Part 1

Preventive treatment of migraine

CHAPTER

2

Preventive therapy for migraine: a narrative 'umbrella' review

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Based on previously published review in Dutch, Ned Tijdschr Geneeskd 2010;154(29):A1512.

ABSTRACT

Background

Migraine is a frequently occurring, disabling disorder. In addition to attack treatment, other useful interventions to reduce the burden of disease (such as preventive treatment) should be applied.

Methods

This is a narrative 'umbrella type' review of preventive migraine treatment based on a search in Medline and Embase. Also presented is an overview of indications for preventive treatment mentioned in guidelines (identified with the same search method), complemented with guidelines from the Guidelines International Network and the National Guideline Clearinghouse.

Results

According to most sources, patients with an average of two or more attacks per month, when using attack treatment, are eligible for preventive treatment. This decision is also based on the (average) duration of attack, severity of attacks, and the response to attack treatment. In the present guidelines there is only limited involvement of patients, whereas this is an essential condition for treatment continuation and success. Before starting prevention, the average attack frequency should be determined, preferably using a headache diary for 2-3 months, because of the highly variable frequency of migraine attacks. None of the currently available preventive medications (such as beta-blockers, sodium valproate, topiramate and candesartan) are specific for migraine. To obtain good outcome, preventive treatment should be titrated up step-by-step to the highest possible dose without side-effects. For about 50% of patients with preventive treatment, a 50% reduction in attack frequency can be achieved and the remaining attacks tend to become less severe.

Interpretation

Preventive treatment of migraine is a worthwhile intervention in primary care, for which beta-blockers and anti-epileptic drugs can be used. For many patients preventive treatment will contribute to a greater reduction in disease burden than can be established with attack treatment alone.

INTRODUCTION

Migraine is a complex, common and disabling disorder of the brain, and its mechanisms are still not completed elucidated [1]. The diagnosis of migraine is sometimes difficult to establish and should be based on the generally accepted criteria of the International Headache Society (IHS 2004) [2].

Preventive treatment of migraine may be considered when, despite optimal attack treatment, the frequency, intensity and duration of attacks severely affect the quality of life. Therefore, prior to initiating preventive treatment, the extent of disease burden should be established. This is difficult and it is not possible to base this on a single consultation. Retrospectively reported symptoms are often not adequately expressed; generally, the last or most violent attack remains strongest in the memory. Furthermore, establishing the migraine burden may be difficult because many patients have a combination of headache types, or have headache as a result of overuse of pain killers, ergotamine or triptans. A headache diary often provides outcome information [3,4], and is essential for revealing clues to the diagnosis, for estimation of use of pain killers, and for determining the frequency of attacks. For a valid estimation of the often strongly fluctuating attack frequency, the diary must be maintained for a period of (minimally) two months [5].

After starting preventive medication, it is recommended that the effectiveness of the treatment be assessed after at least two months use (with the exception of menstrual migraine) [6,7]. In case of preventive treatments, attention should be paid to attack treatment, either via prescribed attack treatment or by self-medication.

These (and other) problems show that it is not an easy decision to start preventive treatment for migraine. Similarly, it is can be difficult to choose between the options. Prior to the decision, it is necessary to establish: the benefits of preventive treatment (specified for all types of treatments), and the threshold from which patients will be eligible for preventive treatment.

This narrative 'umbrella' review aims to provide an overview of the outcome of current preventive treatments, and give an overview of the indications for preventive treatment from relevant guidelines.

METHODS

This review is based on an article previously published in Dutch [8]. For an overview of preventive interventions for migraine, Medline and Embase were searched using the terms migraine and preventive treatment (and synonyms thereof) . We searched for guidelines in the Guideline International Network (GIN) database and the National Guideline Clearinghouse [9,10]. For the present overview a selection was made based the relevance of the resources for the situation in the Netherlands. Because of the diversity in methodology, study endpoints, and drug application schemes and administration,

a systematic analysis of migraine preventive therapy as a whole could not be performed. Therefore, the findings are presented in the format of a so-called `umbrella' review, covering various treatment options.
Summary tables for the various medications were made using Review Manager, version 5.0.24.

Threshold for preventive therapy

The Dutch College of General Practitioners (NHG) guideline on headache, recommends a prevention threshold of two attacks and more [11], whereas the guideline of the Dutch Society of Neurologists states three attacks or more per month as threshold [12]. Other international guidelines provide a divergent range of recommendations (Table 1). Selection of the guidelines in Table 1 was mainly based on the relevance of the guideline (e.g. the number of patients to which it applies). In addition, we present guidelines that are mainly relevant for the Netherlands. We conclude that there is a large diversity in the content of the guidelines, as well as in the factors leading to a decision. The most frequently mentioned factors are:

- attack frequency;
- failure, poor response or side-effects of attack treatment;
- frequency or extent of use of attack treatment;
- reduced quality of life, or inability to perform activities of daily living;
- patient's preference.

Patient preference is mentioned in only a few guidelines. This is in contrast to current opinion that patient preference is a major factor in decision-making related to preventive treatment [1,13-16]. Less mentioned aspects of decision-making on prophylaxis are absenteeism, status after withdrawal of chronic pain treatment, costs of attack treatment, uncommon migraine forms, and frequent or long-lasting aura.

Effectiveness of preventive treatment

The available preventive medicines have not been specifically developed and registered for migraine, and all have other another intended indication. The anti-migraine effects are reported to be 'nicely tolerated'. The effectiveness for roughly all treatments is that in just over 50% of the patients the frequency decreases by 50% [6,7]. In addition, the remaining attacks often become less severe.
General practitioners (GPs) should address a number of potential pitfalls when initiating preventive treatment of migraine. Patients often have motivation problems, partly due to a lack of trust in the efficacy, and frustration when nevertheless attacks occur. Also, many patients resent the daily use of medication [14-16]. Other important pitfalls are a too rapid increase in dose, an insufficiently long or a too low dose, and the use of wrong or obsolete treatments.
A problem often encountered with beta-blockers prescribed for migraine is that they are sometimes changed by drugs belonging to another class (from a cardiovascular perspective), by e.g. cardiologists or internists, thereby losing the benefit for migraine.

Therefore, it is desirable that physicians/neurologists etc. other than GPs have a basic knowledge of the possibilities for preventive treatment of migraine. In addition, patients can also be educated to inform their other caretakers.

Preventive treatments for migraine

Beta-blockers
In the Netherlands, beta-blockers are the most used preventive drugs for migraine and are the first-line choice in the NHG Guideline on headache. The anti-migraine activity is supposed to rely on noradrenergic and serotonergic impact on the central nervous system. In a Cochrane review, 58 trials with a total of 5072 patients were analyzed, in which propranolol was compared 26 times to a placebo and 47 times to another preventive medicine [7]; the daily dosage in these studies ranged from 60-320 mg. Propranolol was more effective than placebo. However, no estimation was possibility of the relation between the effectiveness and dosages used each day [17-20].
The other beta-blockers (metoprolol, atenolol, bisoprolol and nebivolol) were also more effective than placebo, but these drugs do not seem to distinguish themselves from propranolol [21-33]. Because these drugs have less ß2-properties in comparison with propranolol, they may have less side-effects. Beta-blockers with intrinsic sympaticomimetic activity (acebutolol, oxprenolol and pindolol) are not effective in migraine. Side-effects of beta-blockers can be considerable and frequently lead to discontinuation. The occurrence of side-effects shows wide diversity. From the Cochrane review the average percentage of persons dropping-out because of side-effects is 17% [7]. In daily practice, this percentage is probably higher. In case of pregnancy there seem to be no teratogenic effects. Only propranolol and metoprolol are 'labelled' for migraine prevention in the Netherlands. (figure 1, p 30)

Anti-epileptics
The mechanism of anti-epileptics in the preventive treatment of migraine is unclear. Because of the considerable pharmacological impact of these drugs, several assumptions are made. It is assumed that the GABA neurotransmitter, NMDA receptors, catecholamine induced and opioid neurotransmitter systems, and calcium and sodium canals are involved. In the Netherlands two drugs of this group are frequently used: sodium valproate and topiramate. In the Cochrane review, 8 randomized controlled studies with sodium valproate and 7 with topiramate were summarized [6]. Sodium valproate showed to be consistently more effective than placebo [34]. The side-effects of sodium valproate should be taken seriously. In older patients cognitive impairments and Parkinsonism have been reported. The drug is not allowed during pregnancy.
(figure 2, p 31)

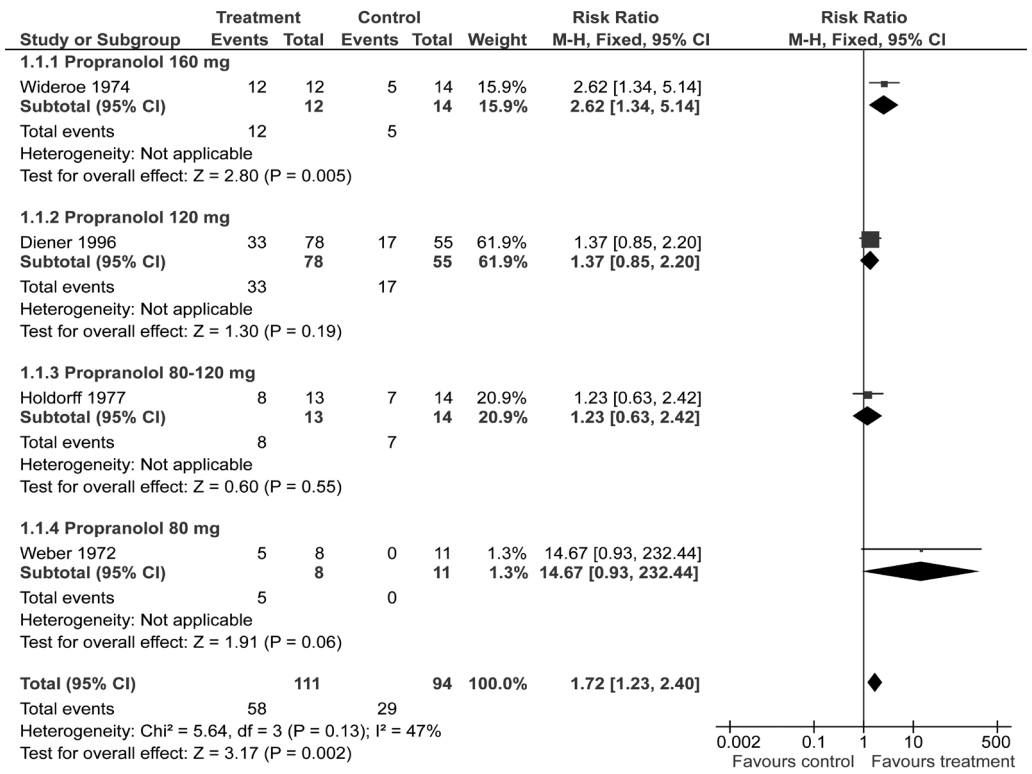

Figure 1. Number of responders in migraine preventive therapy with beta-blockers. Based on Linde K, Cochrane database of reviews 2009[7].

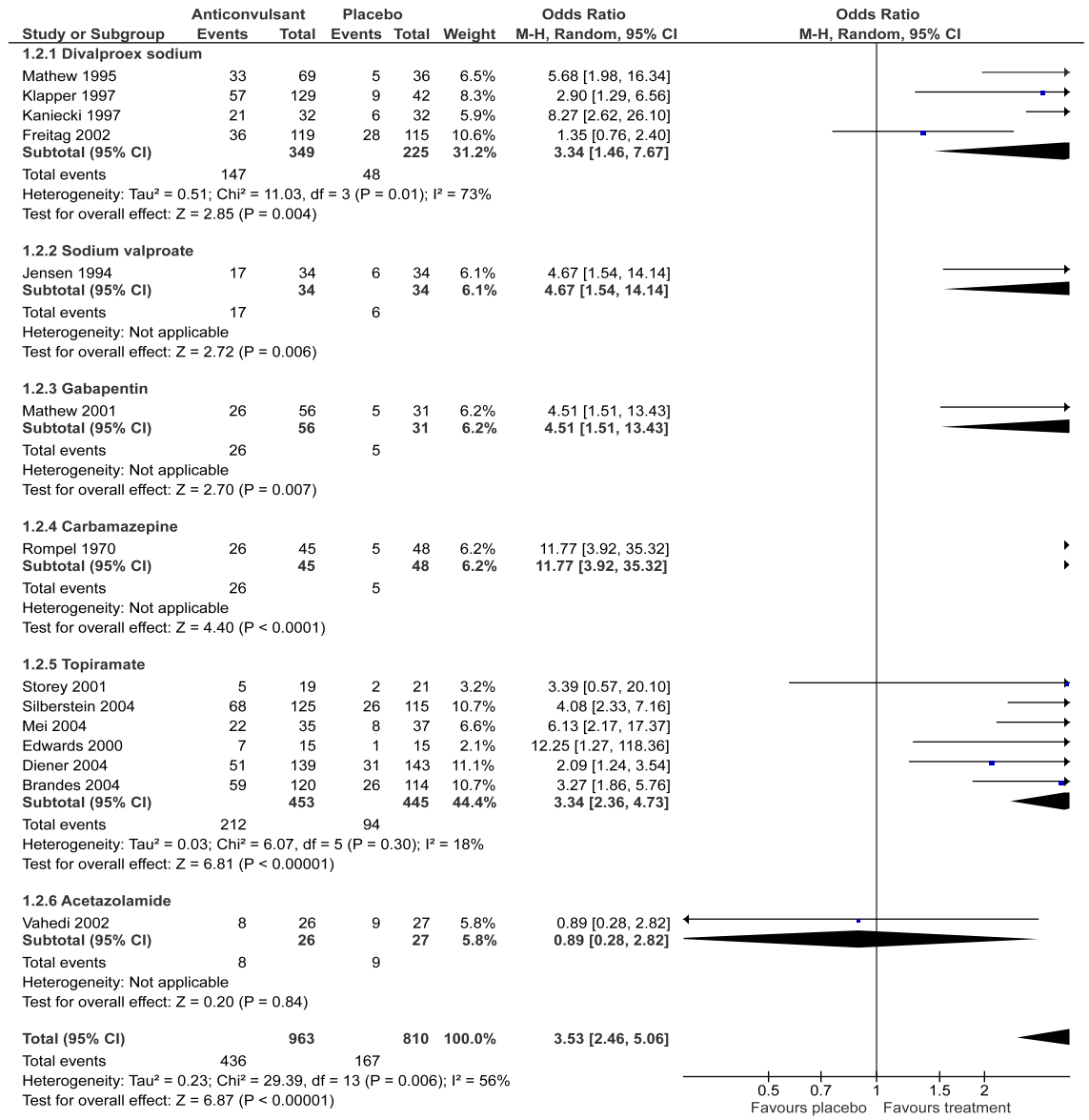

Figure 2. Number of responders in migraine preventive therapy with anti-convulsants. Based on Chronicle E, Cochrane database of reviews 2009[6].

Topiramate has also been shown to improve headache better than placebo [35-38]. The optimum amount is 100 mg daily (in two doses), but many undesirable side-effects have been reported. At a daily dosage of 100 mg side-effects led to discontinuation in 23% of the patients [6]. The drug is not allowed during pregnancy. Two gabapentin trials showed a lowering of migraine attack frequency; however, these studies had methodological shortcomings [39]. After accusations of withholding scientific proof concerning the effectiveness of the drug, doubts related to gabapentin have increased [40]. For the remaining anti-epileptics (carbamazepine, lamotrigine, clonazepam) there is insufficient or no evidence [35,41-43]. In the Cochrane analysis it is concluded that anti-epileptics are an effective preventive treatment of migraine. However, only for sodium valproate and topiramate is there sufficient evidence to justify their use for the prevention of migraine attacks (topiramate is 'labelled' for this indication).

Other treatments in migraine prevention

Of the remaining treatments, flunarizine has been well studied. Nine placebo-controlled studies include a relatively small number of patients [44-52]. In 2 of 9 studies, no advantage of flunarizine was shown compared to placebo [48,49]. The remaining 7 studies showed an advantage. Flunarizine is effective in the prevention of migraine; however, the treatment is no longer popular because of the risk of serious side-effects, such as extrapyramidal dysfunction and drowsiness.

Pizotifen was evaluated in 11 placebo-controlled studies and showed improvement compared with placebo, except in children [53]. However, most of the studies were small, with often no more than 50 patients. Pizotifen is frequently not well tolerated and the most important side-effects are weight increase, fatigue and drowsiness. This means that when weighing the advantages and disadvantages, the result is often negative for pizotifen.

Methysergide has been registered for many years; however, because of the rare side-effects of retroperitoneal, pulmonary and/or endocardial fibrosis, the drug is only to be prescribed by experienced physicians and after very careful assessment.

Antidepressants are frequently prescribed for the treatment of migraine, especially in the USA. Because the evidence for SSRIs is moderate, they are not included in the Dutch guidelines. Amitriptyline can be considered in case of additional tension-type headache, and can be useful in some migraine patients. There is no evidence for the use of SSRIs in migraine [54].

There are studies with lisinopril (ACE inhibitor), candesartan and telmisartan (AII antagonist). The studies with lisinopril and candesartan show benefit, for telmisartan the primary endpoint was not significantly better (probably because of the too small numbers). In spite of the few side-effects of these drugs, the 'level of evidence' is still too low to recommend their large-scale use [55-57].

Acetylsalicylic acid has been used for migraine prevention and some researchers claim success. However, positive preventive effects do not occur in more than 20-26% of the patients and this does not exceed the placebo effect. Therefore, most researchers find

that acetylsalicylic acid is not indicated as preventive migraine therapy [23,58,59].

Three placebo-controlled trials investigated verapamil, but because the results are inconclusive [60-62] there is no place for its use in migraine.

Two placebo-controlled and three open studies in patients with episodic migraine show that the effects of botulinum toxin injections in frontal and occipital muscles do not differ from placebo [63-65]. Trials in patients with chronic migraine (migraine headache on ≥ 15 days/month), have shown that injections with onabotulinumtoxinA lead to a reduction of the impact of migraine [66]. However, whereas the therapeutic gain over placebo was statistically significant, the clinical significance was modest [67].

Riboflavin and coenzyme Q10 each have each been examined in a placebo-controlled study, both being positive. Based on these very limited data, these remedies are not yet recommended [68]. Four out of five controlled studies with tanacetum parthenium (feverfew) were positive [69]; the effectiveness is strongly dependent on the resorption of the obligatory preparation, which limits its practical usability.

Combination therapy in preventive treatment

A few studies explored the combination of different preventive treatments in patients who did not benefit from one single preventive. These studies sometimes include expert opinions or overviews [70-72], case reports or small series [73,74] and a few comparative trials [75-78]. Two studies show a benefit of combination therapy (topiramate plus nortriptyline; beta blocker plus topiramate) [75,76]. In two studies there was no added benefit of the combination (propranolol plus nortriptyline; flunarizine plus topiramate) [77-79]. At present, the use of a combination of different preventives remains uncertain.

Prevention in menstrually-related migraine

The acute treatment of menstrually-related migraine is identical to that of other migraine attacks. Some authors express a preference for naproxen, as this has a reasonable effect on the migraine as well as being effective for menstrual complaints [80].

Pure menstrual migraine attacks occur exclusively on days -2 to +3 of the menstruation period in at least two out of three menstrual cycles. and at on no other moments of the cycle [2].

In menstrually-related migraine all preventive therapies for migraine are applied [81-84]. Because only small studies are available on the efficacy of preventive treatment for menstrually-related migraines, current treatment is actually based on consensus [82-86]. Short-term prevention focuses only on days -2 before to +4 days after start of the menstruation) [83,84,86]. There is also a variation of this strategy, with duration up to 11 days (a somewhat older strategy, day -2 up to +9).

NSAIDs are an option for short-term prophylaxis in general practice, because there is a more or less reliable effect on migraine as well as on menstrual complaints [80,87,88]. As in attack treatment, naproxen is the most often used option [80].

Triptans are also an option in the short-term prophylaxis of migraine [89-96]. Several small studies have shown a consistent positive effect. As the duration of triptan use

does not exceed 6 days each month, medication overuse headache (MOH) is not likely to emerge. When there are also migraine attacks in between menstruations, and those attacks are also treated with triptans, there is a danger of developing MOH . This also applies when using NSAIDs, but for this medication class there is a greater margin. In addition, preventive treatment of menstrual migraines with triptans is relatively costly.

Estrogens are mainly used as short-term prophylaxis. Studies on preventive use of estrogens, especially percutaneous estradiol gel, still show considerable disagreement on effectiveness. Most trials with estrogens show robust effects [83], but some trials have disappointing results [84].

Another option is the continuous use of combined oral contraceptives [83,84,97]. The results are sometimes disappointing; only a proportion of patients respond well to this therapy. Often, when there is a good response to this intervention, there are breakthrough bleedings, resulting in termination of this therapy. A contemporary approach to breakthrough bleedings under continuous oral contraceptive use is that, at the start of a bleeding, a 7-day pause is started. However, it is unclear what the impact of this strategy is on the frequency of migraines.

Because migraine with aura is a risk factor for cerebrovascular accidents and this risk is increased when using oral contraceptives [98], recent guidelines advise not to prescribe oral contraceptives for patients with migraines, especially not for migraine with aura. Young women who have migraine with aura should be strongly advised to stop smoking, and to consider a form of birth control other than oral contraceptives [98].

Preventive treatment in case of medication overuse

The recommended action in case of MOH is withdrawal of the drug that is causing the headache [5,99-102]. In earlier definitions of the IHS classification [2] the disappearance or decrease of the headache after withdrawal was an obligatory criterion for MOH. In the present version, that requirement is replaced by the requirement that the headache should have developed or has markedly worsened during medication overuse. Many studies show a return of daily headache back to a less frequent episodic headache after withdrawal [99,103-120]. In the Netherlands, this knowledge has resulted in the consensus that withdrawal is the preferred approach [11,12]. It is unclear if this approach is sufficiently `evidence based', or just suits Dutch 'culture' (when you use too much of something, this cannot be good and you must stop). And, above all, in the Netherlands, for MOH it is recommended not to add extra drugs.

Some studies on interventions with specific medication have been done on MOH, with varying results. Four studies with topiramate showed a small but significant reduction in headache [121-124]. Studies with sodium valproate also showed relief [125,126]. Sometimes also naproxen is used because of the incorrect assumption that NSAIDs do not increase the risk of MOH [127]. Prednisolone has also been used to reduce withdrawal headache, but this is not supported by controlled clinical trials. Although the evidence is not conclusive [128], the recent European guideline of the European Federation of

Neurological Societies (EFNS) for the treatment of MOH mentions prednisolone for the treatment of withdrawal symptoms, based on three open-label studies and two placebo-controlled trials [129]. The three open-label trials claimed a beneficial effect of prednisolone on the severity and duration of withdrawal symptoms [130-132]. However, due to the low quality, these studies are not a proper basis for a guideline [133]. Of the two placebo-controlled trials, in the largest trial (n=102) prednisolone showed no benefit compared to placebo, and the other smaller trial (n=18) suggests some benefit of prednisolone [128,134]. According to the EFNS, prednisolone may have an advantage, because all other medications even cause MOH. However, it is doubtful whether this is the right argument when claims of efficacy are unsupported. The EFNS guideline also mentioned amitriptyline as a possible treatment for withdrawal symptoms; however, this is also not based on evidence, but on consensus [129].

There are no randomised direct comparisons between withdrawal with and without using supportive medication [111]. Drug intervention studies for MOH only show small improvements. On the other hand, the studies with withdrawal of the causing agent show a consistent effect [135-137].

In conclusion, withdrawal seems to be the best intervention and best matches the Dutch attitude regarding drug use in general. In addition, there is some evidence for the effectiveness of other strategies, such as behavioural therapies [138-147].

Many GPs have noted that MOH has some characteristics of addiction, comparable to alcohol or smoking addiction. Characteristic of MOH is that patients at the acute stage of withdrawal experience a strong increase in headache (rebound phenomenon). MOH patients often experience some results from attack medication; it can temporarily relieve the complaints. In general, patients do not recognize that the daily use of medication is the actual cause of the headache.

Comparative studies on preventive therapy

Many comparative studies between preventive treatments have been performed, with differing combinations, mainly with beta-blockers, sodium valproate, topiramate, flunarizine, pizotifen, methysergide, verapamil, nimodipine and amitriptyline [6,7,79,148-169]. In these studies, the most frequently used comparator is flunarizine [44,47,79,149-164]. As the use of flunarizine often leads to side-effects such as drowsiness, lethargy, weight gain, increased appetite, depression and extrapyramidal symptoms, these comparisons with flunarizine are of limited value for daily practice.

A point of interest is the comparison within the group of anti-epileptic drugs. Only one study has compared sodium valproate with topiramate, and showed a small advantage of topiramate; however, the daily dosages of both drugs were lower than usual [169]. For the remaining drugs no significant differences were shown.

DISCUSSION

In general, preventive treatment of migraine is a well accessible and at times useful intervention, but only when carried out correctly and carefully. As about half the disease burden can be decreased, there is a large gain for patients with a high disease burden. Preventive treatment for migraine is a tailor-made task, adapted to the individual patient. Table 2 presents a summary of the principles of preventive migraine treatment, and table 3 lists the treatments used.

Table 2. Principles of preventive treatment of migraine; recommendations based on the outcome of the present review

Basic principles of preventive migraine treatment	
Indication	– At least two or more attacks per month – Patient preference
Factors to take into account for indication	Attack intensity, duration, response to attack treatment, extent of attack medication, quality of life, and interference with patient activities
Important points	– Based on average attack frequency in three preceding months – Start with low dosage and titrate up step-by-step, until maximal accepted dose without side-effects – Always in combination with provision of attack treatment – Individualized approach to treatment type and dosage (avoid side-effects or interference with lifestyle) – Beta-blockers and anticonvulsants both well applicable in general practice
Duration	– At least 2-3 months before effect assessment – When effective, continuation for 9-12 months – In case of recurrence start preventive treatment again

'First choice' in preventive treatment are beta-blockers (propranolol and metoprolol) and anti-epileptic drugs (sodium valproate and topiramate). 'Second choice' preventives are those which have demonstrated some preventive effect, but with limited evidence. These treatments come into play when 'first choice' treatments are ineffective or not tolerated, and the patient is motivated for further attempts. 'Third choice' treatments have demonstrated preventive effect, but sometimes at the cost of severe side-effects, or only with important and specific terms and conditions. Botulinum toxin does not show convincing benefits in episodic migraine whereas in chronic migraine there can be some benefit; however, the therapeutic gain seems very modest [67].

Table 3. Available medications for the preventive treatment of migraine

	Drug	**Dosage (step by step titration)**
First choice	Propranolol	40-240 mg
	Metoprolol	100-200 mg
	Sodium -valproate	1000 - 1500 mg (mostly 50% compared to epilepsy, phasing out schedule necessary)
	Topiramate	50 bd (25-100 mg)
Second choice	Atenolol, bisoprolol, nebivolol	Regular dosage (titration)
	Candesartan	16 mg
	Lisinopril	5-10 mg
	Telmisartan	80 mg
Third choice (for physicians with special interest)	Pizotifeen	More dis- than advantages, weight gain
	Flunarizine	Rare side effects (extrapyramidal symptoms)
	Methysergide	Interval treatment, serious adverse events
	Amitriptyline	Conflicting evidence
Insufficient evidence, no proven efficacy, too many / serious side-effects	Gabapentin, lamotrigin, SSRIs, acetylsalicylic acid, verapamil, riboflavin, botulinum toxin, tenacetum partenium	

Table 1. Indications for preventive treatment of migraine addressed in guidelines

Organisation	Attack frequency / month	Attack intensity	Attack duration	Response to attack treatment	Extent of attack treatment	Quality of life	Interference with activities	Costs	Patient preference	Additional	Level of care covered*
Dutch College of General Practitioners [11]	2 or more	-	-	-	-	-	-	-	Yes, in agreement	Not in case of MOH	Primary
Domus Medica, Society of General Practitioners, Belgium [176]	2 or more	-	-	Yes	Yes#	-	Yes	-	Yes, willing-ness daily medication	Frequent, very long, or uncomfortable auras	Primary
Migraine in Primary Care Advisers (MIPCA), [177] *England*	4 or more	-	-	Yes	-	-	-	-		-	Primary
American Academy of Family Physicians [178]	2 or more	Yes	Yes#	Yes	> 2 days / week		-	Yes	Yes#	Uncommon migraine conditions	Primary
Dutch Society for Neurologists [12]	3 or more	Yes	-	Yes	> 8 days / month	-	-	-	-	-	Primary and secondary
EFNS (European Federation National Neurological Societies) [179]	2 or more	-	-	Yes	-	-	Yes	-	-	Frequent, very long, or uncomfortable auras	Primary and secondary
AAN (American Neurological Society) [180]	Yes#	-	-	Yes	Yes#	-	Yes	Yes	Yes, opinion on severity	Adverse effect attack treatment, uncom-mon migraine conditions	Primary and secondary
Canadian Medical Association [181]	3 or more	Yes		Yes	-	Yes	-	-	Yes#	-	Primary and secondary
Institute for Clinical Systems Improvement, USA [182]	3 or more	Yes	Yes	-	-	-	-		Yes	-	Primary, second-ary and tertiary
BASH guideline (British Association for the Study of Headache) [183]	Yes#	-	-	Yes	Yes#	-	Yes	-	Yes#	Not in case of MOH,	Primary, second-ary and tertiary
Scottish Intercollegiate Guidelines Network (SIGN) [184]	Yes#	-	-	Yes	-	-	Yes	-	-	Uncommon migraine conditions	Primary, second-ary and tertiary
National Agency of Accreditation and Evaluation in Health, France (ANAES) [185]	Yes#	Yes	-	-	> 6-8 dose / month		Yes	-	-	-	Primary, second-ary and tertiary
German Society for Neurology (DGN) [186]	3 or more	Yes	> 72 hours	Yes	Yes	Yes	Yes	-	-	Uncommon migraine conditions	Primary, second-ary and tertiary
German Migraine and Headache Society (DMKG) [187]	3 or more	-	> 72 hours	Yes	> 10 days / month	Yes	-	-	-	Uncommon migraine conditions	Primary, second-ary and tertiary

 # Unspecified. MOH = medication overuse headache

For combination treatment for prevention of migraine, the study results are so heterogeneous that no clear positioning is possible. At this time it seems not to be recommended to launch preventive combination therapy in primary care, something that might not apply to treatment-resistant cases in secondary or tertiary care.
In practice, first a well-founded diagnosis is needed, preferably based on a headache diary. Only when the patient is convinced of the advantages of preventive therapy can one expect patient compliance. The expectations of patient and physician should be realistic; if not, the probability of treatment failure increases. The dosage scheme must be appropriate for the social (including professional) context of the patient. The treatment choice is partially based on the co-morbidity. The dosage and way of administration must be clear and adequate. Especially for topiramate, slow level-up titration is extremely important. However, also for beta-blockers and certainly for sodium valproate slow level-up is recommend. The slogan is "start low and go slow".
The duration of the treatment before evaluation of its effectiveness should span at least two months. An effective treatment is continued for 6-12 months; after that, a trial of a run-down is advised. Should the frequency of migraine attacks increase, the duration of the treatment will be prolonged. Treatment results and the consequences of the run-down of prophylaxis should be evaluated with a headache diary
The two groups of medication successfully used in the preventive treatment of migraine are beta-blockers and anticonvulsants. However, it is difficult to compare these treatments because they have a totally different action and side-effects, and also different dosage regimens. Therefore, only a narrative review is possible
Also with regard to the indication for preventive therapy, only a narrative approach is possible.
Although there are more overall reviews on the preventive treatment of migraine [1,170-174], they are more superficial in nature, and are generally more positive about the application of preventive drugs in (general) practice than are the authors of this article. These latter reviews seem to lack critical appraisal. Authors often recommend antidepressants, whereas we think they have limited value because of their limited effectiveness. A major difference also lies in the frequent recommendation of SSRIs, which we do not advise. In general, many more drugs are recommended than are discussed in the present review [175].
In most recommendations, the threshold for starting preventive treatment is almost always authority based. Regarding indication, further research into the needs of the patient is warranted [16]. For many patients preventive treatment will contribute to a greater reduction in disease burden compared to attack treatment alone. Preventive treatment of migraine is a worthwhile intervention in primary care, for which both beta-blockers and anti-epileptic drugs can be effectively used.

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