraine: a double-blind placebo-controlled study. *Functional Neurology* 1998; **13**: 47–56.
 98. Diener H, Krupp P, Schmitt T, Steitz G, Milde K, Freytag S, On behalf of the Study Group. Cyclandelate in the prophylaxis of migraine: a placebo-controlled study. *Cephalalgia* 2001; **21**: 66–70.
 99. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. *Archives of Neurology* 1997; **54**: 1141–1145.
 100. Klapper J, on behalf of the Divalproex Sodium in Migraine Prophylaxis Study Group. Divalproex sodium in migraine prophylaxis: a dose-controlled study. *Cephalalgia* 1997; **17**: 103–108.
 101. Silberstein SD, Collins SD, Carlson H. Safety and efficacy of once-daily, extended-release divalproex sodium monotherapy for the prophylaxis of migraine headaches. *Cephalalgia* 2000; **20**: 269.
 102. Freitag F, Collins S, Carlson H, *et al.* A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. *Neurology* 2002; **58**: 1652–1659.
 103. Brandes J, Saper J, Diamond M, *et al.* Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; **291**: 965–973.
 104. Diener H, Tfelt-Hansen P, Dahlöf C, *et al.* Topiramate in migraine prophylaxis: results from a placebo-controlled trial with propranolol as an active control. *Journal of Neurology* 2004; **251**: 943–950.
 105. Mei D, Capuano A, Vollono C, *et al.* Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. *Neurological sciences* 2004; **25**: 245–250.
 106. Silberstein SD, Neto W, Schmitt J, Jacobs D. Topiramate in migraine prevention: results of a large controlled trial. *Archives of Neurology* 2004; **61**: 490–495.
 107. Steiner TJ, Findley LJ, Yuen AWC. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. *Cephalalgia* 1997; **17**: 109–112.
 108. Lampl C, Buzath A, Klinger D, Neumann K. Lamotrigine in the prophylactic treatment of migraine aura – a pilot study. *Cephalalgia* 1999; **19**: 58–63.
 109. Mathew NT, Rapoport A, Saper J, *et al.* Efficacy of gabapentin in migraine prophylaxis. *Headache* 2001; **41**: 119–128.

110. Peto R, Gray R, Collins R, Wheatly K, Hennekens C, Jamrozik K. Randomised trial of prophylactic daily aspirin in male british doctors. *BMJ* 1988; **296**: 313–316.
111. Buring JE, Peto R, Hennekens CH. Low-dose aspirin for migraine prophylaxis. *JAMA* 1990; **264**: 1711–1713.
112. Welch KMA, Ellis DJ, Keenan PA. Successful migraine prophylaxis with naproxen sodium. *Neurology* 1985; **35**: 1304–1310.
113. Ziegler DK, Ellis DJ. Naproxen in prophylaxis of migraine. *Archives of Neurology* 1985; **42**: 582–584.
114. Bellavance AJ, Meloche JP. A comparative study of naproxen sodium, pizotiline and placebo in migraine prophylaxis. *Headache* 1990; **30**: 710–715.
115. Mikkelsen BM, Falk JV. Prophylactic treatment of migraine with tolfenamic acid: a comparative double-blind crossover study between tolfenamic acid and placebo. *Acta Neurologica Scandinavica* 1982; **66**: 105–111.
116. Mikkelsen B, Pedersen KK, Christiansen LV. Prophylactic treatment of migraine with tolfenamic acid, propranolol and placebo. *Acta Neurologica Scandinavica* 1986; **73**: 423–427.
117. Evers S, Mylecharane E. Nonsteroidal antiinflammatory and miscellaneous drugs in migraine prophylaxis. In: Olesen J, Goadsby PJ, Ramadan N, Tfelt-Hansen P, Welch KMA, eds. *The Headaches*, 3rd edn. Philadelphia, PA: Lippincott, 2005: 551–564.
118. Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis: changes in pattern of attacks during a controlled clinical trial. *Journal of neurology, neurosurgery, and psychiatry* 1973; **36**: 684–690.
119. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. *Archives of Neurology* 1979; **36**: 695–699.
120. Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Preskorn SH, Mason J. Migraine prophylaxis. A comparison of propranolol and amitriptyline. *Archives of Neurology* 1987; **44**: 486–489.
121. Ziegler DK, Hurwitz A, Preskorn S, Hassanein R, Seim J. Propranolol and amitriptyline in prophylaxis of migraine: pharmacokinetic and therapeutic effects. *Archives of Neurology* 1993; **50**: 825–830.
122. Zeeberg I, Orholm M, Nielsen JD, Honore PLF, Larsen JJV. Femoxetine in the prophylaxis of migraine – a randomised comparison with placebo. *Acta Neurologica Scandinavica* 1981; **64**: 452–459.
123. Orholm M, Honoré PF, Zeeberg I. A randomized general practice group-comparative study of femoxetine and placebo in the prophylaxis of migraine. *Acta Neurologica Scandinavica* 1986; **74**: 235–239.
124. Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. *Headache* 1992; **32**: 101–104.
125. Steiner TJ, Ahmed F, Findley LJ, MacGregor EA, Wilkinson M. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. *Cephalalgia* 1998; **18**: 283–286.
126. d'Amato CC, Pizza V, Marmolo T, Giordano E, Alfano V, Nasta A. Fluoxetine for migraine prophylaxis: a double-blind trial. *Headache* 1999; **39**: 716–719.
127. Saper JR, Silberstein SD, Lake AE, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. *Headache* 1994; **34**: 497–502.
128. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo-controlled, crossover trial. *BMJ* 2001; **322**: 19–22.
129. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker. A randomized controlled trial. *JAMA* 2002; **289**: 65–69.
130. Schoenen J, Jacqy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis – a randomized controlled trial. *Neurology* 1998; **50**: 466–470.
131. Sandor PS, di Clemente L, Coppola G, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomised controlled trial. *Neurology* 2005; **64**: 713–715.
132. Peikert A, Wilimzig C, Köhne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996; **16**: 257–263.
133. Pfaffenrath V, Wessely P, Meyer C, et al. Magnesium in the prophylaxis of migraine – a double-blind, placebo-controlled study. *Cephalalgia* 1996; **16**: 436–440.
134. Diener HC, Rahlfs VW, Danesch U. The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. *European Neurology* 2004; **51**: 89–97.
135. Lipton RB, Göbel H, Einhüpl KM, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004; **63**: 2240–2244.
136. Pfaffenrath V, Diener HC, Fischer M, Friede M, Henneicke-von Zepelin HH, Investigators. The efficacy and safety of Tanacetum parthenium (feverfew) in migraine prophylaxis – a double-blind, multicentre, randomized placebo-controlled dose-response study. *Cephalalgia* 2002; **22**: 523–532.
137. Pittler MH, Ernst E. Feverfew for preventing migraine. *Cochrane database of systematic reviews* 2004; CD002286.
138. Silberstein SD. Methysergide. *Cephalalgia* 1998; **18**: 421–435.
139. Mylecharane EJ. 5-HT₂ receptor antagonists and migraine therapy. *Journal of Neurology* 1991; **238**(Suppl. 1): S45–S52.
140. Canonico PL, Scapagnini U, Genazzani E, Zanotti A. Dihydroergokryptine (DEK) in the prophylaxis of common migraine: double-blind clinical study vs placebo. *Cephalalgia* 1989; **9**(Suppl. 10): 446–447.
141. Brin MF, Swope DM, O'Brian C, Abbasi S, Pogoda JM. Botox® for migraine: double-blind, placebo-controlled, region-specific evaluation. *Cephalalgia* 2000; **20**: 421–422.
142. Silberstein S, Mathew N, Saper J, Jenkins S. Botulinum toxin type A as a migraine preventive treatment. *Headache* 2000; **40**: 445–450.
143. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine – a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2004; **24**: 838–843.
144. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD, BOTOX CDH Study Group. Botulinum toxin type A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. *Headache* 2005; **45**: 315–324.

145. Walach H, Haeusler W, Lowes T, *et al.* Classical homeopathic treatment of chronic headaches. *Cephalalgia* 1997; **17**: 119–126.
146. Whitmarsh TE, Coleston-Shields DM, Steiner TJ. Double-blind randomized placebo-controlled study of homeopathic prophylaxis of migraine. *Cephalalgia* 1997; **17**: 600–604.
147. Straumsheim P, Borchgrevink C, Mowinckel P, Kierulf H, Hafslund O. Homeopathic treatment of migraine: a double blind, placebo controlled trial of 68 patients. *The British homeopathic journal* 2000; **89**: 4–7.
148. Brandes JL, Visser WH, Farmer MV, *et al.* Montelukast for migraine prophylaxis: a randomized, double-blind, placebo-controlled study. *Headache* 2004; **44**: 581–586.
149. Vahedi K, Taupin P, Djomby R, *et al.* Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial. *Journal of Neurology* 2002; **249**: 206–211.
150. Goldstein DJ, Offen WW, Klein EG, *et al.* Lanepitant, an NK-1 antagonist, in migraine prevention. *Cephalalgia* 2001; **21**: 102–106.
151. Facchinetti F, Fioroni L, Sances G, Romano G, Nappi G, Genazzani AR. Naproxen sodium in the treatment of premenstrual symptoms: a placebo-controlled study. *Gynecologic and Obstetric Investigation* 1989; **28**: 205–208.
152. Sargent J, Solbach P, Damasio H, *et al.* A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. *Headache* 1985; **25**: 320–324.
153. Szekely B, Merryman S, Croft H, Post G. Prophylactic effects of naproxen sodium on perimenstrual headache: a double-blind, placebo-controlled study. *Cephalalgia* 1989; **9**(Suppl. 10): 452–453.
154. Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache* 1990; **30**: 705–709.
155. Newman L, Mannix LK, Landy S, *et al.* Naratriptan as short-term prophylaxis in menstrually associated migraine: a randomised, double-blind, placebo-controlled study. *Headache* 2001; **41**: 248–256.
156. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 2004; **63**: 261–269.
157. De Lignieres B, Mauvais-Javis P, Mas JML, Mas JL, Touboul PJ, Bousser MG. Prevention of menstrual migraine by percutaneous oestradiol. *BMJ* 1986; **293**: 1540.
158. Dennerstein L, Morse C, Burrows G, Oats J, Brown J, Smith M. Menstrual migraine: a double blind trial of percutaneous oestradiol. *Gynecological Endocrinology* 1988; **2**: 113–120.
159. Pradalier A, Vincent D, Beaulieu PH, Baudesson G, Launay J-M. Correlation between estradiol plasma level and therapeutic effect on menstrual migraine. In: *Proceedings of the 10th Migraine Trust Symposium*. London 1994: 129–132.
160. Smits MG, van den Meer YG, Pfeil JPJM, Rijnierse JJMM, Vos AJM. Perimenstrual migraine: effect of Estraderm® TTS and the value of contingent negative variation and exteroceptive temporalis muscle suppression test. *Headache* 1994; **34**: 103–106.
161. Källen B, Lygner PE. Delivery outcome in women who used drugs for migraine during pregnancy with special reference to sumatriptan. *Headache* 2001; **41**: 351–356.
162. Fox AW, Chambers CD, Anderson PO, Diamond ML, Spierings EL. Evidence-based assessment of pregnancy outcome after sumatriptan exposure. *Headache* 2002; **42**: 8–15.
163. Evers S, Pothmann R, Überall M, Naumann E, Gerber WD. Therapie idiopathischer Kopfschmerzen im Kindesalter. *Nervenheilkunde* 2001; **20**: 306–315.
164. Überall MA, Wenzel D. Intranasal sumatriptan for the acute treatment of migraine in children. *Neurology* 1999; **52**: 1507–1510.
165. Winner P, Rothner AD, Saper J, *et al.* A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. *Pediatrics* 2000; **106**: 989–997.
166. Ahonen K, Hämäläinen M, Rantala H, Hoppu K. Nasal sumatriptan is effective in treatment of migraine attacks in children: a randomized trial. *Neurology* 2004; **62**: 883–887.
167. Hämäläinen ML, Hoppu K, Santavuori P. Sumatriptan for migraine attacks in children: a randomized placebo-controlled study. Do children with migraine attacks respond to oral sumatriptan differently from adults? *Neurology* 1997; **48**: 1100–1103.
168. Evers S. Drug treatment of migraine in children. A comparative review. *Paediatric drugs* 1999; **1**: 7–18.
169. Winner P, Lewis D, Visser H, Jiang K, Ahrens S, Evans JK, Rizatriptan Adolescent Study Group. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double-blind, placebo-controlled study. *Headache* 2002; **42**: 49–55.
170. Solomon GD, Cady RK, Klapper JA, Earl NL, Saper JR, Ramadan NM. Clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of migraine. *Neurology* 1997; **49**: 1219–1225.
171. Tepper SJ, Donnan GA, Dowson AJ, *et al.* A long-term study to maximise migraine relief with zolmitriptan. *Current medical research and opinion* 1999; **15**: 254–271.