ORIGINAL ARTICLE

Self-medication of migraine and tension-type headache: summary of the evidence-based recommendations of the Deutsche Migräne und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesellschaft (ÖKSG) and the Schweizerische Kopfwehgesellschaft (SKG)

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Abstract The current evidence-based guideline on self-medication in migraine and tension-type headache of the German, Austrian and Swiss headache societies and the German Society of Neurology is addressed to physicians engaged in primary care as well as pharmacists and patients. The guideline is especially concerned with the description of the methodology used, the selection process of the literature used and which evidence the recommendations are based upon. The following recommendations about self-medication in migraine attacks can be made: The efficacy of the fixed-dose combination of acetaminophen, acetylsalicylic acid and caffeine and the monotherapies with ibuprofen or naratriptan or acetaminophen or phenazone are scientifically proven and recommended as first-line therapy. None of the substances used in self-medication in migraine prophylaxis can be seen as effective. Concerning the self-medication in tension-type headache, the following therapies can be recommended as first-line therapy: the fixed-dose combination of acetaminophen, acetylsalicylic acid and caffeine as well as the fixed combination of acetaminophen and caffeine as well as the monotherapies with ibuprofen or acetylsalicylic acid or diclofenac. The four scientific societies hope that this guideline will help to improve the treatment of headaches which largely is initiated by the patients themselves without any consultation with their physicians.

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Introduction

The first "evidence-based guidelines on the self-medication of migraine and tension-type headache" were presented by the German Migraine and Headache Society (DMKG) in 2004 [1]. Although the guidelines from 2004 have been widely disseminated and have attracted broad attention, it remains important to emphasise the particular importance

of a scientifically accurate and comprehensible procedure as suggestions for the self-medication of headache are still given based solely on individual experiences, on a subjectively limited selection of studies, on misinterpretations, or on results of methodologically unacceptable studies. New treatment alternatives and new scientific findings from the past few years have necessitated an updating of the guidelines of 2004. These were compiled together with the German Society of Neurology (DGN), the Austrian Headache Society (ÖKSG) and the Swiss Headache Society (SKG). Thus, the advice for patients regarding self-medication of migraine and tension-type headache is for the first time in the German-speaking countries evidence-based.

Headache types

About 90% of people with headaches suffer from either migraine, tension-type headache or a combination of the two. From a medical perspective these are not dangerous even though they can, in part, encroach quite considerably on the sufferer's quality of life. While there is broad knowledge about the pathophysiological mechanisms of migraine with and without aura, the pathophysiology of tension-type headache is largely unknown. According to the current headache classification of the International Headache Society (IHS) [2], peripheral mechanisms are very likely to play an important role in sporadic and in frequently occurring episodic tension-type headache with or without association of pericranial pain sensitivity (ICHD-II: 2.1 and 2.2). In contrast, central pain mechanisms are thought to be paramount in chronic tension-type headache (ICHD-II: 2.3). Many patients are unaware of the association between pain and tensions in the head and shoulder muscles and their increased sensitivity to pain in manual palpation, although this occurs in approximately half of patients. This pain and tension of the pericranial muscles is frequently perceived by patients as an illness in its own right, and is thus additionally treated with analgesics independent of their headache disease.

Self-treatment of primary headaches

Primary headaches such as migraine with and without aura and episodic tension-type headache can be treated by the patients him- or herself. However, the first diagnosis should be made by a physician and additional visits are recommended when:

- headaches occur more than 10 days per month,
- headaches are accompanied by additional symptoms such as motor weakness, sensory, visual or balance disturbances, double vision or vertigo,

- headaches are accompanied by mental or cognitive changes such as disturbances of short-term memory or disturbances of orientation to time, place and person,
- headaches manifest for the first time beyond age 40,
- headaches are unusual in intensity, duration and/or localisation,
- headaches first appear during or after physical exercise and/or are very severe and radiate out from the neck,
- headaches are accompanied by high fever,
- headaches appear after head injury,
- headaches increase in frequency, intensity and duration despite treatment,
- headaches occur together with epileptic seizures and disturbances in consciousness,
- headaches no longer respond to the previously effective medications.

In case of doubt, a visit to the doctor is always advisable.

Selection of the evaluated active ingredients and active ingredient combinations

These recommendations for the self-medication of migraine and tension-type headache should provide help for the affected patients and physicians in selecting suitable medicines for self-medication. Only pharmaceutical medications and fixed-dose combinations thereof, which are not subject to a doctor's prescription in Germany, Austria and Switzerland, are evaluated. Based on standard units (tablets, suppositories etc.), together, these represented at least 80% of the self-medication market in the three countries in 2007. In addition, for acute treatment, naratriptan is evaluated (available in Germany without prescription since 2007) and as prophylactics, cyclandelate, butterbur and magnesium (not permitted as self-medication drugs in Germany) are assessed. The individual and maximum daily doses of the analgesics or fixed-dose combinations, as well as those of naratriptan, can differ in the three countries, and not all active ingredients or combinations thereof are available without prescription in all three countries.

Homeopathic medicines are not considered in these recommendations, as they should be prescribed in the framework of a multidimensional therapeutic concept. Although dietary supplements do not constitute medicinal products, a series of active ingredients and particularly fixed-dose combinations are offered as "dietetic foodstuff for special medical purposes (balanced diet)", for instance "for the treatment of migraine". For this reason, α-lipoic acid, the coenzyme Q10, riboflavin, orally administered magnesium and melatonin which is subject to prescription in Europe are included in the scientific evaluation of these recommendations.

Methods

These therapy recommendations correspond to the quality features of an "evidence-based expert guideline" which is characterised by the systematic research evaluation and synthesis of the best available scientific evidence, and quality assurance through the detailed explanation of the methods used, the underlying goals, values, premises and scientific evidence, which are all documented in a comprehensible and complete manner [3–8]. In the development of these recommendations the necessary decisions of the group of authors ensued in the framework of a priori defined codes of practice.

Literature search

Systematic literature searches with the goal of identifying all clinical headache studies for the active ingredients or active ingredient combinations of interest were conducted using MEDLINE and the Cochrane Central Register of Controlled Trials. The following search structure was applied for the active ingredients already considered in the therapy recommendations of 2004 for the period of January 2002 to December 2007, and for the newly added active ingredients for the period 1966 to December 2007:

[(<drug>) and (headache# or migraine) and clinical trial]

If the search did not result in any hits, the criterion clinical trial was omitted.

These very simple search structures aimed above all to minimise the "retrieval bias", i.e. the non-discovery of published literature. As a systematic literature search is also unable to offer any guarantee of discovering all relevant publications [9], it was supplemented by a manual literature search of the authors' literature collections, which led in particular to the identification of non-English-language publications [10], consequently reducing a possible "language bias".

Primarily, the search was limited to publications in English and German. Corresponding MEDLINE or Cochrane literature searches were also conducted for the dietary supplements α-lipoic acid, coenzyme Q10, riboflavin, orally administered magnesium and melatonin (only available on prescription). In this respect attention was paid to the fact that not all relevant journals on dietary supplements are recorded in MEDLINE [11].

Literature selection (search criteria)

To be included in these therapy recommendations, the publications had to fulfil the following criteria regarding study quality and scientific evidence:

- Full publication of double-blind controlled, clinical studies on the treatment of headache disorders with medications that can be obtained over-the-counter in Germany, Austria or Switzerland, and which in terms of individual dose, or where applicable daily dose, do not exceed the maximum doses available without prescription;
- controlled studies without placebo group were only included in the evaluation if there was active control of a drug or fixed-dose combination thereof, whose efficacy is proven in terms of these recommendations.

To avoid bias [12, 13], publications which fulfilled one or several of the following criteria were excluded:

- Abstracts, congress posters, congress information
- Observational studies
- Casuistics and clinical case series
- Clinical studies in which the clinical symptoms of headache disorders only constitute an accompanying criterion.
- Short publications
- Unpublished study reports
- Pharmacokinetic or bioavailability studies
- Review articles
- Clinical studies with children

"Pharmacy-based observational studies" or "pharmacy-based post marketing surveillance studies" are suitable for gaining insights into the intended use and for the safety or tolerability of medicines [14]. However, they are not suitable to prove the efficacy of medicines as they do not fulfil the underlying scientific criteria for this purpose [12, 15–21], such as:

- Randomisation of individual patients (not of pharmacies)
- Blinding
- Placebo control, which is particularly essential for (headache) pain therapy due to the variable placebo effect [22]
- Quality assurance (monitoring, source data verification, audits) are only possible in a pharmacy observational study to a very limited extent, or not at all.
- Responder rate and analysis of "missing values"
- The "branding" (trademark) as part of the placebo effect
- Presence of a specific selection bias ("users of a particular preparation in the pharmacy observational study" rate "their medicine").

In order to avoid a "multiple publication bias", i.e. a distortion of the evaluation through a multiple publication of results of the same study, only the qualitatively best publication was evaluated in each case. Short publications do not contain all of the necessary information for an

Table 1 Study-quality score

1 Clear definition of the objective of the study
2 Study design adequate for the objective of the study
3 Clear definition of the primary endpoint
4 Clear definition of the secondary endpoints
5 Adequate blinding of the study (at least double-blind)
6 Adequate randomisation and adequate description of the randomisation
7 Adequate presentation of early terminations/withdrawals from the study
8 Placebo-control group
9 A priori sample size calculation
10 Patient population representative of self-medication (patients e.g. with mild to moderately severe migraine and/or tension-type headache; no in-patients)
11 Adequate statistical methods and analysis
12 Correct interpretation of the statistical results

accurate evaluation [23]; the same applies for abstracts, congress posters, congress information and overview works (reviews) [24].

Evaluation criteria

Evaluation criteria for the individual clinical studies

The therapy studies identified as "clinically relevant" for the evaluation of drugs and fixed-dose combinations thereof were rated on the one hand in terms of "study quality" (this comprises among other criteria the methodology, design, and internal and external validity), and on the other hand in terms of the "scientific evidence", i.e. the degree of proven effect (efficacy).

Study quality: Study quality was rated on a 4-point scale (from A to D) on the basis of the method of Evans and Pollock [25] and of a specially developed study quality score (Table 1), the evaluation categories of which had been a priori defined. The method of Evans and Pollack constitutes a score system with 33 items. The study quality score emphasises quality features which are of particular importance for the development of these therapy recommendations.

Scientific evidence: The scientific evidence, which rates the results of the study concerned for the respective question, was categorised in accordance with the guidelines of the US Headache Consortium [26, 27] by means of a five-point scale (+++; ++; +; (+); =).

Evaluation criteria for the active ingredients or fixed-dose combinations

We refrained from using a pool of data from the therapy studies identified as "clinically relevant", as the small amount of studies for each active ingredient or fixed-dose combination differ too greatly in methodological terms in many cases.

Quality of scientific evidence: The quality of scientific evidence was rated on a 4-point scale from A to D.

Scientific evidence of efficacy: The scientific evidence of efficacy was rated on a 5-point scale, which had also been a priori defined, from +++ to 0. Due to large differences in design, in the examined endpoints, and in the sample sizes, we refrained from conducting a meta-analysis, as was also the case in the recommendations of 2004 [28, 29]. Hence, no effect measures such as Odds Ratios or the like are available.

Clinical impression of effectiveness: The clinical impression of effectiveness was rated by the authors on a 5-point scale in accordance with the guidelines of the US Headache Consortium from +++ to 0 [26, 27].

Clinical impression of tolerability: The clinical impression of tolerability was rated by the authors on a 5-point scale in accordance with the guidelines of the US Headache Consortium [26, 27] as well as further literature, from +++ to 0.

Recommendations for medicinal therapy

On the basis of evaluations of the active ingredients or combinations thereof regarding their quality, and the scientific evidence of efficacy, the recommendations for medicinal therapy of migraine and tension-type headache were updated under consideration of the clinical impression of effectiveness. As an identical methodology was applied in the therapy recommendations of 2004 and the current update, the evaluations of the therapy studies from 2004, supplemented with the evaluations of the newly added studies, formed the basis for the following three recommendation categories:

- "Remedy of first choice": this recommendation was only assigned if

  (a) the quality of scientific evidence was rated with "A",
  (b) the scientific evidence of efficacy was rated with at least "++",
  (c) the clinical impression of effectiveness was rated with at least "++", and
  (d) the tolerability was rated with "++".

- "Remedy of second choice": this recommendation was only given if

  (a) the quality of scientific evidence was rated with "B",
  (b) the scientific evidence of efficacy was rated with at least "(+)",
  (c) the clinical impression of effectiveness was rated with at least "+", and

(d) the tolerability was rated with "+".

- "only in individual cases": This advice was issued if

(a) the quality of scientific evidence was rated with "C or D",
(b) the scientific evidence of efficacy was poorer than "(+)",
(c) the clinical impression of efficacy was rated with at least "+", and
(d) the tolerability was rated with at least "+".

The category "only in individual cases" is not a recommendation in the actual sense; rather, it aims to take into account the circumstance that different drugs and fixed-dose combinations thereof are effective and tolerated based on the clinical impression, but there is currently no or only deficient scientific evidence available on their efficacy in the treatment of migraine and tension-type headache.

Differentiated recommendations
within a recommendation category

With these therapy recommendations, the available comparative studies were used for the first time to depict possible differences in efficacy between the individual active ingredients or fixed-dose combinations within an evaluation category. The basis for the consisted of therapeutic comparative studies which were rated with A or B regarding quality of scientific evidence in the recommendations of 2004 or in the supplementary evaluations of this update. Only those comparative studies were considered in which active ingredients or active ingredient combinations were compared with one another in doses, which are permitted for self-medication in terms of these recommendations.

The evaluation categories were a priori defined as follows:

- "clearly superior" (≫): Results of at least one study, evaluated as confirmatory, show a statistically significant better efficacy in favour of one of the treatments in terms of the primary endpoint. Furthermore, a consistency is also shown regarding superior efficacy in the secondary endpoints, and there are no contradictory therapeutic comparative studies (quality of scientific evidence: A or B).
- "superior" (>): Results of at least one study, evaluated as confirmatory, show a statistically significant better efficacy in favour of one of the treatments in terms of the primary endpoint. There are no contradictory therapeutic comparative studies (quality of scientific evidence: A or B).
- "not superior" ([>=<]): Results of one study, evaluated as confirmatory, do not show statistically better efficacy

(test of superiority: "superiority trial") in the primary endpoint in favour of one of the treatments. These studies are not to be confused with the so-called "equivalence" or "non-inferiority" studies (see [13, 30, 31]).
- "no comparative studies" ([∼]): indicated when no comparative studies are available.

From the general evaluation of the comparative studies, or if no such studies are available, the order of mentions of the active ingredients or fixed-dose combinations within a recommendation category ensues from the evaluation of the quality of scientific evidence, the scientific evidence of efficacy, the clinical impression of effectiveness and the tolerability.

Results of the systematic literature search

For the total of 30 active ingredients or active ingredient combinations, the systematic literature search taking into account both formulations of the search terms (i.e. with and without the term "clinical trial") resulted in 148 hits in MEDLINE and 67 in Cochrane. Excluding multiple citations within the search, 139 hits remained in MEDLINE; no multiple citations occurred in Cochrane. In accordance with the inclusion and exclusion criteria of the search, and considering the respective permitted dosage and application form for each drug or each fixed-dose combination, 37 relevant publications were identified in MEDLINE, and 22 relevant publications were found in Cochrane for the search period of January 2002 to December 2007. For ASA + lithium, ASA + sodium, ASA + vitamin C + caffeine, diclofenac, dimenhydrinate, dimenhydrinate + paracetamol, lavandula + peppermint, naratriptan, phenazone + propyphenazone and propyphenazone + caffeine, the search was conducted for the period from 1966 to 2007, as due to their importance in at least one of the three countries (A, CH and D), these active ingredients and fixed-dose combinations had been newly added to these therapy recommendations. In accordance with the procedure of recommendations of 2004 [1], therapy studies in which both migraine and tension-type headache were treated were considered in the evaluation of both headache forms. It should be noted in this respect that in one study of approximately 1,750 headache patients, only 60% of the patients whose headache had been diagnosed on the basis of anamnesis corresponded with the diagnosis of headache episodes treated in the study [32]. This should also apply for other headache studies with OTC analgesics.

For the following drugs or fixed-dose combinations, as in 2004 [1], no clinically relevant therapy studies are available:

- for the monoanalgesics: ibuprofen lysinate, naproxen or naproxen sodium (in doses up to 220 mg), propyphenazone
- for the combination analgesics: ASA + caffeine, ASA + lithium, ASA + sodium, ASA + vitamin C, ASA + vitamin C + caffeine, ASA + paracetamol + vitamin C, paracetamol + propyphenazone + caffeine, phenazone + paracetamol + caffeine, phenazone + propyphenazone
- for the phyto-combination: lavandula + peppermint
- for migraine prophylactics: cyclandelate

In view of the frequent use of antipyretic analgesics and other headache and migraine drugs for self-medication worldwide, the number of adequate, randomised and controlled clinical studies is low. Nevertheless, it can be established that in the last few years, several studies corresponding to the "state of the art" have been published, which now find their way into the current recommendations. Including the additions from the manual searches, a total of 35 studies, published in 34 publications [33–66] are newly considered in these recommendations compared to those from 2004 [1].

Recommendations for medicinal therapy

From the German Migraine and Headache Society (DMKG), the German Society of Neurology (DGN), the Austrian Headache Society (ÖKSG) and the Swiss Headache Society (SKG), the following of the mono-analgesics and fixed-dose combinations available for self-medication of headaches in Germany, Austria and Switzerland are recommended:

- For migraine: The fixed-dose combination ASA + paracetamol + caffeine (as the highlighted recommendation); ASA, ibuprofen, naratriptan, paracetamol and phenazone as further remedies of first choice. None of the migraine prophylactics received a recommendation.
- For tension-type headache: The fixed-dose combination ASA + paracetamol + caffeine (as the highlighted recommendation); ASA, diflofenac (12.5 and 25 mg), ibuprofen (only 400 mg) and the fixed-dose combination paracetamol + caffeine as further remedies of first choice, paracetamol as a remedy of second choice.

The detailed evaluations can be found in Tables 2, 3, 4.

Remarks on the analysed studies

The following points should be noted from the analysis of the studies:

- The study quality of 13 studies, all published in the period between 1997 and 2006, were evaluated with "A", while several "B" studies only narrowly missed the "A" rating. The study quality has improved compared to the recommendations of 2004 and the publications corresponded more well to the requirements of the "CONSORT statement" [67]. Nevertheless, information gaps in the publication of clinical studies still too frequently remained open, rendering it difficult to evaluate them [68].
- For many of the studies evaluated as "A" regarding the study quality, in terms of the question of interest, the difference in efficacy compared to the placebo effect was nevertheless not a priori defined as a primary endpoint. If it was only examined as a secondary endpoint, the evaluation "no confirmatory proof of efficacy for…" is made. In the case of several primary endpoints, for an "A" rating, the problem of multiple statistical testing had to be discussed or considered accordingly in the statistical methodology.

Despite the overall improved study quality, again, various methodological weak points were notable in the analysed studies, including:

- Lack of a priori definition of the primary endpoint (to be tested in a confirmatory manner) and lack of an unambiguous delimitation for the secondary endpoints (to be analysed descriptively/exploratively).
- Consequently, multiple statistical testing of several endpoints without or with only insufficient adjustment of the chosen significance level, or the use of inadequate statistical methods [21, 69–71].
- Inadequate distinction between descriptive statistics and inferential statistics. Descriptive statistics summarise the study results and only apply for the patients in the concrete study. Inferential statistics enable a generalisation of the study results beyond the study population [72]. In various publications (descriptive statistically) significant results of secondary endpoints are repeatedly incorrectly drawn upon as proof of the efficacy of a treatment. These incorrect statements are found particularly frequently in the abstracts, the discussion and the conclusion of the respective publications. Consequently, they also clearly violate the CONSORT guidelines [67] regarding interpretation of the results under consideration of the study hypotheses, the possible causes of distortions ("bias") and the problems brought about by multiple statistical testing and multiple target criteria. This thus also impedes the generalisablity of study results (external validity) [67].
- Lack of a priori defined sample size calculations leading to insufficient sample sizes and ultimately insufficient statistical power [73]; studies with an

Table 2 Recommendations of the DMKG, DGN, ÖKG and SKG for self-medication of acute migraine attacks with and without aura

Drug or fixed-dose combination	Quality of the scientific evidence	Scientific evidence of efficacy	Clinical impression of effectiveness	Clinical impression of tolerability	Comments	Recommendation for self-medication
Two tablets of the fixed combination: (250–265 mg) acetylsalicylic acid + (200–265 mg) paracetamol + (50–65 mg) caffeine	A	+++	++	+++	Highlighted recommendation on the basis of the analysed comparative studies	Drug of first choice
Acetylsalicylic acid (900–1,000 mg)	A	+++	++	++	As tablet and as effervescent tablet	Drug of first choice
Ibuprofen (400 mg)	A	+++	++	+++		Drug of first choice
Naratriptan (2.5 mg)	A	++	++	+++		Drug of first choice
Paracetamol (1,000 mg)	A	++	+	+++		Drug of first choice
Phenazone (1,000 mg)	A	++	++	++		Drug of first choice
Acetylsalicylic acid + paracetamol	C	(+)	++	+		Only in individual cases
Naproxen resp. naproxen-sodium	D	0	+	++	Efficacy from 200 mg to 250 mg naproxen or naproxen-sodium is not proven	Only in individual cases
Acetylsalicylic acid + vitamin C	D	0	++	++	ASA dose per tablet at least 400 mg	Only in individual cases
Phenazone-containing combinations	D	0	+	++		Only in individual cases
Propyphenazone (also combinations)	D	0	+	++		Only in individual cases

Table 3 Recommendations of the DMKG, DGN, ÖKG and SKG for self-medication of tension-type headache

Drug or fixed-dose combination	Quality of the scientific evidence	Scientific evidence of efficacy	Clinical impression of effectiveness	Clinical impression of tolerability	Commentary	Recommendation for self-medication
Two tablets of the fixed combination: acetylsalicylic acid (250–265 mg) + paracetamol (200–265 mg) + caffeine (50–65 mg)	A	+++	++	+++	Highlighted recommendation on the basis of the analysed comparative studies	Drug of first choice
Acetylsalicylic acid 1,000 mg	A	++	++	++		Drug of first choice
Diclofenac 12.5 mg	A	++	++	++		Drug of first choice
Diclofenac 25 mg	A	++	++	++	Only in Germany since 2007 prescription free	Drug of first choice
Ibuprofen 400 mg	A	++	++	+++	For 200 mg ibuprofen no data on efficacy	Drug of first choice
Two tablets of the fixed combination: paracetamol (500 mg) + caffeine (65 mg)	A	++	++	+++		Drug of first choice
Paracetamol 1,000 mg	B	+	+	+++		Drug of second choice
Acetylsalicylic acid + paracetamol	C	(+)	++	+++		Only in individual cases
Acetylsalicylic acid + vitamin C	D	0	++	++		Only in individual cases
Naproxen resp. naproxen sodium	D	0	+	++	Efficacy from 200 to 250 mg naproxen or naproxen-sodium is not proofed	Only in individual cases
Phenazone or phenazone-containing combinations	D	0	+	++		Only in individual cases
Propyphenazone mono or in combinations	D	0	+	++		Only in individual cases

Table 4 Recommendations of the DMKG, DGN, ÖKG and SKG for self-medication with migraine-prophylactics

Drug	Quality of scientific evidence	Scientific evidence of efficacy	Clinical impression of effectiveness	Clinical impression of tolerability	Commentary	Recommendation for self-medication
Cyclandelat	D	0	+	++		Only in individual cases
Petasites	C	+	++	++		Only in individual cases

insufficient sample size can thus lose their ethical justification [74].

- Insufficient description of the research question, study methodology, implementation and statistical analysis of the study (e.g. lack of or insufficient information on blinding, on procedure and on ensuring randomisation, on study dropouts, on confidence intervals) [75].

The definition of the primary endpoints was not consistent in the various studies. This renders the comparative evaluation of the scientific evidence for the efficacy of the individual drugs and fixed-dose combinations more difficult. For this reason, they were evaluated as described by the study authors. Finally, therapeutic effect was usually greater in the older studies than in the more recent ones. This phenomenon which is often described in the literature is attributed among other things to a "fading of reported effectiveness", brought about in particular through baseline differences [76] and to other systematic distortions.

Remarks on active ingredients and active ingredient combinations

The following remarks on several of the analysed studies should help to make the evaluations in these recommendations transparent and comprehensible.

Acetylsalicylic acid (ASA)

In the so-called "EMSASI study" with a double-blind randomised, three-way cross-over design, 312 patients with migraine were each administered a single dose of 1,000 mg ASA, 400 mg ibuprofen, 50 mg sumatriptan and placebo [37]. The study documents the efficacy of 1,000 mg ASA as an effervescent tablet compared to placebo in the percentage responder rate of the 2-h value (4-point verbal scale). As all other comparisons only constitute secondary endpoints, their results only count as descriptive for the study population, cannot be generalised and can therefore not be taken into account for the differentiated recommendations within an evaluation category. For instance, in the study, although the question is posed of whether 1,000 mg ASA is just as effective as 50 mg sumatriptan or as 400 mg ibuprofen, this is not reflected in the study design. To achieve this, an equivalence approach with an a priori defined non-

inferiority margin would have to have been chosen [30, 31, 77]. The study therefore shows neither an equivalence of 1,000 mg ASA with sumatriptan 50 mg, nor with ibuprofen 400 mg, and can equally not be seen as proof of efficacy for sumatriptan 50 mg or ibuprofen 400 mg. Unfortunately, these results are wrongly interpreted and reported on numerous occasions in this respect [78–81].

In a five-arm, double-blind randomised parallel group study with the treatment groups ASA 500 and 1,000 mg, paracetamol 500 and 1,000 mg and placebo, a total of 638 patients with episodic tension-type headache were included in the intention-to-treat analysis 542 [63]. As a primary endpoint, the comparison of 1,000 mg ASA compared to placebo was established in the percentage responder rate of the 2-h value (definition 4-point verbal rating scale so-called Glaxo criterion). All other comparisons were declared as secondary endpoints, "considered hypothesis-generating in nature", and thus only to gain hypotheses for further investigations. The superior efficacy of 1,000 mg ASA compared to placebo could be proved in this study. As all other comparisons merely constitute secondary endpoints and cannot be generalised, they can also not be taken into account for the differentiated recommendations within an evaluation category. The selected manner of presenting the results in this publication renders it considerably more difficult to interpret them correctly. This could be a reason why this study has been misinterpreted on several occasions [78, 82].

Acetylsalicylic acid + paracetamol + caffeine

In a large, randomised, double-blind study with a parallel group design, only patients were included who had successfully treated their headaches themselves with prescription-free pain medications [39]. The approximately 1,750 patients therefore represented typical OTC headache patients. In the primary target criterion, "time until reaching a 50% pain reduction", the superior efficacy of two tablets of the fixed-dose combination of ASA + paracetamol + caffeine was shown compared to 1,000 mg ASA, 1,000 mg paracetamol, the combination of ASA and paracetamol, and compared to 100 mg caffeine and placebo. All verum treatments differed significantly from placebo (with the exception of caffeine). The statistical analyses of the secondary endpoints also confirmed the

superiority of the triple combination compared to the combination without caffeine, as well as all single substances and placebo, meaning that the results are consistent. Their clinical relevance was confirmed through analyses of the global efficacy rating of the patients [83].

Diclofenac–potassium

As both 12.5 and 25 mg diclofenac–potassium were switched from the "prescription only" status to selfmedication in Germany in the last few years, they are considered for the first time in these recommendations. In a double-blind randomised, multicentre study, diclofenac–potassium 12.5 and 25 mg, 400 mg ibuprofen and placebo were compared in 684 patients with episodic tension-type headache in a parallel group design [49]. As a "primary efficacy variable", the TOTPAR-3, the weighted "total pain relief", was indicated over a period of 3 h following intake of the medication. This indication is insufficient as a definition of an endpoint, as only the measurement parameter, but not the allocation of the treatment group comparisons can be given as a "primary" or "secondary" endpoint. The formulation of the null hypothesis is also lacking. If it can be assumed that the study should primarily yield the proof of efficacy for diclofenac 12.5 and 25 mg, and all other comparisons were defined as secondary endpoints, then the indicated statistical procedure of "Fisher's protected procedure" would be sufficient for the multiple confirmatory comparisons of diclofenac–potassium 12.5 and 25 mg versus placebo. If all three groups were to be tested in a confirmatory manner, then it would be necessary to carry out Fisher's protected procedure "within each group" on the $\alpha/3$ significance level. From the overall picture of the publication, it can be concluded that the comparisons of "ibuprofen 400 mg versus placebo", "diclofenac–potassium 12.5 mg versus placebo" and "diclofenac–potassium 25 mg versus placebo" should constitute the primary endpoints of the study and the comparisons between the verum treatments the secondary endpoints. With this study which can otherwise be attested as having a good study quality, the proof of efficacy for 12.5 and 25 mg diclofenac–potassium is yielded for the acute treatment of tension-type episodic headache. The assertion that "Moreover, this efficacy is similar to that of ibuprofen 400 mg …" is only descriptively valid for the study population and cannot be generalised; for this reason, the study was also not taken into account for the differentiated recommendations within an evaluation category.

Naratriptan

Naratriptan became available as a single dose of 2.5 mg without prescription in Germany in 2006. In total, the systematic literature searches resulted in seven clinically relevant therapy studies. Five of these studies, however, cannot be evaluated as confirmatory evidence for 2.5 mg naratriptan for the treatment of migraine as they were either dose-finding studies [47, 48] or the primary endpoints referred to other research questions or were not clearly defined [34, 40, 55].

In a double-blind randomised, multi-centre study, naratriptan was compared in the doses 2.5 or 1 mg versus placebo, 2.5 versus 0.25 mg or 0.1 mg and 1 versus 0.1 mg in 613 patients in a parallel group design [48]. Again, only the measurement parameter, and not the definition of the treatment group comparisons, is given as "primary" or "secondary" endpoint. Multiple statistical testing is not considered in the design of the study either in the form of a hierarchical test procedure or in the form of a α-adjustment. The results compared to placebo can only be judged as descriptive and thus can not be generalised and do not constitute a confirmatory proof of efficacy.

In a further dose-finding study using a parallel group design, a single dose of 1, 2.5, 5, 7.5 and 10 mg naratriptan as well as 100 mg sumatriptan and placebo were compared in 643 migraine patients [47]. As multiple statistical testing is not considered in the design of the study, comparisons versus placebo can only be judged as descriptive and do not constitute a confirmatory proof of efficacy.

With a single dose of rizatriptan (10 mg), naratriptan (2.5 mg) and placebo, 522 migraine patients were treated in a randomised, double-blind parallel group study (double-dummy) [34]. The test hypothesis "rizatriptan 10 mg would be superior to naratriptan 2.5 mg in time to headache relief up to 2 h after drug administration" is formulated in a methodologically exemplary manner, and the question of multiple statistical testing is correctly addressed: "as there was only one primary endpoint and one primary comparison, there was no need for multiplicity adjustment for primary time point". The comparisons versus placebo are consequently secondary endpoints, meaning that the study cannot be seen as a confirmatory proof of efficacy for naratriptan in terms of these recommendations.

In a randomised, double-blind parallel group study comparable in terms of design, single doses of eletriptan (40 mg), naratriptan (2.5 mg) and placebo were compared in 548 migraine patients [40]. Again, the primary endpoint is formulated clearly: "the primary comparison was between eletriptan 40 mg and naratriptan 2.5 mg, and consisted of the proportion of subjects with a headache response at 2 h after the first dose of study treatment for the migraine attack". Moreover, the question of multiple statistical testing is correctly addressed: "no adjustment was made for multiple comparisons". The comparisons versus placebo are consequently secondary endpoints, meaning

that the study can also not be seen as a confirmatory proof of efficacy for naratriptan in accordance with these recommendations.

Almost 700 migraine patients were treated in a randomised, double-blind four-period cross-over study with a single dose of 0.25, 1, and 2.5 mg naratriptan as well as placebo [55]; however, the study was evaluated regarding efficacy as a parallel group comparison (sample size estimation: 125 per group). Again, in this study, only the measurement parameter is indicated, and no clear definition is made of the treatment group comparisons as "primary" or "secondary" endpoint. In the study design, multiple statistical testing is not considered either in the form of a hierarchical test procedure or in the form of a α-adjustment; thus it does not constitute a confirmatory proof of efficacy for naratriptan 2.5 mg in line with these recommendations.

Migraine patients ($N = 347$) who responded poorly to sumatriptan were all treated in a two-phase study first with 50 mg sumatriptan. Non-responders ($N = 206$) to sumatriptan then received, in a randomised, double-blind parallel group design 2.5 mg naratriptan or placebo [61]. In the primary endpoint "conversion from moderate or severe pain to mild or no pain at 4 h after use of test medication", naratriptan 2.5 mg proved to be statistically significantly superior to placebo treatment. However, the proof of efficacy was generated in a specific subgroup, namely migraine patients who responded poorly to sumatriptan, and therefore cannot be concluded for the general population without further investigation.

Patients ($N = 227$) with menstrual migraine received, in a randomised, double-blind parallel, group study, a single dose of 2.5 mg naratriptan or placebo [54]. In the primary endpoint, the "percentage of subjects who were completely free of pain 4 h after medication", the naratriptan 2.5 mg treatment proved to be statistically significantly superior to placebo treatment. Again, the proof of efficacy refers to a specific subgroup, namely female patients with menstrual migraine, and cannot be concluded for the general population without further investigation.

According to the general evaluation of naratriptan 2.5 mg, despite the various limitations in the available studies, a proof of effectiveness for the treatment of migraine can be assumed. As naratriptan and other triptans have not yet been examined in typical self-medication patients, such studies are necessary and desirable in the future [84].

Summary of efficacy data

Table 5 provides a summary of efficacy data of 11 randomized clinical studies which are considered in the evaluation of the recommendations for self-medication of acute migraine attacks with and without aura or tension-type headache, including only trials with drugs recommended as first or second choice.

Butterbur as a migraine prophylaxis

For a double-blind randomised, placebo-controlled, parallel group study on migraine prophylaxis [85] including 60 migraine patients, who following a 4-week "run-in phase" had received either 50 mg *Petasites hybridus* extract for 12 weeks or placebo, a post-hoc reanalysis [36] was conducted. The "frequency of migraine attacks per 4 weeks" was defined as the primary efficacy variable. In the analysis, the frequency of attacks was then determined consecutively for the verum and the placebo group over the 4-month duration of the study. As neither a hierarchical test procedure nor an adjustment of the significance level for multiple statistical testing ensued on the basis of the primary publication [85], this study can only be judged in exploratory terms as a pilot study and cannot be evaluated as a confirmatory study in the sense of a proof of efficacy.

In a double-blind randomised, placebo-controlled parallel group study (migraine prophylaxis), following a 4-week run-in phase, 233 patients received 50 or 75 mg of a *Petasites hybridus* extract or placebo [51]. In total, three primary comparisons between the treatment groups were defined and tested, namely (1) 75 mg Petasites extract versus placebo, (2) 50 mg Petasites extract versus placebo and (3) 75 versus 50 mg Petasites extract. The multiple test procedure was not taken into account either in the study methodology or the results section of the publication, and the chosen statistical procedure enables no confirmatory proof of efficacy for any of the three endpoints.

Remarks on comparative studies

In the development of differentiated recommendations within an evaluation category, it was only possible to consider studies in which the comparison between the drugs or fixed-dose combinations constituted the primary endpoint and which were rated with A or B regarding study quality. In total, four studies met these criteria [39, 44, 56, 86]; three further studies could not be considered [37, 49, 63]. Further comparative studies on the determination of the therapeutic status of the various active ingredients would be necessary and desirable.

Remarks on the tolerability of the active ingredients or active ingredient combinations

There continue to be few meaningful comparative studies on the tolerability of prescription-free analgesics in their

Table 5 Summary of efficacy data of 11 randomized clinical studies (only drugs recommended as first or second choice)

Indication and drug	Active drug	Placebo	Therapeutic gain	Primary endpoint of the study	Literature reference
Migraine/ETTH	Secondary endpoints:			Kaplan–Meier estimator of the proportion of patients with 50% pain relief during the first 4 h after drug intake	Diener et al. [39, 109]
fixed-dose combination of 500 mg ASA + 400 mg paracetamol + 100 mg caffeine	PID at 2 h VAS: 44.7 mm	PID at 2 h VAS: 24.6 mm	$\Delta = 20.1$ mm		
	≥50% pain reduction at 2 h: 77% of patients	≥50% pain reduction at 2 h: 47% of patients	$\Delta = 30\%$		
Migraine	Primary endpoint:			TOTPAR-2 sum of pain relief scores at 2 h postdose (5-point VRS)	Goldstein et al. [44]
fixed-dose combination of 500 mg ASA + 500 mg paracetamol + 130 mg caffeine	TOTPAR-2 at 2 h: 2.7	TOTPAR-2 at 2 h: 2.0	$\Delta = 0.7$		
ETTH	Primary endpoint:			TOTPAR-4 sum of pain relief scores at 4 h postdose (5-point VRS)	Migliardi et al. [56]
fixed-dose combination of 1,000 mg paracetamol + 130 mg caffeine	study 1: TOTPAR-4: 10.45 ± 0.20	study 1: TOTPAR-4: 8.82 ± 0.30	$\Delta = 1.63$		
	study 2: TOTPAR-4: 10.54 ± 0.19	study 2: TOTPAR-4: 7.86 ± 0.32	$\Delta = 2.68$		
Migraine	Primary endpoint: response rate at 2 h: 52.5% of patients	response rate at 2 h: 30.6% of patients	$\Delta = 21.9\%$	Number of patients (in %) with headache relief from grade 3 or 2 to grade 1 or 0 at 2 h (4-point VRS)	Diener et al. [37]
1,000 mg ASA					
Migraine	Primary endpoint:			Number of patients (in %) with headache relief from grade 3 or 2 to grade 1 or 0 at 2 h (4-point VRS)	Lipton et al. [52]
1,000 mg ASA	response rate at 2 h: 52% of patients	response rate at 2 h: 34% of patients	$\Delta = 18\%$		
ETTH	Primary endpoint:			Number of patients (in %) with headache relief to grade 1 or 0 at 2 h (7-point VRS)	Steiner et al. [63]
1,000 mg ASA	response rate at 2 h: (7-point VRS): 75.7%	response rate at 2 h: (7-point VRS): 54.5%	$\Delta = 21.2\%$		
ETTH	Primary endpoint:			TOTPAR-3 (time-weighted sum of pain relief scores at 3 h)	Kubitzek et al. [49]
12.5 mg diclofenac-K	TOTPAR-3: 5.23 ± 2.71	TOTPAR-3: 3.49 ± 3.02	$\Delta = 1.74$		
	secondary endpoint:				
	complete pain relief at 2 h: 18.1% of patients	complete pain relief at 2 h: 7.8% of patients	$\Delta = 10.3\%$		
ETTH	Primary endpoint:			TOTPAR-3 (time-weighted sum of pain relief scores at 3 h)	Kubitzek et al. [49]
25 mg diclofenac-K	TOTPAR-3: 5.55 ± 2.95	TOTPAR-3: 3.49 ± 3.02	$\Delta = 2.06$		
	secondary endpoint:				
	complete pain relief at 2 h: 22.6% of patients	complete pain relief at 2 h: 7.8% of patients	$\Delta = 14.8\%$		
ETTH	Primary endpoint:			TOTPAR-3 (time-weighted sum of pain relief scores at 3 h)	Kubitzek et al. [49]
400 mg ibuprofen	TOTPAR-3: 5.37 ± 3.07	TOTPAR-3: 3.49 ± 3.02	$\Delta = 1.88$		
	secondary endpoint:				
	complete pain relief at 2 h: 21.9% of patients	complete pain relief at 2 h: 7.8% of patients	$\Delta = 14.1\%$		
Migraine	Primary endpoint:			Number of patients (in %) with headache relief from grade 3 or 2 to grade 1 or 0 at 2 h (4-point VRS)	Kellstein et al. [110]
400 mg ibuprofen	response rate at 2 h: 72.3% of patients	response rate at 2 h: 50% of patients	$\Delta = 22.3\%$		
	secondary endpoints:				
	PID at 2 h VAS: 1.23 ± 0.97	PID at 2 h VAS: 0.71 ± 0.87	$\Delta = 0.52$		
	pain free (cumulative): 27.7% of patients	pain free (cumulative): 13.4% of patients	$\Delta = 14.3\%$		
Migraine	Primary endpoint:			Number of patients (in %) with headache relief from grade 3 or 2 to grade 1 or 0 at 4 h (4-point VRS)	Lipton et al. [111]
1,000 mg paracetamol	response rate at 2 h: 57.8% of patients	response rate at 2 h: 38.7% of patients	$\Delta = 19.1\%$		
	secondary endpoint:	secondary endpoint:			
	pain free (cumulative): 22.4% of patients	pain free (cumulative): 11.3% of patients	$\Delta = 11.1\%$		

Table 5 continued

Indication and drug	Active drug	Placebo	Therapeutic gain	Primary endpoint of the study	Literature reference
ETTH 1,000 mg paracetamol	Secondary endpoint: response rate at 2 h (7-point VRS): 71.2%	response rate at 2 h (7-point VRS): 54.5%	Δ = 16.7%	Number of patients (in %) with headache relief to grade 1 or 0 at 2 h (7-point VRS)	Steiner et al. [63]
Migraine 1,000 mg phenazone	Primary endpoint: response rate at 2 h: 48.6% of patients	response rate at 2 h: 27.2% of patients	Δ = 21.4%	Number of patients (in %) with headache relief from grade 3 or 2 to grade 1 or 0 at 4 h (4-point VRS)	Göbel et al. [42]
	secondary endpoint: pain free at 2 h postdose: 27.6% of patients	secondary endpoint: pain free at 2 h postdose: 13.6% of patients	Δ = 14%		
Migraine 2.5 mg nartriptan	Primary endpoint: response rate at 4 h: 41% of patients	response rate at 4 h: 19% of patients	Δ = 22%	Number of patients (in %) with headache relief from grade 3 or 2 to grade 1 or 0 at 4 h (4-point VRS)	Stark et al. [61]
	secondary endpoint: response rate at 2 h: 25% of patients	response rate at 2 h: 10% of patients	Δ = 15%		

ASA acetylsalicylic acid, *ETTH* episodic tension-type headache, *PID* pain intensity differences, therapeutic gain: defined as response of the active drug minus placebo response, *TOTPAR* total pain relief, *VAS* visual analog scale (100 mm), *VRS* verbal rating scale

recommended application, although such studies should be encouraged [80, 87]. The controlled studies on the proof of efficacy are frequently ill-suited for generating reliable data beyond acute use as for example the sample sizes are too low in this respect. Safety and tolerability studies normally include several thousand or ten thousand patients, depending on the research question [88].

To date, only one study has compared the tolerability of ASA, ibuprofen and paracetamol in short-term use (up to 7 days) [89]. Paracetamol and ibuprofen showed a comparable safety and tolerability, which was significantly superior to that of ASA. Further interesting approaches for a comparative evaluation of the safety and tolerability of non-narcotic analgesics [90] and triptans [91], respectively, should be referred to at this point.

Evaluation of dietary supplements

For advising headache patients, it must apply in particular also for the risk–benefit evaluation of dietary supplements that: "Academicians must resist pressure to present unproven therapies as realistic alternatives for medications with scientific proof of safety and efficacy. They must stress the value of evidence-based medicine and urge students and pharmacists to recommend only those medications with evidence-based proof of safety and efficacy" [77].

A notable number of studies with dietary supplements have been conducted compared to medicine-based studies, each with a very small number of subjects. For these studies, the limitations formulated by McQuay and Moore apply as follows: "The lessons are that information from individual trials of small size should be treated with circumspection in pain and probably other therapeutic areas, and that variations seen in trials of small size is probably artefactual…" [92] or "A small trial has only a small chance of correctly detecting a difference (or no difference) at conventional levels of significance", as West cautions in his Editorial [93].

Magnesium

From the analyses of the therapy recommendations of 2004, it emerged that there was no proof of efficacy in the form of double-blind randomised studies for orally administered magnesium in migraine prophylaxis. For this reason, the evaluation "only in individual cases" was given. As magnesium is not approved in Germany for migraine prophylaxis, it is only listed in the text in these recommendations, as with the other dietary supplements and is no longer listed in the recommendation table.

As in 2004, the systematic literature search on magnesium in migraine prophylaxis resulted in four publications. From a small, randomised, double-blind study in 24 patients with menstrual migraine [94], no statements on the efficacy of magnesium in migraine prophylaxis can be derived. A further double-blind randomised study [95] in 81 patients showed, after 3-month use, a statistically significant superiority of 600 mg magnesium compared to placebo in the third treatment month. A double-blind randomised study [96] which was to include 150 patients, was abandoned following an interim evaluation of 69 patients, as the superiority over placebo treatment, also of a 3-month treatment with 486 mg magnesium, no longer appeared to be achievable. This study is problematic with regard to

various methodological points, meaning that it is not possible to correctly interpret the results of its primary endpoint. A further study [65] implemented in children cannot be taken into account for these recommendations which are targeted at adults. All studies were implemented with different magnesium salts and different galenic formulations and doses, rendering the evaluation of the therapeutic benefit difficult.

From an overall view of the available data, it is possible to speak of substantiated evidence, but not of a proof of efficacy of magnesium for migraine prophylaxis. Further randomised, placebo-controlled, double-blind studies would be necessary for this purpose. Nevertheless, from a purely clinical-pragmatic perspective, magnesium is frequently used for migraine prophylaxis in pregnant women.

Coenzyme Q10

The systematic literature search on the coenzyme Q10 resulted in three publications on migraine prophylaxis, one of which was a larger cases series on coenzyme Q10 supplementation in children and adolescents [97] and one of which was a small, open study in 32 migraine patients [98]. From both investigations, no proof of efficacy can be derived for the coenzyme Q10 for migraine prophylaxis due to methodological reasons. A further small, double-blind randomised study [99] in 43 patients did show a statistically significant superiority over placebo following 3-month use, but this can be attributed to the surprisingly low placebo effect. Methodological ambiguities clearly limit the expressiveness of the study, such that from the overall view of the available data, a proof of efficacy of the coenzyme Q10 for migraine prophylaxis cannot yet be judged as having been provided. For this purpose, further randomised, placebo-controlled, double-blind studies would be necessary.

Riboflavin (Vitamin B$_2$)

The systematic literature search for riboflavin and migraine prophylaxis resulted in four publications. In one publication [100], a combination preparation was examined, but contained no data on riboflavin as a single substance. From two small, open, non-controlled studies in 23 [101] and 49 patients [102], no conclusions can be derived on the efficacy of riboflavin in migraine prophylaxis. In a further small, double-blind randomised study [103] in 55 patients, a statistically significant superiority over placebo was shown after 3-month use, but this can be attributed to the surprisingly low placebo effect. From an overall view of the available data, there are indications but no proof of the efficacy of riboflavin (vitamin B$_2$) for migraine prophylaxis. For this purpose, a further, larger, randomised, placebo-controlled double-blind study would be necessary.

α-Lipoic acid

Whether the intake of α-lipoic acid is effective for migraine prophylaxis was examined in a small study with 44 patients [104]. This was methodologically insufficient and did not generate any statistically significant results. The efficacy of α-lipoic acid can thus currently not be answered. Further clinical studies would be necessary here.

Omega-3 fatty acids

The extent to which the intake of omega-3 fatty acids is effective for migraine prophylaxis was examined in a larger, double-blind randomised, placebo-controlled parallel group study [105]. Following 3-month use, no statistically significant superiority over placebo was shown for polyunsaturated omega-3 fatty acids in terms of attack frequency in the third treatment month (primary target criterion); thus, there was no proof of efficacy.

Melatonin

Melatonin is a prescription medicine and not permitted for migraine prophylaxis. Although the MEDLINE search produced 87 hits for melatonin, no single randomised, controlled clinical study was among them. The question of whether the administration of melatonin is effective for migraine prophylaxis cannot be answered on the basis of a short publication on a small, open, uncontrolled study of 30 patients [106]. Further clinical studies would be necessary for this purpose which the authors also call for in the cited study [107, 108].

Combination of dietary supplements

According to the results of a systematic literature search, no scientifically reliable proof of efficacy for prophylaxis or acute therapy of migraine has yet been generated either for the individual dietary supplements or for combinations of these supplements among one another and/or, for example, with vitamins and trace elements. Thus, this question remains unanswered.

Medication-overuse headache

Medication-overuse headache is a serious problem concerning the therapy of some headache patients. On the basis of the available literature results the four scientific societies claim that patients who take headache- and migraine medications on a regular basis on more than 10–15 days per month have an increased risk for the development of medication-overuse headache independent

of whether mono- or combined drugs are involved. More important than the composition of the drugs is the frequency of their consumption. The recommendation therefore states that headache- and migraine medications should not be taken for more than three consecutive days and on more than 10 days per month. However, the quality of evidence for this recommendation based on consensus is low. It is not clear how many patients are helped versus how many are hurt (by pain under-treatment) by this advice, as this has not been studied, as Scher et al. recently stated [112]. All relevant aspects of this topic are going to be discussed in a new treatment guideline for medication-overuse headache, which is prepared by the DMKG, DGN, ÖKG and SKG within the next months.

Conflict of interest These guidelines were developed without support from the pharmaceutical industry. The preparation costs were carried by the DMKG. The authors individually declare the following conflicts of interest (donations as fees or research support from pharmaceutical companies):

Hans-Christoph Diener: Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Johnson & Johnson, Lilly, LaRoche, 3 M Medica, MSD, Novartis, Pierre Fabre, Pfizer, SanofiAventis, Schaper und Brümmer, Weber & Weber.

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Gunther Haag: Berlin Chemie, Boehringer Ingelheim, GlaxoSmithKline, Grünenthal, Janssen-Cilag, MSD.

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