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**CME ARTICLE**

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

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**Background:** Migraine is one of the most frequent disabling neurological conditions with a major impact on the patients' quality of life.
**Objectives:** To give evidence-based or expert recommendations for the different drug treatment procedures in the particular migraine syndromes based on a literature search and the consensus of an expert panel.
**Methods:** All available medical reference systems were screened for the range 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 European Federation of Neurological Societies (EFNS) resulting in level A, B, or C recommendations and good practice points.
**Recommendations:** For the acute treatment of migraine attacks, oral non-steroidal antiinflammatory drug (NSAID) and triptans are recommended. The administration should follow the concept of stratified treatment. Before intake of NSAID and triptans, oral metoclopramide or domperidone is recommended. In very severe attacks, intravenous acetylsalicylic acid or subcutaneous sumatriptan are drugs of first choice. Status migrainosus can be treated by cortoicosteroids, although this is not universally held to be helpful, or dihydroergotamine. 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 include 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. 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 nearly unchanged. The different migraine syndromes with specific aura features, however, were classified in a new system. The diagnostic criteria for all migraine syndromes have been published on the homepage of the IHS (http://www.i-h-s.org).

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 2009). All papers published in English, German, or French were

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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 email. A second draft was then written by the chairman and again discussed by email. All recommendations had to be agreed to by all members of the task force unanimously.

## Drug treatment of migraine attacks

Several large randomized, placebo-controlled trials have been published on the acute management of migraine. In most of these trials, successful treatment of migraine attacks was defined by the following criteria [5]:

- pain free after 2 h
- improvement of headache from moderate or severe to mild or none after 2 h [6]
- 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 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 [7–10], ibuprofen 200–800 mg [8,10–12], diclofenac 50–100 mg [13–15], phenazon 1000 mg [16], metamizol 1000 mg [17], tolfenamic acid 200 mg [18], and paracetamol 1000 mg [19]. 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 [20–22]. Intravenous ASA was more effective than subcutaneous ergotamine [23]; intravenous metamizol was superior to placebo in migraine without and with aura [24]. Lysine-ASA in combination with metoclopramide had comparable efficacy as sumatriptan [9]. Effervescent ASA 1000 mg is probably as effective as ibuprofen 400 mg and as sumatriptan 50 mg [10,25,26].

Also the selective COX-2 inhibitors have been investigated in clinical trials. Valdecoxib 20–40 mg and rofecoxib 25–50 mg, the latter one not available on the market any more, have shown efficacy in acute migraine treatment [27–30]. Table 1 presents an overview of analgesics with efficacy in acute migraine treatment.

**Table 1** 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

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

In order to prevent drug overuse headache, the intake of simple analgesics should be restricted to 15 days per month and the intake of combined analgesics to 10 days per month.

### Antiemetics

The use of antiemetics in acute migraine attacks is recommended to treat nausea and potential emesis and because it is assumed that these drugs improve the resorption af analgesics [31–33]. However, there are no prospective, placebo-controlled randomized trials to prove this assertion. Metoclopramide also has a genuine mild analgesic efficacy when given orally [34] and a higher efficacy when given intravenously [35]. There is no evidence that the fixed combination of an antiemetic with an analgesic is more effective than the analgesic 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 2 presents the antiemetics recommended for the use in migraine attacks.

### Ergot alkaloids

There are only very few randomized, placebo-controlled trials on the efficacy of ergot alkaloids in the

**Table 2** Antiemetics recommended for the acute treatment of migraine attacks

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

acute migraine treatment [36]. In comparative trials, triptans showed better efficacy than ergot alkaloids [37–40]. The advantage of ergot alkaloids is a lower recurrence rate in some patients. Therefore, these substances should be restricted to patients with very long migraine attacks or with regular recurrence. The only compounds with sufficient evidence of efficacy are ergotamine tartrate and dihydroergotamine 2 mg (oral and suppositories, respectively). Ergot alkaloids can induce drug overuse headache very fast and in very low doses [41]. Therefore, their use must be limited to 10 days per month. Major side effects are nausea, vomiting, paraesthesia, 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-$HT_{1B/1D}$ receptor agonists sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan (order in the year of marketing), so-called triptans, are migraine medications and should not be applied in other headache disorders except cluster headache. The different triptans for migraine therapy are presented in Table 3. The efficacy of all triptans has been proven in large placebo-controlled trials of which metaanalyses have been published [42,43]. For sumatriptan [9,44] and zolmitriptan [45] 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 nonresponders to NSAID, triptans are effective [46]. Sumatriptan 6 mg subcutaneously is more effective than intravenous ASA 1000 mg s.c. but has more side effects [47]. 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 [48–52]. It is still debated whether triptans are less efficacious or even may fail when taken after the onset of allodynia during a migraine attack [49,53], with randomized controlled trials not supporting a difference for allodynic patients [52,54]. A strategy of strictly early intake can, however, lead to frequent drug treatment in certain patients. The use of triptans is restricted to maximum 9 days per month by the IHS criteria; in epidemiological studies, the risk for chronification became significant at 12 days per month of triptan intake [55]. Otherwise, the induction of a drug overuse headache is possible for all triptans [41,56,57].

One typical problem of attack treatment in migraine is headache recurrence defined as a worsening of headache after pain free or mild pain has been achieved with a drug within 24 h [58]. About 15–40% (depending on the primary and the lasting efficacy of the drug) of the patients taking an oral triptan experience

**Table 3** 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, mg | Level | Comment |
|---|---|---|---|
| Sumatriptan | 25, 50, 100 (oral including rapid-release) | A | 100 mg sumatriptan is reference to all triptans |
| | 25 (suppository) | A | |
| | 10, 20 (nasal spray) | A | |
| | 6 (subcutaneous) | A | |
| Zolmitriptan | 2.5, 5 (oral including disintegrating form) | A | |
| | 2.5, 5 (nasal spray) | A | |
| Naratriptan | 2.5 (oral) | A | Less but longer efficacy than sumatriptan |
| Rizatriptan | 10 (oral including | A | 5 mg when taking propranolol wafer form) |
| Almotriptan | 12.5 (oral) | A | Probably less side effects than sumatriptan |
| Eletriptan | 20, 40 (oral) | A | 80 mg allowed if 40 mg not effective |
| Frovatriptan | 2.5 (oral) | A | Less but longer efficacy than sumatriptan |

General side effects for all triptans: chest symptoms, nausea, distal paraesthesia, 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, severe liver or kidney failure.

 

recurrence. A second dose of the triptan is effective in most cases [59]. If the first dose of a triptan is not effective, a second dose is useless. Combining an NSAID with a triptan (naproxen with sumatriptan) reduces headache recurrence [60].

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 [61,62]. Reports on severe adverse events also exist for other triptans and for ergotamine tratrate. 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 [63,64]. Contraindications for the use of triptans are untreated arterial hypertension, coronary heart disease, Raynaud's disease, history of ischaemic stroke, pregnancy, lactation, and severe liver or renal failure.

Owing 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 phase before headache has developed [65,66].

#### Comparison of triptans

Some minor differences between triptans exist which will be discussed in order to give a guidance which triptan to use in an individual patient. A triptan can be efficacious even if another triptan was not [67,68].

Subcutaneous sumatriptan has the fastest onset of efficacy of about 10 min [69]. Oral rizatriptan and eletriptan need about 30 min, oral sumatriptan, almotriptan, and zolmitriptan need about 45–60 min [42], and naratriptan and frovatriptan need up to 4 h for the onset of efficacy [70,71]. Zolmitriptan nasal spray has a shorter duration until efficacy than oral zolmitriptan [72]. There is no evidence that different oral formulations such as rapidly disolving tablets, wafer forms, or rapid release forms [73] 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 [74]. Sumatriptan nasal spray has the same efficacy as oral sumatriptan 50 mg or 100 mg. 25 mg oral sumatriptan is less effective than the higher doses but has less side effects [42]. Sumatriptan suppositories are about as effective as oral sumatriptan 50 or 100 mg and should be given to patients with vomiting [75–77]. 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 [78–80]. Eletriptan 80 mg is the most effective oral triptan but also has the most side effects [42].

The highest recurrence rate is observed after subcutaneous sumatriptan. Naratriptan and frovatriptan show the lowest recurrence rates but have poor initial response rates. Frovatriptan has been compared with sumatriptan but the recurrence data has never been made public, which at least calls the assertion that is has a lower recurrence rate into question. It might be that triptans with a longer half-life time have a lower recurrence rate [81], although if frovatriptan does not have a lower recurrence rate this argument would no longer be tenable. Another problem in clinical practice is inconsistency of efficacy. Therefore, efficacy only in two of three attacks is regarded as good. Rizatriptan in combination with dexamethasone seems to be significantly more effective than rizatriptan alone, although this combination is associated with a higher rate of adverse events [82].

#### Other drugs

There is some evidence that the intravenous application of valproic acid in a dose of 300–800 mg is efficacious also in the acute treatment of migraine attacks [83,84], and similarly an older study for intravenous flunarizine [85]. However, the evidence is weak. Tramadol in combination with paracetamol has also shown efficacy in acute migraine attacks [86]. However, opioids are of only minor efficacy, no modern controlled trials are available for these substances; opioids and tranquilizers should not be used in the acute treatment of migraine.

## Migraine prophylaxis

Prophylactic drugs for the treatment of migraine with good efficacy and tolerability and evidence of efficacy are betablockers, calcium channel blockers, antiepileptic drugs, NSAID, 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 extremely useful. 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 4. Tables 5 and 6 present drugs recommended as second or third choice when the drugs of Table 4 are not effective, contraindicated, or when comorbidity of the patients suggests the respective drug of second or third choice.

**Table 4** Recommended substances (drugs of first choice) for the prophylactic drug treatment of migraine

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

**Table 5** 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 |
| Venlafaxine | 75–150 | B |
| Naproxen | $2 \times 250$–500 | B |
| Petasites | $2 \times 75$ | B |
| Bisoprolol | 5–10 | B |

**Table 6** 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 | $3 \times 6.25$ mg | C |
| Riboflavin | 400 mg | C |
| Coenzyme Q10 | 300 mg | C |
| Candesartan | 16 mg | C |
| Lisinopril | 20 mg | C |
| Methysergide | 4–12 mg | C |

### 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 metoprolol [87–91] and propranolol [87,88,92–98]. Also, bisoprolol [91,99], timolol [93,100], and atenolol [101] 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 [90,98,102–111]. The dose is 5–10 mg, female patients seem to benefit from lower doses than male patients [112]. Another 'non-specific' calcium channel blocker, cyclandelate, has also been studied but with conflicting results [107,113–116]. As the better designed studies were negative, cyclandelate cannot be recommended.

### Antiepileptic drugs

Valproic acid in a dose of at least 600 mg [117–120] and topiramte in a dose between 25 and 100 mg [121–124] are the two antiepileptic drugs with evidence of efficacy in more than one placebo-controlled trial. The efficacy rates are comparable to those of metoprolol, propranolol, and flunarizine. Topiramate is also efficacious in the prophylaxis of chronic migraine and may have some effect in migraine with medication overuse [125,126]. Other antiepileptic drugs studied in migraine prophylaxis are lamotrigine and gabapentin. Lamotrigine did not reduce the frequency of migraine attacks but may be effective in reducing the frequency of migraine auras [127,128]. Gabapentin showed efficacy in one placebo-controlled trial in doses between 1200 and 1600 mg using a non-intention-to-treat analysis [129]. Oxcarbazepine was without any efficacy in a very recent study [130].

### NSAID

In some comparative trials, ASA was equivalent to or worse than a comparator (with known efficacy in migraine) but never has achieved a better efficacy than placebo in direct comparison. In two large cohort trials, ASA 200–300 mg reduced the frequency of migraine attacks [131,132]. Naproxen 1000 mg was better than

 

placebo in three controlled trials [133–135]. Also tolfenamic acid showed efficacy in two placebo-controlled trials [136,137].

#### 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 [138–141]. Since 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 [142,143]. Fluoxetine in doses between 10 and 40 mg was effective in three [144–146] and not effective in one placebo-controlled trial [147]. Venlafaxine extended release (dose 75–150 mg) has shown efficacy in one placebo-controlled [148] and two open trials [149,150] and can therefore be recommended as a second choice antidepressant in migraine prophylaxis.

#### Miscellaneous drugs

The antihypertensive drugs lisinopril [151] and candesartan [152] showed efficay 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 [153,154]. For oral magnesium, conflicting studies (one positive, one negative) have been published [155,156]. 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 [157,158]. Another herbal remedy, feverfew (Tanacetum parthenium), has been studied in several placebo-controlled trials with conflicting results. Also, the two most recent and best designed studies showed a negative [159] and a positive [160] result; a Cochrane review resulted in a negative meta-analysis of all controlled studies on tanacetum [161].

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 162). 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 [163]. Pizotifen is not generally recommended because the efficacy is not better than in the substances mentioned above and the side effects (dizziness, weight gain) are classified as very severe by the task force and limit the use too much [164]. Some experts have found it useful in childhood migraine. Ergot alkaloids have also been used in migraine prophylaxis. The evidence for dihydroergotamine is weak since several studies reported both positive and negative results (for review see 162).

Botulinum toxin was studied so far in four published placebo-controlled trials [165–168]. Only one study showed an efficacy for the low-dose (but not the high-dose) treatment with botulinum toxin [165]. In another study, a *post hoc* analysis of a subgroup of chronic migraine patients without further prophylactic treatment showed benefit from botulinum toxin A [168]. This indication is currently evaluated in a trial program.

No efficacy in migraine prophylaxis has been shown for homoeopathic remedies [169–171]; for montelukast [172]; for acetazolamide 500 mg per day [173]; and for lanepitant [174].

## Specific situations

#### Emergency situation

Patients with a severe migraine attack in an emergency situation have often already tried oral medication without any success. Treatment of first choice in this situation is the intravenous application of 1000 mg ASA with or without metoclopramide [47]. Alternatively, 6 mg subcutaneous sumatriptan can be given. For the treatment of a status migrainosus, 50–100 mg prednisone or 10 mg dexamethasone is recommended by expert consensus. In placebo-controlled trials, however, no consistent efficacy of this procedure in the acute treatment of migraine attacks [175] or in the prevention of recurrence could be proven [176–179]. Also by expert consensus and supported by open label studies, dihydroergotamine 2 mg (nasal spray or suppositories) is recommended for severe migraine attacks [29]. The intravenous application of metamizol was significantly superior to placebo but can cause severe arterial hypotension and allergic reactions [24,180]. The intravenous application of paracetamol was not efficacious in a placebo-controlled trial in acute migraine attacks [181].

#### Menstrual migraine

Different drug regimes have been studied to treat menstrual migraine. 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 [182]. Its specific effects on menstrual migraine (550 mg twice daily) have also been evaluated [183–185]. In one trial [183], patients reported fewer and less severe headaches during the week before menstruation than patients treated with placebo. 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 [185], but in the other both severity and analgesic requirements were decreased [184]. Even triptans have been used as short-term prophylaxis of menstrual migraine. For naratriptan ($2 \times 1$ mg per day for 5 days starting 2 days prior to the expected onset of menses) and for frovatriptan ($2 \times 2.5$ mg given for 6 days perimenstrually), superiority over placebo has been shown [186–188]; however, it can happen that the menstrual migraine attack is delayed into another time of the menstrual cycle [188].

Another prophylactic treatment regime of menstrual migraine is oestrogen replacement therapy. The best evidence, although not as effective as betablockers or other first line prophylactic drugs, has been achieved for transdermal estradiol (not $< 100$ $\mu$g given for 6 days perimenstrually as a gel or a patch) [189–192]. A recent study, however, did not show efficacy of hormone replacement with respect to attack frequency during the whole menstrual cycle [193].

#### Migraine in pregnancy

There are no specific clinical trials evaluating drug treatment of migraine during pregnancy, most of the migraine drugs are contraindicated. If migraine occurs during pregnancy, only paracetamol is allowed during the whole period. NSAID 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, NSAID 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 [194–198]. Similar results have been published for rizatriptan [199]. Based on the published data, administration of triptans in the first trimester of pregnancy is recommended by expert consensus if the child is more at risk by severe attacks with vomiting than by the potential impact of the triptan. For migraine prophylaxis, only magnesium and metoprolol are recommended during pregnancy (level B recommendation) [200].

#### 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 per kg body weight and paracetamol 15 mg per kg body weight [201]. 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 [202–204], the recommended dose for adolescents from the age of 12 is 10 mg. Oral triptans did not show significant efficacy in the first placebo-controlled childhood and adolescents studies [205–207]. This was in particular because of 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 to 17 [208,209]. In recent trials, oral zolmitriptan 2.5 mg [210], nasal zolmitriptan 5 mg [211], and oral rizatriptan 5–10 mg [212] have been superior to placebo in acute migraein treatment. Ergotamine should not be used in children and adolescents. Also children and adolescents can develop drug-induced headache due to analgesic, ergotamine, or triptan overuse.

For migraine prophylaxis, flunarizine 10 mg and propranolol 40–80 mg per day showed the best evidence of efficacy in children and adolescents [206,213]. Recently, topiramate in a dose between 15 and 200 mg showed efficacy in children and adolescents as well [214,215]. Other drugs have not been studied or did not show efficacy in appropriate studies.

## Need of update

These recommendations should be updated within 3 years and should be complemented by recommendations for the non-drug treatment of migraine.

## Conflicts of interest

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