THE UNIVERSITY OF ARIZONA | MEL AND ENID ZUCKERMAN COLLEGE OF PUBLIC HEALTH

2012

Medical Marijuana for the Treatment of Migraine Headaches:

An Evidence Review

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Acknowledgements

This report was written for The Arizona Department of Health Services, Contract No: ADHS12-017291, under the advisement of the ADHS Medical Marijuana Advisory Committee and acknowledge assistance from the Arizona Health Science Librarians-Phoenix and Tucson.

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Introduction

Purpose of the Evidence Review

This review evaluates evidence on cannabis use in adults for the treatment of migraine headaches. The Arizona Department of Health Services (ADHS) funded this report to assist in assessing migraines as a condition to add to those that qualify for the use of medical marijuana in Arizona.

Background

Pursuant to A.R.S. § 36-2801.01, the public may petition the Arizona Department of Health Services (ADHS) to add debilitating medical conditions to those listed in A.R.S. 36-2801(3). The ADHS established the manner in which it shall consider petitions to add debilitating medical conditions in A.A.C. R9-17-106. A.A.C. R9-17-106(C) states, ADHS "shall accept requests for the addition of a medical condition to the list of debilitating medical conditions in R9-17-201 in January and July of each calendar year starting in January 2012". After receiving requests for adding conditions the ADHS requests a report on the scientific evidence on the use of cannabis for this condition from the University of Arizona College of Public Health. In addition the Department holds a public hearing to hear public testimony on the condition and its treatment with cannabis. The Department Medical Advisory Committee then considers the totality of the evidence in deciding to add a condition to the list, or not.

Scope of the Evidence Review

List of Key Questions

Benefits and harms of cannabis therapy for migraine headaches

1. What are the benefits (short and long-term benefits) of cannabis use for treatment or prevention of migraine headaches?
2. What are the harms (short and long-term harms) of cannabis use for the treatment or prevention of migraine headaches?

Conflicts of Interest

The reviewer had no conflicts of interest to disclose.

Methods

Literature Search and Strategy

The topics of cannabis use and migraine headaches where searched in the following databases: The Cochrane Library, Ovid MEDLINE®, Web of Science, Dynamed, Google Scholar, National Center for Complimentary and Alternative Medicine, and PsycINFO. Bibliographies in the articles identified through these databases were hand searched for additional pertinent articles. A detailed description of the search terms can be found in Appendix 1.

Inclusion and Exclusion Criteria

Studies that met all of the following criteria were included:

1. Evaluated adults (≥ 18 years old) with migraine or cluster headaches
2. English language
3. Human study
4. Were relevant to one of the key questions

Studies that were excluded include those that were:

1. Animal studies
2. Editorials or opinions
3. Descriptions of biochemical and pathophysiological pathways
4. Not relevant to the key questions

The original intent was to restrict the search to clinical trials, cohort and case control studies. Due to the paucity of studies of this type found, we also included cross sectional studies and case reports.

Quality Assessment

Types of studies available to assess are listed and described in Appendix 2. Observational studies were assessd using the main domains described in tools commonly used (Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomized intervention studies. Health Technology Assessment 2003;**7**(27)). The overall quality of the evidence is ranked using GRADE methodology demonstrated in Appendix 3. (Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60.)

Studies Submitted by the Public

The scientific literature submitted by the public in support of including migraine headaches was also assessed using the same methodology.

Results

The search resulted in 20 articles, 14 of these did not meet the inclusion criteria. Each included article is summarized in table 1. Articles that were listed in the search but that did not meet the inclusion criteria are listed in table 2. Only one article was submitted by the public and it was in the list uncovered by the search and is indicated by an * in table 1.

There were a total of 6 articles that met the inclusion criteria and 3 were by the same author. Four articles were case reports. Among them there were a total of 4 patients with migraine headaches (although it is unclear in 2 if these were actually migraine type headaches) who reported relief of migraines with marijuana or dronabinol. Three individuals reported on set of migraines upon stopping marijuana use and one reported on set of possible migraine with joint use of marijuana and ectasy. There were two articles reporting a cross sectional study. One appears to be a subset of the other but this is not clear. Neither directly addresses the clinical question of effectiveness and both studies are of extremely low quality.

Table 1
Articles Included in the Review

Article and Citation	Description and Design of Study	Findings	Quality
1. Noyes R, Baram D. Cannibis Analgesia. Comprehensive Psychiatry 1974;15(6):531-535.	Case reports. 1 patient with migraine headaches and 2 patients with headaches that might have been migraines, in the USA.	All 3 reported pain relief with the use of marijuana. One reported a decreased frequency of headaches with regular marijuana use.	Very low. Case reports.
2. Robbins MS, Tarshish T, Soloman S, Grosberg BM. Cluster attacks responsive to recreational cannabis and dronabinol. Headache 2009; June:914-916 *	Case report of a single patient in the USA.	His cluster headaches were responsive to cannabis and then also to dronabinol.	Very low. Case report.
3. El-Mallakh RS, Kansler HR, Kamanitz JR. Headaches and psychoactive substance use. Headache 1991;31:584-587.	Cross sectional study asking about headaches. 236 patients admitted to substance abuse ward in the U.S., 80 with history of migraines.	Mean age of onset of migraines was 2 years before mean age of onset of substance abuse. Substances abused not described. Unknown how many were marijuana users. No data on effect of abused drugs on headaches.	Very low Biased sample, subject to recall bias. Poor quality of the data collected.
4. El-Mallakh RS. Marijuana and migraine. Headache 1987;27:442-443.	3 case reports of long term marijuana users in the U.S..	All 3 on cessation of marijuana use developed migraine headaches. One was also a cocaine user. Very little clinical or demographic information on any of the patients.	Very low
5. El-Mallakh RS. Migraine headaches and drug abuse. Southern Medical Journal 1989;82:805.	Cross sectional study of 54 patients admitted to an inpatient drug and alcohol abuse program at one center in Connecticut. It is not clear but this population appears to be the same as citation 3.	Those with migraine headaches were more likely to be using marijuana and cocaine than those with other headache types. (80% vs 54%)	Very low. Letter to the editor with very little information. Biased sample. High non response rate (46%)
6. Trittibach P, Frueh BE, Goldblum D. Bilateral angle-closure glaucoma after combined consumption of ecstasy and marijuana. American Journal of Emergency Medicine 2005;23:813-814.	Case study of woman in Switzerland who had also been in Africa.	Ophthalmological migraine and angle closure glaucoma occurred on several occasions after using ecstasy and marijuana together and resolved after she stopped.	Very low.

Table 2

Articles Not Included

Author, title, citation	Content	Reason not used
7. Bagshaw SM. Medical efficacy of cannabinoids and marijuana: a comprehensive review of the literature. Journal of Palliative Care 2002;18:111-122.	A review of the literature but not a systematic review of the quality of the literature. References on migraine treatment were checked to see if there were any not found in the library search.	Does not contain any new information. It is a summary of already existing studies.
8. Russo E. Cannibis for migraine treatment: the once and future prescription? An historical and scientific review. Pain 1998;76:3-8.	A historical review of the use of cannabis for treatment of migraines. References on were checked to see if there were any not found in the library search.	A very interesting historical article with no useable scientific data.
9. Taylor FR. Nutraceuticals and headache: the biological basis. Headache 2011;51: 484-501.	A review of the basic science of migraine mechanisms and research on proposed mechanism of action of magnesium, riboflavin, coenzyme Q10, petasites, feverfew, marijuana and oxygen/hyperbaric oxygen.	A review of possible CNS receptor sites and mechanisms of action of cannabis and various forms of cannabis. No clinical data provided. References were checked to see if any relevant ones included.
10. Volfe Z, Dvilansky A, Nathan I. Cannibinoids block release of serotonin from platelets induced by plasma from migraine patients. International Journal of Clinical Pharmacology Research 1985;4:243-246.	Biochemical study on blood from 7 patients.	Not a clinical trial. Very preliminary data on a small number of subjects. Clinical relevance uncertain.
11. Juhasz G. et al. Variations in the cannabinoid receptor 1 gene predispose to migraine. Neuroscience Letters 2009;461:116-120.	Gene association study of cannabinoid receptor 1 (CB 1) gene with migraine as diagnosed by 3 of the most predictive symptoms.	Very preliminary study of a potential pathophysiological mechanism. The odds ratios and likelihood ratios are not very impressive.
12. Napchan U, Buse DC, Loder W. The use of marijuana or synthetic cannabinoids for the treatment of headache. Headache 2011; 51:502-505.	Commentary on two articles published previously; citation #2 above and a cross sectional study published in German with 6.6 % of cannabis users reporting they used it for migraines.	Commentary.
13. Evans RW, Ramadan NM. Are cannabis based chemicals helpful in headache? Headache 2004;44:726-727.	Case report.	Headache not due to migraine
14. Cupini LM, et al. Degradation of endocannabinoids in chronic migraine and medication overuse headache. Neurobiology of disease 2008;30: 186-189.	Study of biochemical pathophysiological pathways.	Does not address the key questions.
15. Rossi C, Pini LA, Cupini ML, Calabresi P. Endocannabinoids in platelets of chronic migraine patients and medication overuse headache patients: relation with serotonin levels. European Journal of Clinical Pharmacology 2008;64:1-8.	Study of biochemical pathophysiological pathways.	Does not address the key questions.
16. Russo EB. Clinical endocannabinoid deficiency: can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment resistant conditions? Neuroendocrinology letters 2004;25:31-39.	Review of pathophysiology.	Does not address the key questions.
17. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. California Medical Association Journal 2008;178(13):1669-78.	Review of published articles on adverse effects.	Does not address migraine specifically.
18. Cupini LM, Bari M, Argiro G, et al.	Study of potential pathophysiology pathways.	Does not address the key question

	Biochemical changes in endocannabinoid system are expressed in platelets of female but not male migraineurs. Cephalalgia 2005;26:277-281.		
19.	Sarchielli P, Pini LA, Coppola F, et al. Endocannabinoids in chronic migraine: CSF findings suggest a system failure. Neuropsychopharmacology 2007;32:1384-1390.	Study of potential pathophysiology mechanisms.	Does not address the key question.
20.	Robson B. Therapeutic aspects of cannabis and cannabinoinds. British Journal of Psychiatry 2001;178:107-115.	1996 review of medical use and evidence behind it.	No mention of migraines.

Conclusions

We could not find any research that directly addressed the key questions. The most relevant literature was of very low quality and no conclusions can be drawn about the benefits or harms of marijuana use for the treatment of migraines.

Current Treatment Guidelines for Migraines

A search of the guideline clearinghouse resulted in one clinical guideline on the treatment of migraine headaches, from the European Federation of Neurological Societies. (Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS, European Federation of Neurological Societies. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. European Journal of Neurology 2009 Sep;16(9):968-81.) It is included as an attachment.

Appendix 1

Search Terms

"Migraine Disorders"[Mesh]

Covers these Entry Terms:
* Disorder, Migraine
* Disorders, Migraine
* Migraine Disorder
* Migraine
* Migraines
* Migraine Headache
* Headache, Migraine
* Headaches, Migraine
* Migraine Headaches
* Acute Confusional Migraine
* Acute Confusional Migraines
* Migraine, Acute Confusional
* Migraines, Acute Confusional
* Status Migrainosus
* Hemicrania Migraine
* Hemicrania Migraines
* Migraine, Hemicrania
* Migraines, Hemicrania
* Migraine Variant
* Migraine Variants
* Variant, Migraine
* Variants, Migraine
* Sick Headache
* Headache, Sick
* Headaches, Sick
* Sick Headaches
* Abdominal Migraine
* Abdominal Migraines
* Migraine, Abdominal
* Migraines, Abdominal
* Cervical Migraine Syndrome
* Cervical Migraine Syndromes
* Migraine Syndrome, Cervical
* Migraine Syndromes, Cervical
* Migraine with Aura
* Migraine without Aura
* Ophthalmoplegic Migraine

ANDED with:

((("Marijuana Abuse"[Mesh]) OR "Cannabis"[Mesh]) OR Tetrahydrocannabinol"[Mesh])\cannabinoids

Appendix 2

Description of Study Types

BOX 1 *Taxonomy of study designs to assess the effectiveness of an intervention*

Experimental designs
A study in which the investigator has control over at least some study conditions, particularly decisions concerning the allocation of participants to different intervention groups.

1. ***Randomised controlled trial***
   Participants are randomly allocated to intervention or control groups and followed up over time to assess any differences in outcome rates. Randomisation with allocation concealment ensures that on average known and unknown determinants of outcome are evenly distributed between groups.
2. ***Quasi-randomised trial***
   Participants are allocated to intervention or control groups by the investigator, but the method of allocation falls short of genuine randomisation and allocation concealment (e.g. allocated by date of birth, hospital record number, etc.)
3. ***Non-randomised trial/quasi-experimental study***
   The investigator has control over the allocation of participants to groups, but does not attempt randomisation (e.g. patient or physician preference). Differs from a 'cohort study' in that the intention is experimental rather than observational.

Observational designs
A study in which natural variation in interventions (or exposure) among study participants is investigated to explore the effect of the interventions (or exposure) on health outcomes.

4. ***Controlled before-and-after study***
   A follow-up study of participants who have received an intervention and those who have not, measuring the outcome variable both at baseline and after the intervention period, comparing either final values if the groups are comparable at baseline, or change scores. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.
5. ***Concurrent cohort study***
   A follow-up study that compares outcomes between participants who have received an intervention and those who have not. Participants are studied during the same (concurrent) period either prospectively or, more commonly, retrospectively.
6. ***Historical cohort study***
   A variation on the traditional cohort study where the outcome from a new intervention is established for participants studied in one period and compared with those who did not receive the intervention in a previous period, i.e. participants are not studied concurrently.
7. ***Case–control study***
   Participants with and without a given outcome are identified (cases and controls respectively) and exposure to a given intervention(s) between the two groups compared.
8. ***Before-and-after study***
   Comparison of outcomes from study participants before and after an intervention is introduced. The before and after measurements may be made in the same participants, or in different samples. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.
9. ***Cross-sectional study***
   Examination of the relationship between disease and other variables of interest as they exist in a defined population at one particular time point.
10. ***Case series***
    Description of a number of cases of an intervention and outcome (no comparison with a control group).

Appendix 3

GRADE Method to Assess Overall Quality of the Evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or
	Very low	Imprecision -1 Serious -2 Very serious	+1 Would suggest a spurious effect when results show no effect
		Publication bias -1 Likely -2 Very likely	

Appendix 4

List of Articles Reviewed

1. Noyes R, Baram D. Cannibis Analgesia. Comprehensive Psychiatry 1974;15(6):531-535.
2. Robbins MS, Tarshish T, Soloman S, Grosberg BM. Cluster attacks responsive to recreational cannabis and dronabinol. Headache 2009; June:914-916
3. El-Mallakh RS, Kansler HR, Kamanitz JR. Headaches and psychoactive substance use. Headache 1991;31:584-587
4. El-Mallakh RS. Marijuana and migraine. Headache 1987;27:442-443.
5. El-Mallakh RS. Migraine headaches and drug abuse. Southern Medical Journal 1989;82:805.
6. Trittibach P, Frueh BE, Goldblum D. Bilateral angle-closure glaucoma after combined consumption of ecstasy and marijuana. American Journal of Emergency Medicine 2005;23:813-814.
7. Bagshaw SM. Medical efficacy of cannabinoids and marijuana: a comprehensive review of the literature. Journal of Palliative Care 2002;18:111-122.
8. Russo E. Cannibis for migraine treatment: the once and future prescription? An historical and scientific review. Pain 1998;76:3-8.
9. Taylor FR. Nutraceuticals and headache: the biological basis. Headache 2011;51: 484-501.
10. Volfe Z, Dvilansky A, Nathan I. Cannibinoids block release of serotonin from platelets induced by plasma from migraine patients. International Journal of Clinical Pharmacology Research 1985;4:243-246.
11. Juhasz G, Lazary J, Chase D, Pegg E, et al. Variations in the cannabinoid receptor 1 gene predispose to migraine. Neuroscience Letters 2009;461:116-120.
12. Napchan U, Buse DC, Loder W. The use of marijuana or synthetic cannabinoids for the treatment of headache. Headache 2011; 51:502-505.
13. Evans RW, Ramadan NM. Are cannabis based chemicals helpful in headache? Headache 2004;44:726-727.
14. Cupini LM, Costa C, Sarchielli P Mari M, et al. Degradation of endocannabinoids in chronic migraine and medication overuse headache. Neurobiology of disease 2008;30: 186-189.
15. Rossi C, Pini LA, Cupini ML, Calabresi P. Endocannabinoids in platelets of chronic migraine patients and medication overuse headache patients: relation with serotonin levels. European Journal of Clinical Pharmacology 2008;64:1-8.
16. Russo EB. Clinical endocannabinoid deficiency: can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment resistant conditions? Neuroendocrinology letters 2004;25:31-39.
17. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. California Medical Association Journal 2008;178(13):1669-78.
18. Cupini LM, Bari M, Argiro G, et al. Biochemical changes in endocannabinoid system are expressed in platelets of female but not male migraineurs. Cephalalgia 2005;26:277-281.
19. Sarchielli P, Pini LA, Coppola F, et al. Endocannabinoids in chronic migraine: CSF findings suggest a system failure. Neuropsychopharmacology 2007;32:1384-1390.
20. Robson B. Therapeutic aspects of cannabis and cannabinoinds. British Journal of Psychiatry 2001;178:107-115.

European Journal of Neurology 2009, **16:** 968–981 doi:10.1111/j.1468-1331.2009.02748.x

CME ARTICLE

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

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Keywords:
evidence-based medicine, migraine, prophylaxis, triptans

Received 25 March 2009
Accepted 3 June 2009

Background: Migraine is one of the most frequent disabling neurological conditions with a major impact on the patients' quality of life.
Objectives: To give evidence-based or expert recommendations for the different drug treatment procedures in the particular migraine syndromes based on a literature search and the consensus of an expert panel.
Methods: All available medical reference systems were screened for the range of clinical studies on migraine with and without aura and on migraine-like syndromes. The findings in these studies were evaluated according to the recommendations of the European Federation of Neurological Societies (EFNS) resulting in level A, B, or C recommendations and good practice points.
Recommendations: For the acute treatment of migraine attacks, oral non-steroidal antiinflammatory drug (NSAID) and triptans are recommended. The administration should follow the concept of stratified treatment. Before intake of NSAID and triptans, oral metoclopramide or domperidone is recommended. In very severe attacks, intravenous acetylsalicylic acid or subcutaneous sumatriptan are drugs of first choice. Status migrainosus can be treated by cortoicosteroids, although this is not universally held to be helpful, or dihydroergotamine. For the prophylaxis of migraine, betablockers (propranolol and metoprolol) flunarizine, valproic acid, and topiramate are drugs of first choice. Drugs of second choice for migraine prophylaxis include amitriptyline, naproxen, petasites, and bisoprolol.

Objectives

These guidelines aim to give evidence-based recommendations for the drug treatment of migraine attacks and of migraine prophylaxis. The non-drug management (e.g. behavioral therapy) will not be included. The definitions follow the diagnostic criteria of the International Headache Society (IHS).

Background

The second edition of the classification of the IHS provided a new subclassification of different migraine syndromes [1]. The basic criteria for migraine attacks remained nearly unchanged. The different migraine syndromes with specific aura features, however, were classified in a new system. The diagnostic criteria for all migraine syndromes have been published on the homepage of the IHS (http://www.i-h-s.org).

The recommendations are based on the scientific evidence from clinical trials and on the expert consensus by the respective task force of the EFNS. The legal aspects of drug prescription and drug availability in the different European countries will not be considered. The definitions of the recommendation levels follow the EFNS criteria [2].

Search strategy

A literature search was performed using the reference databases MedLine, Science Citation Index, and the Cochrane Library; the key words used were 'migraine' and 'aura' (last search in January 2009). All papers published in English, German, or French were

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This is a Continuing Medical Education article, and can be found with corresponding questions on the internet at http://www.efns.org/content.php?pid=132. Certificates for correctly answering the questions will be issued by the EFNS

considered when they described a controlled trial or a case series on the treatment of at least five patients. In addition, a review book [3] and the German treatment recommendations for migraine [4] were considered.

Method for reaching consensus

All authors performed an independent literature search. The first draft of the manuscript was written by the chairman of the task force. All other members of the task force read the first draft and discussed changes by email. A second draft was then written by the chairman and again discussed by email. All recommendations had to be agreed to by all members of the task force unanimously.

Drug treatment of migraine attacks

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

- pain free after 2 h
- improvement of headache from moderate or severe to mild or none after 2 h [6]
- consistent efficacy in two of three attacks
- no headache recurrence and no further drug intake within 24 h after successful treatment (so-called sustained pain relief or pain free).

Analgesics

Drugs of first choice for mild or moderate migraine attacks are analgesics. Evidence of efficacy in migraine treatment in at least one placebo-controlled study has been obtained for acetylsalicylic acid (ASA) up to 1000 mg [7–10], ibuprofen 200–800 mg [8,10–12], diclofenac 50–100 mg [13–15], phenazon 1000 mg [16], metamizol 1000 mg [17], tolfenamic acid 200 mg [18], and paracetamol 1000 mg [19]. In addition, the fixed combination of ASA, paracetamol, and caffeine is effective in acute migraine treatment and is also more effective than the single substances or combinations without caffeine [20–22]. Intravenous ASA was more effective than subcutaneous ergotamine [23]; intravenous metamizol was superior to placebo in migraine without and with aura [24]. Lysine-ASA in combination with metoclopramide had comparable efficacy as sumatriptan [9]. Effervescent ASA 1000 mg is probably as effective as ibuprofen 400 mg and as sumatriptan 50 mg [10,25,26].

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

Table 1 Analgesics with evidence of efficacy in at least one study on the acute treatment of migraine, the level of recommendation also considers side effects and consistency of the studies

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

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

Antiemetics

The use of antiemetics in acute migraine attacks is recommended to treat nausea and potential emesis and because it is assumed that these drugs improve the resorption af analgesics [31–33]. However, there are no prospective, placebo-controlled randomized trials to prove this assertion. Metoclopramide also has a genuine mild analgesic efficacy when given orally [34] and a higher efficacy when given intravenously [35]. There is no evidence that the fixed combination of an antiemetic with an analgesic is more effective than the analgesic alone. Metoclopramide 20 mg is recommended for adults and adolescents, in children domperidon 10 mg should be used because of the possible extrapyramidal side effects of metoclopramide. Table 2 presents the antiemetics recommended for the use in migraine attacks.

Ergot alkaloids

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

Table 2 Antiemetics recommended for the acute treatment of migraine attacks

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

acute migraine treatment [36]. In comparative trials, triptans showed better efficacy than ergot alkaloids [37–40]. The advantage of ergot alkaloids is a lower recurrence rate in some patients. Therefore, these substances should be restricted to patients with very long migraine attacks or with regular recurrence. The only compounds with sufficient evidence of efficacy are ergotamine tartrate and dihydroergotamine 2 mg (oral and suppositories, respectively). Ergot alkaloids can induce drug overuse headache very fast and in very low doses [41]. Therefore, their use must be limited to 10 days per month. Major side effects are nausea, vomiting, paraesthesia, and ergotism. Contraindications are cardiovascular and cerebrovascular diseases, Raynaud's disease, arterial hypertension, renal failure, and pregnancy and lactation.

Triptans (5-$HT_{1B/1D}$-agonists)

The 5-$HT_{1B/1D}$ receptor agonists sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan (order in the year of marketing), so-called triptans, are migraine medications and should not be applied in other headache disorders except cluster headache. The different triptans for migraine therapy are presented in Table 3. The efficacy of all triptans has been proven in large placebo-controlled trials of which metaanalyses have been published [42,43]. For sumatriptan [9,44] and zolmitriptan [45] comparative studies with ASA and metoclopramide exist. In these comparative studies, the triptans were not or only a little more effective than ASA. In about 60% of nonresponders to NSAID, triptans are effective [46]. Sumatriptan 6 mg subcutaneously is more effective than intravenous ASA 1000 mg s.c. but has more side effects [47]. Triptans can be effective at any time during a migraine attack. However, there is evidence that the earlier triptans are taken the better their efficacy is [48–52]. It is still debated whether triptans are less efficacious or even may fail when taken after the onset of allodynia during a migraine attack [49,53], with randomized controlled trials not supporting a difference for allodynic patients [52,54]. A strategy of strictly early intake can, however, lead to frequent drug treatment in certain patients. The use of triptans is restricted to maximum 9 days per month by the IHS criteria; in epidemiological studies, the risk for chronification became significant at 12 days per month of triptan intake [55]. Otherwise, the induction of a drug overuse headache is possible for all triptans [41,56,57].

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

Table 3 Different triptans for the treatment of acute migraine attacks (order in the time of marketing), not all doses or application forms are available in all European countries

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

General side effects for all triptans: chest symptoms, nausea, distal paraesthesia, fatigue.
General contraindications: arterial hypertension (untreated), coronary heart disease, cerebrovascular disease, Raynaud's disease, pregnancy and lactation, age under 18 (except sumatriptan nasal spray) and age above 65, severe liver or kidney failure.

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

After application of sumatriptan, severe adverse events have been reported such as myocardial infarction, cardiac arrhythmias, and stroke. The incidence of these events was about 1 in 1 000 000 [61,62]. Reports on severe adverse events also exist for other triptans and for ergotamine tratrate. However, all of the reported patients had contraindications against triptans or the diagnosis of migraine was wrong. In population-based studies, no increased risk of vascular events could be detected for triptan users as compared with a healthy population [63,64]. Contraindications for the use of triptans are untreated arterial hypertension, coronary heart disease, Raynaud's disease, history of ischaemic stroke, pregnancy, lactation, and severe liver or renal failure.

Owing to safety aspects, triptans should not be taken during the aura although no specific severe adverse events have been reported. The best time for application is the very onset of headache. Furthermore, triptans are not efficacious when taken during the aura phase before headache has developed [65,66].

Comparison of triptans

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

Subcutaneous sumatriptan has the fastest onset of efficacy of about 10 min [69]. Oral rizatriptan and eletriptan need about 30 min, oral sumatriptan, almotriptan, and zolmitriptan need about 45–60 min [42], and naratriptan and frovatriptan need up to 4 h for the onset of efficacy [70,71]. Zolmitriptan nasal spray has a shorter duration until efficacy than oral zolmitriptan [72]. There is no evidence that different oral formulations such as rapidly disolving tablets, wafer forms, or rapid release forms [73] act earlier than others.

Pain relief after 2 h as the most important efficacy parameter is best in subcutaneous sumatripan with up to 80% responders [74]. Sumatriptan nasal spray has the same efficacy as oral sumatriptan 50 mg or 100 mg. 25 mg oral sumatriptan is less effective than the higher doses but has less side effects [42]. Sumatriptan suppositories are about as effective as oral sumatriptan 50 or 100 mg and should be given to patients with vomiting [75–77]. Naratriptan and frovatriptan (2.5 mg) are less effective than sumatriptan 50 or 100 mg but have less side effects. The duration until the onset of efficacy is longer in these two triptans as compared with all others. Rizatriptan 10 mg is a little more effective than sumatriptan 100 mg. Oral zolmitriptan 2.5 or 5 mg, almotriptan 12.5 mg and eletriptan 40 mg show a similar efficacy and similar side effects [78–80]. Eletriptan 80 mg is the most effective oral triptan but also has the most side effects [42].

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

Other drugs

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

Migraine prophylaxis

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

prophylactic drug treatment of migraine should be considered and discussed with the patient when:

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

A migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by at least 50% within 3 months. For therapy evaluation, a migraine diary is extremely useful. In the following paragraphs, the placebo-controlled trials in migraine prophylaxis are summarized. The recommended drugs of first choice, according to the consensus of the Task Force, are given in Table 4. Tables 5 and 6 present drugs recommended as second or third choice when the drugs of Table 4 are not effective, contraindicated, or when comorbidity of the patients suggests the respective drug of second or third choice.

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

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

Table 5 Drugs of second choice for migraine prophylaxis (evidence of efficacy, but less effective or more side effects than drugs of Table 6)

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

Table 6 Drugs of third choice for migraine prophylaxis (only probable efficacy)

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

Betablockers

Betablockers are clearly effective in migraine prophylaxis and very well studied in a lot of placebo-controlled, randomized trials. The best evidence has been obtained for metoprolol [87–91] and propranolol [87,88,92–98]. Also, bisoprolol [91,99], timolol [93,100], and atenolol [101] might be effective but evidence is less convincing compared with propranolol and metoprolol.

Calcium channel blockers

The 'non-specific' calcium channel blocker flunarizine has been shown to be effective in migraine prophylaxis in several studies [90,98,102–111]. The dose is 5–10 mg, female patients seem to benefit from lower doses than male patients [112]. Another 'non-specific' calcium channel blocker, cyclandelate, has also been studied but with conflicting results [107,113–116]. As the better designed studies were negative, cyclandelate cannot be recommended.

Antiepileptic drugs

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

NSAID

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

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

Antidepressants

The only antidepressant with consistent efficacy in migraine prophylaxis is amitriptyline in doses between 10 and 150 mg. It has been studied in four older placebo-controlled trials, all with positive results [138–141]. Since the studies with amitriptyline were small and showed central side effects, this drug is recommended only with level B. For femoxetine, two small positive placebo-controlled trials have been published [142,143]. Fluoxetine in doses between 10 and 40 mg was effective in three [144–146] and not effective in one placebo-controlled trial [147]. Venlafaxine extended release (dose 75–150 mg) has shown efficacy in one placebo-controlled [148] and two open trials [149,150] and can therefore be recommended as a second choice antidepressant in migraine prophylaxis.

Miscellaneous drugs

The antihypertensive drugs lisinopril [151] and candesartan [152] showed efficay in migraine prophylaxis in one placebo-controlled trial each. However, these results have to be confirmed before the drugs can definitely be recommended. The same is true for high-dose riboflavin (400 mg) and coenzyme Q10 which have shown efficacy in one placebo-controlled trial each [153,154]. For oral magnesium, conflicting studies (one positive, one negative) have been published [155,156]. A herbal drug with evidence of efficacy is butterbur root extract (Petasites hybridus). This has been shown for a remedy with 75 mg in two placebo-controlled trials [157,158]. Another herbal remedy, feverfew (Tanacetum parthenium), has been studied in several placebo-controlled trials with conflicting results. Also, the two most recent and best designed studies showed a negative [159] and a positive [160] result; a Cochrane review resulted in a negative meta-analysis of all controlled studies on tanacetum [161].

In older studies, clonidine, pizotifen and methysergide have shown efficacy in migraine prophylaxis. The more recent and better designed studies on clonidine, however, did not confirm any efficacy (for review see 162). Methysergide, which is clearly effective, can be recommended for short-term use only (maximum 6 months per treatment period) because of potentially severe side effects [163]. Pizotifen is not generally recommended because the efficacy is not better than in the substances mentioned above and the side effects (dizziness, weight gain) are classified as very severe by the task force and limit the use too much [164]. Some experts have found it useful in childhood migraine. Ergot alkaloids have also been used in migraine prophylaxis. The evidence for dihydroergotamine is weak since several studies reported both positive and negative results (for review see 162).

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

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

Specific situations

Emergency situation

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

Menstrual migraine

Different drug regimes have been studied to treat menstrual migraine. On the one hand, acute migraine treatment with triptans has been studied showing the same efficacy of triptans in menstrual migraine attacks as compared with non-menstrual migraine attacks. On the other hand, short-term prophylaxis of menstrual migraine has been studied.

Naproxen sodium (550 mg twice daily) has been shown to reduce pain including headache in the premenstrual syndrome [182]. Its specific effects on menstrual migraine (550 mg twice daily) have also been evaluated [183–185]. In one trial [183], patients reported fewer and less severe headaches during the week before menstruation than patients treated with placebo. In the other two placebo-controlled trials, naproxen sodium, given during 1 week before and 1 week after the start of menstruation, resulted in fewer perimenstrual headaches; in one study, severity was not reduced [185], but in the other both severity and analgesic requirements were decreased [184]. Even triptans have been used as short-term prophylaxis of menstrual migraine. For naratriptan (2×1 mg per day for 5 days starting 2 days prior to the expected onset of menses) and for frovatriptan (2×2.5 mg given for 6 days perimenstrually), superiority over placebo has been shown [186–188]; however, it can happen that the menstrual migraine attack is delayed into another time of the menstrual cycle [188].

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

Migraine in pregnancy

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

Triptans and ergot alkaloids are contraindicated. For sumatriptan, a large pregnancy register has been established with no reports of any adverse events or complications during pregnancy which might be attributed to sumatriptan [194–198]. Similar results have been published for rizatriptan [199]. Based on the published data, administration of triptans in the first trimester of pregnancy is recommended by expert consensus if the child is more at risk by severe attacks with vomiting than by the potential impact of the triptan. For migraine prophylaxis, only magnesium and metoprolol are recommended during pregnancy (level B recommendation) [200].

Migraine in children and adolescents

The only analgesics with evidence of efficacy for the acute migraine treatment in childhood and adolescents are ibuprofen 10 mg per kg body weight and paracetamol 15 mg per kg body weight [201]. The only antiemetic licensed for the use in children up to 12 years is domperidon. Sumatriptan nasal spray 5–20 mg is the only triptan with positive placebo-controlled trials in the acute migraine treatment of children and adolescents [202–204], the recommended dose for adolescents from the age of 12 is 10 mg. Oral triptans did not show significant efficacy in the first placebo-controlled childhood and adolescents studies [205–207]. This was in particular because of high placebo responses of about 50% in this age group. In *post hoc* analyses, however, 2.5–5 mg zolmitriptan were effective in adolescents from the age of 12 to 17 [208,209]. In recent trials, oral zolmitriptan 2.5 mg [210], nasal zolmitriptan 5 mg [211], and oral rizatriptan 5–10 mg [212] have been superior to placebo in acute migraein treatment. Ergotamine should not be used in children and adolescents. Also children and adolescents can develop drug-induced headache due to analgesic, ergotamine, or triptan overuse.

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

Need of update

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

Conflicts of interest

The present guidelines were developed without external financial support. The authors report the following financial supports: Stefan Evers: Salary by the University of Münster; honoraries and research grants by Addex Pharm, AGA Medical, Allergan, Almirall, AstraZeneca, Berlin Chemie, Boehringer, CoLucid, Desitin, Eisai, GlaxoSmithKline, Ipsen Pharma, Janssen Cilag, MSD, Novartis, Pfizer, Pharm Allergan, Pierre Fabre, Reckitt-Benckiser, UCB. Judit Áfra: Salary by the Hungarian Ministry of Health. Achim Frese: Private Praxis; honorary by Berlin Chemie. Peter

J. Goadsby: Salary from University of California, San Francisco; honorarium or research grants in 2008 from Almirall, Boston Scientific, Colucid, Eli-Lilly, GSK, J&J, MAP Pharmaceuticals MSD, Medtronic and Neuralieve. Mattias Linde: Salary by the Swedish government; honoraries by AstraZeneca, GlaxoSmithKline, MSD, Nycomed, Pfizer. Arne May: Salary by the University Hospital of Hamburg; honoraries by Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, GlaxoSmithKline, Janssen Cilag, MSD, Pfizer. Peter S. Sándor: Salary by the University Hospital of Zurich; honoraries by AstraZeneca, GlaxoSmithKline, Janssen Cilag, Pfizer, Pharm Allergan.

References

1. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 2nd edition. *Cephalalgia* 2004; **24**(Suppl 1)**:** 1–160.
2. Brainin M, Barnes M, Baron JC, *et al*. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *Eur J Neurol* 2004; **11:** 577–581.
3. Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA, eds. *The Headaches*, 3rd edn. Philadelphia, PA: Lippincott, Williams & Wilkins, 2006: 553–566.
4. Evers S, May A, Fritsche G, *et al*. Akuttherapie und Prophylaxe der Migräne. Leitlinie der Deutschen Migräne- und Kopfschmerzgesellschaft und der Deutschen Gesellschaft für Neurologie. *Nervenheilkunde* 2008; **27:** 933–949.
5. Tfelt-Hansen P, Block G, Dahlöf C, *et al*. Guidelines for controlled trials of drugs in migraine: second edition. *Cephalalgia* 2000; **20:** 765–786.
6. Pilgrim AJ. The methods used in clinical trials of sumatriptan in migraine. *Headache* 1993; **33:** 280–293.
7. Chabriat H, Joire JE, Danchot J, Grippon P, Bousser MG. Combined oral lysine acetylsalicylate and metoclopramide in the acute treatment of migraine: a multicentre double-blind placebo- controlled study. *Cephalalgia* 1994; **14:** 297–300.
8. Nebe J, Heier M, Diener HC. Low-dose ibuprofen in self-medication of mild to moderate headache: a comparison with acetylsalicylic acid and placebo. *Cephalalgia* 1995; **15:** 531–535.
9. Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaert RG, Schoenen J, Chazot G. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; **346:** 923–926.
10. Diener HC, Bussone G, de Liano H, *et al*. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalalgia* 2004; **24:** 947–954.
11. Havanka-Kanniainen H. Treatment of acute migraine attack: ibuprofen and placebo compared. *Headache* 1989; **29:** 507–509.
12. Kloster R, Nestvold K, Vilming ST. A double-blind study of ibuprofen versus placebo in the treatment of acute migraine attacks. *Cephalalgia* 1992; **12:** 169–171.
13. Karachalios GN, Fotiadou A, Chrisikos N, Karabetsos A, Kehagioglou K. Treatment of acute migraine attack with diclofenac sodium: a double-blind study. *Headache* 1992; **32:** 98–100.
14. Dahlöf C, Björkman R. Diclofenac-K (50 and 100 mg) and placebo in the acute treatment of migraine. *Cephalalgia* 1993; **13:** 117–123.
15. The Diclofenac-K/Sumatriptan Migraine Study Group. Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal antiinflammatory drug, diclofenac-potassium, in comparison to oral sumatriptan and placebo. *Cephalalgia* 1999; **19:** 232–240.
16. Göbel H, Heinze A, Niederberger U, Witt T, Zumbroich V. Efficacy of phenazone in the treatment of acute migraine attacks: a double-blind, placebo-controlled, randomized study. *Cephalalgia* 2004; **24:** 888–893.
17. Tulunay FC, Ergun H, Gulmez SE, *et al*. The efficacy and safety of dipyrone (Novalgin) tablets in the treatment of acute migraine attacks: a double-blind, cross-over, randomized, placebo-controlled, multi-center study. *Funct Neurol* 2004; **19:** 197–202.
18. Myllyla VV, Havanka H, Herrala L, *et al*. Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: comparable effect in a double-blind, randomized, controlled, parallel-group study. *Headache* 1998; **38:** 201–207.
19. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med* 2000; **160:** 3486–3492.
20. Lipton RB, Stewart WF, Ryan RE, Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain – three double-blind, randomized, placebo-controlled trials. *Arch Neurol* 1998; **55:** 210–217.
21. Diener H, Pfaffenrath V, Pageler L. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multi-centre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 2005; **25:** 776–787.
22. Goldstein J, Silberstein SD, Saper JR, Ryan RE Jr, Lipton RB. Acetaminophen, aspirin, and caffeine in combination versus ibuprofen for acute migraine: results from a multicenter, double-blind, randomized, parallel-group, single-dose, placebo-controlled study. *Headache* 2006; **46:** 444–453.
23. Limmroth V, May A, Diener HC. Lysine-acetylsalicylic acid in acute migraine attacks. *Eur Neurol* 1999; **41:** 88–93.
24. Bigal ME, Bordini CA, Tepper SJ, Speciali JG. Intravenous dipyrone in the acute treatment of migraine without aura and migraine with aura: a randomized, double blind, placebo controlled study. *Headache* 2002; **42:** 862–871.
25. Diener HC, Eikermann A, Gessner U, *et al*. Efficacy of 1000 mg effervescent acetylsalicylic acid and sumatriptan in treating associated migraine symptoms. *Eur Neurol* 2004; **52:** 50–56.
26. Lampl C, Voelker M, Diener HC. Efficacy and safety of 1000 mg effervescent aspirin: individual patient data meta-analysis of three trials in migraine headache and

migraine accompanying symptoms. *J Neurol* 2007; **254:** 705–712.
27. Kudrow D, Thomas HM, Ruoff G, *et al*. Valdecoxib for treatment of a single, acute, moderate to severe migraine headache. *Headache* 2005; **45:** 1151–1162.
28. Misra UK, Jose M, Kalita J. Rofecoxib versus ibuprofen for acute treatment of migraine: a randomised placebo controlled trial. *Postgrad Med J* 2004; **80:** 720–723.
29. Saper J, Dahlöf C, So Y, *et al*. Rofecoxib in the acute treatment of migraine: a randomized controlled clinical trial. *Headache* 2006; **46:** 264–275.
30. Silberstein S, Tepper S, Brandes J, *et al*. Randomised placebo-controlled trial of rofecoxib in the acute treatment of migraine. *Neurology* 2004; **62:** 1552–1557.
31. Ross-Lee LM, Eadie MJ, Heazlewood V, Bochner F, Tyrer JH. Aspirin pharmacokinetics in migraine. The effect of metoclopramide. *Eur J Clin Pharmacol* 1983; **24:** 777–785.
32. Waelkens J. Dopamine blockade with domperidone: bridge between prophylactic and abortive treatment of migraine? A dose-finding study. *Cephalalgia* 1984; **4:** 85–90.
33. Schulman E, Dermott K. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache* 2003; **43:** 729–733.
34. Ellis GL, Delaney J, DeHart DA, Owens A. The efficacy of metoclopramide in the treatment of migraine headache. *Ann Emerg Med* 1993; **22:** 191–195.
35. Friedman BW, Corbo J, Lipton RB, *et al*. A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. *Neurology* 2005; **64:** 463–468.
36. Tfelt-Hansen P, Saxena PR, Dahlöf C, *et al*. Ergotamine in the acute treatment of migraine. A review and European consensus. *Brain* 2000; **123:** 9–18.
37. The Multinational Oral Sumatriptan Cafergot Comparative Study Group. A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine. *Eur Neurol* 1991; **31:** 314–322.
38. Christie S, Göbel H, Mateos V, *et al*. Crossover comparison of efficacy and preference for rizatriptan 10 mg versus ergotamine/caffeine in migraine. *Eur Neurol* 2003; **49:** 20–29.
39. Diener HC, Reches A, Pascual J, *et al*. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison. *Eur Neurol* 2002; **47:** 99–107.
40. Lainez MJ, Galvan J, Heras J, Vila C. Crossover, double-blind clinical trial comparing almotriptan and ergotamine plus caffeine for acute migraine therapy. *Eur J Neurol* 2007; **14:** 269–275.
41. Evers S, Gralow I, Bauer B, *et al*. Sumatriptan and ergotamine overuse and drug-induced headache: a clinicoepidmiologic study. *Clin Neuropharmacol* 1999; **22:** 201–206.
42. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; **358:** 1668–1675.
43. Goadsby PB, Lipton RB, Ferrai MD. Migraine: current understanding and management. *N Engl J Med* 2002; **346:** 257–270.
44. The Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. A study to compare oral sumatriptan with oral aspirin plus oral metoclopramide in the acute treatment of migraine. *Eur Neurol* 1992; **32:** 177–184.
45. Geraud G, Compagnon A, Rossi A. Zolmitriptan versus a combination of acetylsalicylic acid and metoclopramide in the acute oral treatment of migraine: a double-blind, randomised, three-attack study. *Eur Neurol* 2002; **47:** 88–98.
46. Diamond M, Hettiarachchi J, Hilliard B, Sands G, Nett R. Effectiveness of eletriptan in acute migraine: primary care for Excedrin nonresponders. *Headache* 2004; **44:** 209–216.
47. Diener HC, for the ASASUMAMIG Study Group. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. *Cephalalgia* 1999; **19:** 581–588.
48. Pascual J, Cabarrocas X. Within-patient early versus delayed treatment of migraine attacks with almotriptan: the sooner the better. *Headache* 2002; **42:** 28–31.
49. Burstein R, Collins B, Jakubowski M. Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. *Ann Neurol* 2004; **55:** 19–26.
50. Dowson A, Massiou H, Lainez J, Cabarrocas X. Almotriptan improves response rates when treatment is within 1 hour of migraine onset. *Headache* 2004; **44:** 318–322.
51. Cady R, Martin V, Mauskop A, *et al*. Efficacy of rizatriptan 10 mg administered early in a migraine attack. *Headache* 2006; **46:** 914–924.
52. Goadsby PJ, Zanchin G, Geraud G, *et al*. Early versus non-early intervention in acute migraine – 'Act when Mild – AwM'. A double-blind placebo-controlled trial of almotriptan. *Cephalalgia* 2008; **28:** 383–391.
53. Linde M, Mellberg A, Dahlöf C. Subcutaneous sumatriptan provides symptomatic relief at any pain intensity or time during the migraine attack. *Cephalalgia* 2006; **26:** 113–121.
54. Cady R, Martin V, Mauskop A, *et al*. Symptoms of cutaneous sensitivity pre-treatment and post-treatment: results from the rizatriptan TAME studies. *Cephalalgia* 2007; **27:** 1055–1060.
55. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008; **48:** 1157–1168.
56. Limmroth V, Kazarawa S, Fritsche G, Diener HC. Headache after frequent use of new serotonin agonists zolmitriptan and naratriptan. *Lancet* 1999; **353:** 378.
57. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001; **57:** 1694–1698.
58. Ferrari MD. How to assess and compare drugs in the management of migraine: success rates in terms of response and recurrence. *Cephalalgia* 1999; **19**(Suppl 23)**:** 2–8.
59. Ferrari MD, James MH, Bates D, *et al*. Oral sumatriptan: effect of a second dose, and incidence and treatment of headache recurrences. *Cephalalgia* 1994; **14:** 330–338.

60. Brandes JL, Kudrow D, Stark SR, *et al*. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007; **297:** 1443–1454.
61. O'Quinn S, Davis RL, Guttermann DL, *et al*. Prospective large-scale study of the tolerability of subcutaneous sumatriptan injection for the acute treatment of migraine. *Cephalalgia* 1999; **19:** 223–231.
62. Welch KMA, Mathew NT, Stone P, Rosamond W, Saiers J, Gutterman D. Tolerability of sumatriptan: clinical trials and post-marketing experience. *Cephalalgia* 2000; **20:** 687–695.
63. Velentgas P, Cole JA, Mo J, Sikes CR, Walker AM. Severe vascular events in migraine patients. *Headache* 2004; **44:** 642–651.
64. Hall G, Brown M, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; **62:** 563–568.
65. Bates D, Ashford E, Dawson R, *et al*. Subcutaneous sumatriptan during the migraine aura. *Neurology* 1994; **44:** 1587–1592.
66. Olesen J, Diener HC, Schoenen J, Hettiarachchi J. No effect of eletriptan administration during the aura phase of migraine. *Eur J Neurol* 2004; **11:** 671–677.
67. Diener HC, Gendolla A, Gebert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. *Headache* 2005; **45:** 874–882.
68. Tfelt-Hansen P. Sumatriptan for the treatment of migraine attacks – a review of controlled clinical trials. *Cephalalgia* 1993; **13:** 238–244.
69. Stark S, Spierings EL, McNeal S, Putnam GP, Bolden-Watson CP, O'Quinn S. Naratriptan efficacy in migraineurs who respond poorly to oral sumatriptan. *Headache* 2000; **40:** 513–520.
70. Goadsby PJ. Role of naratriptan in clinical practice. *Cephalalgia* 1997; **17:** 472–473.
71. Markus F, Mikko K. Frovatriptan review. *Expert Opin Pharmacother* 2007; **8:** 3029–3033.
72. Charlesworth BR, Dowson AJ, Purdy A, Becker WJ, Boes-Hansen S, Färkkilä M. Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs* 2003; **17:** 653–667.
73. Dahlöf C, Cady R, Poole AC. Speed of onset and efficacy of sumatriptan fast-disintegrating/rapid release tablets: results of two replicate randomised, placebo-controlled studies. *Headache Care* 2004; **1:** 277–280.
74. The Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. *N Engl J Med* 1991; **325:** 316–321.
75. Becker WJ, on behalf of the Study Group. A placebo-controlled, dose-defining study of sumatriptan nasal spray in the acute treatment of migraine. *Cephalalgia* 1995; **15**(Suppl 14)**:** 271–276.
76. Ryan R, Elkind A, Baker CC, Mullican W, DeBussey S, Asgharnejad M. Sumatriptan nasal spray for the acute treatment of migraine. *Neurology* 1997; **49:** 1225–1230.
77. Tepper SJ, Cochran A, Hobbs S, Woessner M. Sumatriptan suppositories for the acute treatment of migraine. *Int J Clin Pract* 1998; **52:** 31–35.
78. Goldstein J, Ryan R, Jiang K, *et al*. Crossover comparison of rizatriptan 5 mg and 10 mg versus sumatriptan 25 and 50 mg in migraine. *Headache* 1998; **38:** 737–747.
79. Tfelt-Hansen P, Teall J, Rodriguez F, *et al*. Oral rizatriptan versus oral sumatriptan: a direct comparative study in the acute treatment of migraine. *Headache* 1998; **38:** 748–755.
80. Tfelt-Hansen P, Ryan RE. Oral therapy for migraine: comparisons between rizatriptan and sumatriptan. A review of four randomized, double-blind clinical trials. *Neurology* 2000; **55**(Suppl 2)**:** S19–S24.
81. Geraud G, Keywood C, Senard JM. Migraine headache recurrence: relationship to clinical, pharmacological, and pharmacokinetic properties of triptans. *Headache* 2003; **43:** 376–388.
82. Bigal M, Sheftell F, Tepper S, Tepper D, Ho TW, Rapoport A. A randomized double-blind study comparing rizatriptan, dexamethasone, and the combination of both in the acute treatment of menstrually related migraine. *Headache* 2008; **48:** 1286–1293.
83. Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. *Headache* 2001; **41:** 976–980.
84. Leniger T, Pageler L, Stude P, Diener HC, Limmroth V. Comparison of intravenous valproate with intravenous lysine-acetylsalicylic acid in acute migraine attacks. *Headache* 2005; **45:** 42–46.
85. Soyka D, Taneri Z, Oestreich W, Schmidt R. Flunarizine i.v. in the acute treatment of the migraine attack. A double-blind placebo-controlled study. *Cephalalgia* 1988; **8**(Suppl 8)**:** 35–40.
86. Silberstein SD, Freitag FG, Rozen TD, *et al*. Tramadol/acetaminophen for the treatment of acute migraine pain: findings of a randomized, placebo-controlled trial. *Headache* 2005; **45:** 1317–1327.
87. Kangasniemi P, Hedman C. Metoprolol and propranolol in the prophylactic treatment of classical and common migraine. A double-blind study. *Cephalalgia* 1984; **4:** 91–96.
88. Olsson JE, Behring HC, Forssman B, *et al*. Metoprolol and propranolol in migraine prophylaxis: a double-blind multicenter study. *Acta Neurol Scand* 1984; **70:** 160–168.
89. Steiner TJ, Joseph R, Hedman C, Rose FC. Metoprolol in the prophylaxis of migraine: parallel group comparison with placebo and dose-ranging follow-up. *Headache* 1988; **28:** 15–23.
90. Sorensen PS, Larsen BH, Rasmussen MJK, *et al*. Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. *Headache* 1991; **31:** 650–657.
91. Wörz R, Reinhardt-Benmalek B, Grotemeyer KH. Bisoprolol and metoprolol in the prophylactic treatment of migraine with and without aura - a randomized double-blind cross-over multicenter study. *Cephalalgia* 1991; **11**(Suppl 11)**:** 152–153.
92. Diamond S, Medina JL. Double blind study of propranolol for migraine prophylaxis. *Headache* 1976; **16:** 24–27.
93. Tfelt-Hansen P, Standnes B, Kangasniemi P, Hakkarainen H, Olesen J. Timolol vs. propranolol vs. placebo in common migraine prophylaxis: a double-blind multicenter trial. *Acta Neurol Scand* 1984; **69:** 1–8.
94. Nadelmann JW, Stevens J, Saper JR. Propranolol in the prophylaxis of migraine. *Headache* 1986; **26:** 175–182.

95. Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Long acting propranolol in the prophylaxis of migraine. Comparison of the daily doses of 80 mg and 160 mg. *Headache* 1988; **28:** 607–611.
96. Ludin H-P. Flunarizine and propranolol in the treatment of migraine. *Headache* 1989; **29:** 218–223.
97. Holroyd KA, Penzien DB, Cordingley GE. Propranolol in the management of recurrent migraine: a meta-analytic review. *Headache* 1991; **31:** 333–340.
98. Gawel MJ, Kreeft J, Nelson RF, Simard D, Arnott WS. Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. *Can J Neurol Sci* 1992; **19:** 340–345.
99. van de Ven LLM, Franke CL, Koehler PJ. Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. *Cephalalgia* 1997; **17:** 596–599.
100. Stellar S, Ahrens SP, Meibohm AR, Reines SA. Migraine prevention with timolol. A double-blind crossover study. *JAMA* 1984; **252:** 2576–2580.
101. Johannsson V, Nilsson LR, Widelius T, *et al*. Atenolol in migraine prophylaxis a double-blind cross-over multicentre study. *Headache* 1987; **27:** 372–374.
102. Louis P. A double-blind placebo-controlled prophylactic study of flunarizine in migraine. *Headache* 1981; **21:** 235–239.
103. Diamond S, Schenbaum H. Flunarizine, a calcium channel blocker, in the prophylactic treatment of migraine. *Headache* 1983; **23:** 39–42.
104. Amery WK, Caers LI, Aerts TJL. Flunarizine, a calcium entry blocker in migraine prophylaxis. *Headache* 1985; **25:** 249–254.
105. Bono G, Manzoni GC, Martucci N, *et al*. Flunarizine in common migraine: Italian cooperative trial. II. Long-term follow-up. *Cephalalgia* 1985; **5**(Suppl 2)**:** 155–158.
106. Centonze V, Tesauro P, Magrone D, *et al*. Efficacy and tolerability of flunarizine in the prophylaxis of migraine. *Cephalalgia* 1985; **5**(Suppl 2)**:** 163–168.
107. Nappi G, Sandrini G, Savoini G, Cavallini A, de Rysky C, Micieli G. Comparative efficacy of cyclandelate versus flunarizine in the prophylactic treatment of migraine. *Drugs* 1987; **33**(Suppl 2)**:** 103–109.
108. Freitag FG, Diamond S, Diamond M. A placebo controlled trial of flunarizine in migraine prophylaxis. *Cephalalgia* 1991; **11**(Suppl 11)**:** 157–158.
109. Bassi P, Brunati L, Rapuzzi B, Alberti E, Mangoni A. Low dose flunarizine in the prophylaxis of migraine. *Headache* 1992; **32:** 390–392.
110. Diamond S, Freitag FG. A double blind trial of flunarizine in migraine prophylaxis. *Headache Q* 1993; **4:** 169–172.
111. Balkan S, Aktekin B, Önal Z. Efficacy of flunarizine in the prophylactic treatment of migraine. *Gazi Med J* 1994; **5:** 81–84.
112. Diener H, Matias-Guiu J, Hartung E, *et al*. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia* 2002; **22:** 209–221.
113. Gerber WD, Schellenberg R, Thom M, *et al*. Cyclandelate versus propranolol in the prophylaxis of migraine – a double-blind placebo-controlled study. *Funct Neurol* 1995; **10:** 27–35.
114. Diener HC, Föh M, Iaccarino C, *et al*. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. *Cephalalgia* 1996; **16:** 441–447.
115. Siniatchkin M, Gerber WD, Vein A. Clinical efficacy and central mechanisms of cyclandelate in migraine: a double-blind placebo-controlled study. *Funct Neurol* 1998; **13:** 47–56.
116. Diener H, Krupp P, Schmitt T, *et al*. Cyclandelate in the prophylaxis of migraine: a placebo-controlled study. *Cephalalgia* 2001; **21:** 66–70.
117. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. *Arch Neurol* 1997; **54:** 1141–1145.
118. Klapper J, on behalf of the Divalproex Sodium in Migraine Prophylaxis Study Group. Divalproex sodium in migraine prophylaxis: a dose-controlled study. *Cephalalgia* 1997; **17:** 103–108.
119. Silberstein SD, Collins SD, Carlson H. Safety and efficacy of once-daily, extended-release divalproex sodium monotherapy for the prophylaxis of migraine headaches. *Cephalalgia* 2000; **20:** 269.
120. Freitag F, Collins S, Carlson H, *et al*. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. *Neurology* 2002; **58:** 1652–1659.
121. Brandes J, Saper J, Diamond M, *et al*. Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; **291:** 965–973.
122. Diener H, Tfelt-Hansen P, Dahlöf C, *et al*. Topiramate in migraine prophylaxis: results from a placebo-controlled trial with propranolol as an active control. *J Neurol* 2004; **251:** 943–950.
123. Mei D, Capuano A, Vollono C, *et al*. Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. *Neurol Sci* 2004; **25:** 245–250.
124. Silberstein SD, Neto W, Schmitt J, Jacobs D. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004; **61:** 490–495.
125. Diener HC, Bussone G, Van Oene JC, *et al*. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007; **27:** 814–823.
126. Silberstein SD, Lipton RB, Dodick DW, *et al*. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007; **47:** 170–180.
127. Steiner TJ, Findley LJ, Yuen AWC. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. *Cephalalgia* 1997; **17:** 109–112.
128. Lampl C, Buzath A, Klinger D, Neumann K. Lamotrigine in the prophylactic treatment of migraine aura – a pilot study. *Cephalalgia* 1999; **19:** 58–63.
129. Mathew NT, Rapoport A, Saper J, *et al*. Efficacy of gabapentin in migraine prophylaxis. *Headache* 2001; **41:** 119–128.
130. Silberstein S, Saper J, Berenson F, Somogyi M, McCague K, D'Souza J. Oxcarbazepine in migraine headache: a double-blind, randomized, placebo-controlled study. *Neurology* 2008; **70:** 548–555.
131. Peto R, Gray R, Collins R, Wheatly K, Hennekens C, Jamrozik K. Randomised trial of prophylactic daily aspirin in male British doctors. *BMJ* 1988; **296:** 313–316.
132. Buring JE, Peto R, Hennekens CH. Low-dose aspirin for migraine prophylaxis. *JAMA* 1990; **264:** 1711–1713.
133. Ziegler DK, Ellis DJ. Naproxen in prophylaxis of migraine. *Arch Neurol* 1985; **42:** 582–584.

134. Welch KMA, Ellis DJ, Keenan PA. Successful migraine prophylaxis with naproxen sodium. *Neurology* 1985; **35:** 1304–1310.
135. Bellavance AJ, Meloche JP. A comparative study of naproxen sodium, pizotyline and placebo in migraine prophylaxis. *Headache* 1990; **30:** 710–715.
136. Mikkelsen BM, Falk JV. Prophylactic treatment of migraine with tolfenamic acid: a comparative double-blind crossover study between tolfenamic acid and placebo. *Acta Neurol Scand* 1982; **66:** 105–111.
137. Mikkelsen B, Pedersen KK, Christiansen LV. Prophylactic treatment of migraine with tolfenamic acid, propranolol and placebo. *Acta Neurol Scand* 1986; **73:** 423–427.
138. Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis: changes in pattern of attacks during a controlled clinical trial. *J Neurol Neurosurg Psychchiatry* 1973; **36:** 684–690.
139. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. *Arch Neurol* 1979; **36:** 695–699.
140. Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Preskorn SH, Mason J. Migraine prophylaxis. A comparison of propranolol and amitriptyline. *Arch Neurol* 1987; **44:** 486–489.
141. Ziegler DK, Hurwitz A, Preskorn S, Hassanein R, Seim J. Propranolol and amitriptyline in prophylaxis of migraine: pharmacokinetic and therapeutic effects. *Arch Neurol* 1993; **50:** 825–830.
142. Orholm M, Honoré PF, Zeeberg I. A randomized general practice group-comparative study of femoxetine and placebo in the prophylaxis of migraine. *Acta Neurol Scand* 1986; **74:** 235–239.
143. Zeeberg I, Orholm M, Nielsen JD, Honore PLF, Larsen JJV. Femoxetine in the prophylaxis of migraine – a randomised comparison with placebo. *Acta Neurol Scand* 1981; **64:** 452–459.
144. Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. *Headache* 1992; **32:** 101–104.
145. Steiner TJ, Ahmed F, Findley LJ, MacGregor EA, Wilkinson M. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. *Cephalalgia* 1998; **18:** 283–286.
146. d'Amato CC, Pizza V, Marmolo T, Giordano E, Alfano V, Nasta A. Fluoxetine for migraine prophylaxis: a double-blind trial. *Headache* 1999; **39:** 716–719.
147. Saper JR, Silberstein SD, Lake AE, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. *Headache* 1994; **34:** 497–502.
148. Ozyalcin SN, Talu GK, Kiziltan E, Yucel B, Ertas M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005; **45:** 144–152.
149. Adelman LC, Adelman JU, von Seggern R, Mannix LK. Venlafaxine extended release (XR) for the prophylaxis of migraine and tension-type headache: a retrospective study in a clinical setting. *Headache* 2000; **40:** 572–580.
150. Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungen B. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. *Clin Neurol Neurosurg* 2004; **107:** 44–48.
151. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo-controlled, crossover trial. *BMJ* 2001; **322:** 19–22.
152. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker. A randomized controlled trial. *JAMA* 2002; **289:** 65–69.
153. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis – a randomized controlled trial. *Neurology* 1998; **50:** 466–470.
154. Sandor PS, di Clemente L, Coppola G, *et al*. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomised controlled trial. *Neurology* 2005; **64:** 713–715.
155. Pfaffenrath V, Wessely P, Meyer C, *et al*. Magnesium in the prophylaxis of migraine – a double-blind, placebo-controlled study. *Cephalalgia* 1996; **16:** 436–440.
156. Peikert A, Wilimzig C, Köhne-Volland R. Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996; **16:** 257–263.
157. Diener HC, Rahlfs VW, Danesch U. The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. *Eur Neurol* 2004; **51:** 89–97.
158. Lipton RB, Göbel H, Einhäupl KM, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004; **63:** 2240–2244.
159. Pfaffenrath V, Diener HC, Fischer M, Friede M, Henneicke-von Zepelin HH, Investigators. The efficacy and safety of Tanacetum parthenium (feverfew) in migraine prophylaxis – a double-blind, multicentre, randomized placebo-controlled dose–response study. *Cephalalgia* 2002; **22:** 523–532.
160. Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-von Zepelin HH. Efficacy and safety of 6.25 mg t.i.d. feverfew CO2-extract (MIG-99) in migraine prevention - a randomized, double-blind, multicentre, placebo-controlled study. *Cephalalgia* 2005; **25:** 1031–1041.
161. Pittler MH, Ernst E. Feverfew for preventing migraine. *Cochrane Database Syst Rev* 2004; **1:** CD002286.
162. Evers S, Mylecharane E. Nonsteroidal antiinflammatory and miscellaneous drugs in migraine prophylaxis. In: Olesen J, Goadsby PJ, Ramadan N, Tfelt-Hansen P, Welch KMA, eds. *The Headaches*, 3rd edn. Philadelphia, PA: Lippincott, 2006: 553–566.
163. Silberstein SD. Methysergide. *Cephalalgia* 1998; **18:** 421–435.
164. Mylecharane EJ. 5-HT2 receptor antagonists and migraine therapy. *J Neurol* 1991; **238**(Suppl 1)**:** S45–S52.
165. Silberstein S, Mathew N, Saper J, Jenkins S. Botulinum toxin type A as a migraine preventive treatment. *Headache* 2000; **40:** 445–450.
166. Brin MF, Swope DM, O'Brian C, Abbasi S, Pogoda JM. Botox® for migraine: double-blind, placebo-controlled, region-specific evaluation. *Cephalalgia* 2000; **20:** 421–422.
167. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine – a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2004; **24:** 838–843.
168. Dodick DW, Mauskop A, Elkind AH, *et al*. Botulinum toxin type A for the prophylaxis of chronic daily head-

ache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. *Headache* 2005; **45:** 315–324.
169. Whitmarsh TE, Coleston-Shields DM, Steiner TJ. Double-blind randomized placebo-controlled study of homoeopathic prophylaxis of migraine. *Cephalalgia* 1997; **17:** 600–604.
170. Walach H, Haeusler W, Lowes T, *et al*. Classical homeopathic treatment of chronic headaches. *Cephalalgia* 1997; **17:** 119–126.
171. Straumsheim P, Borchgrevink C, Mowinckel P, Kierulf H, Hafslund O. Homeopathic treatment of migraine: a double blind, placebo controlled trial of 68 patients. *Br Homeopath J* 2000; **89:** 4–7.
172. Brandes JL, Visser WH, Farmer MV, *et al*. Montelukast for migraine prophylaxis: a randomized, double-blind, placebo-controlled study. *Headache* 2004; **44:** 581–586.
173. Vahedi K, Taupin P, Djomby R, *et al*. Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial. *J Neurol* 2002; **249:** 206–211.
174. Goldstein DJ, Offen WW, Klein EG, *et al*. Lanepitant, an NK-1 antagonist, in migraine prevention. *Cephalalgia* 2001; **21:** 102–106.
175. Friedman BW, Greenwald P, Bania TC, *et al*. Randomized trial of IV dexamethasone for acute migraine in the emergency department. *Neurology* 2007; **69:** 2038–2044.
176. Baden EY, Hunter CJ. Intravenous dexamethasone to prevent the recurrence of benign headache after discharge from the emergency department: a randomized, double-blind, placebo-controlled clinical trial. *CJEM* 2006; **8:** 393–400.
177. Donaldson D, Sundermann R, Jackson R, Bastani A. Intravenous dexamethasone vs placebo as adjunctive therapy to reduce the recurrence rate of acute migraine headaches: a multicenter, double-blinded, placebo-controlled randomized clinical trial. *Am J Emerg Med* 2008; **26:** 124–130.
178. Innes GD, Macphail I, Dillon EC, Metcalfe C, Gao M. Dexamethasone prevents relapse after emergency department treatment of acute migraine: a randomized clinical trial. *CJEM* 1999; **1:** 26–33.
179. Rowe BH, Colman I, Edmonds ML, Blitz S, Walker A, Wiens S. Randomized controlled trial of intravenous dexamethasone to prevent relapse in acute migraine headache. *Headache* 2008; **48:** 333–340.
180. Bigal ME, Bordini CA, Speciali JG. Intravenous metamizol (Dipyrone) in acute migraine treatment and in episodic tension-type headache – a placebo-controlled study. *Cephalalgia* 2001; **21:** 90–95.
181. Leinisch E, Evers S, Kaempfe N, *et al*. Evaluation of the efficacy of intravenous acetaminophen in the treatment of acute migraine attacks: a double-blind, placebo-controlled parallel group multicenter study. *Pain* 2005; **117:** 396–400.
182. Facchinetti F, Fioroni L, Sances G, Romano G, Nappi G, Genazzani AR. Naproxen sodium in the treatment of premenstrual symptoms: a placebo-controlled study. *Gynecol Obstet Invest* 1989; **28:** 205–208.
183. Sargent J, Solbach P, Damasio H, *et al*. A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. *Headache* 1985; **25:** 320–324.
184. Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache* 1990; **30:** 705–709.
185. Szekely B, Merryman S, Croft H, Post G. Prophylactic effects of naproxen sodium on perimenstrual headache: a double-blind, placebo-controlled study. *Cephalalgia* 1989; **9**(Suppl 10)**:** 452–453.
186. Newman L, Mannix LK, Landy S, *et al*. Naratriptan as short-term prophylaxis in menstrually associated migraine: a randomised, double-blind, placebo-controlled study. *Headache* 2001; **41:** 248–256.
187. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 2004; **63:** 261–269.
188. Mannix LK, Savani N, Landy S, *et al*. Efficacy and tolerability of naratriptan for short-term prevention of menstrually related migraine: data from two randomized, double-blind, placebo-controlled studies. *Headache* 2007; **47:** 1037–1049.
189. De Lignieres B, Mauvais-Javis P, Mas JML, Mas JL, Touboul PJ, Bousser MG. Prevention of menstrual migraine by percutaneous oestradiol. *BMJ* 1986; **293:** 1540.
190. Dennerstein L, Morse C, Burrows G, Oats J, Brown J, Smith M. Menstrual migraine: a double blind trial of percutaneous oestradiol. *Gynecol Endocrinol* 1988; **2:** 113–120.
191. Smits MG, van den Meer YG, Pfeil JPJM, Rijnierse JJMM, Vos AJM. Perimenstrual migraine: effect of Estraderm® TTS and the value of contingent negative variation and exteroceptive temporalis muscle suppression test. *Headache* 1994; **34:** 103–106.
192. Pradalier A, Vincent D, Beaulieu PH, Baudesson G, Launay J-M. Correlation between estradiol plasma level and therapeutic effect on menstrual migraine. *Proc 10th Migraine Trust Symp* 1994; 129–132.
193. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. *Neurology* 2006; **67:** 2159–2163.
194. O'Quinn S, Ephross SA, Williams V, Davis RL, Gutterman DL, Fox AW. Pregnancy and perinatal outcomes in migraineurs using sumatriptan: a prospective study. *Arch Gynecol Obstet* 1999; **263:** 7–12.
195. Olesen C, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J. Pregnancy outcome following prescription for sumatriptan. *Headache* 2000; **40:** 20–24.
196. Källen B, Lygner PE. Delivery outcome in women who used drugs for migraine during pregnancy with special reference to sumatriptan. *Headache* 2001; **41:** 351–356.
197. Fox AW, Chambers CD, Anderson PO, Diamond ML, Spierings EL. Evidence-based assessment of pregnancy outcome after sumatriptan exposure. *Headache* 2002; **42:** 8–15.
198. Loder E. Safety of sumatriptan in pregnancy: a review of the data so far. *CNS Drugs* 2003; **17:** 1–7.
199. Evans EW, Lorber KC. Use of 5-HT1 agonists in pregnancy. *Ann Pharmacother* 2008; **42:** 543–549.
200. Goadsby PJ, Goldberg J, Silberstein SD. The pregnant migraineur: what can be done? *Br Med J* 2008; **336:** 1502–1504.

201. Evers S, Kropp P, Pothmann R, Heinen F, Ebinger F. Therapie idiopathischer Kopfschmerzen im Kindes- und Jugendalter. *Nervenheilkunde* 2008; **27:** 1127–1137.
202. Überall MA, Wenzel D. Intranasal sumatriptan for the acute treatment of migraine in children. *Neurology* 1999; **52:** 1507–1510.
203. Winner P, Rothner AD, Saper J, *et al*. A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. *Pediatrics* 2000; **106:** 989–997.
204. Ahonen K, Hämäläinen M, Rantala H, Hoppu K. Nasal sumatriptan is effective in treatment of migraine attacks in children: a randomized trial. *Neurology* 2004; **62:** 883–887.
205. Hämäläinen ML, Hoppu K, Santavuori P. Sumatriptan for migraine attacks in children: a randomized placebo-controlled study. Do children with migraine attacks respond to oral sumatriptan differently from adults? *Neurology* 1997; **48:** 1100–1103.
206. Evers S. Drug treatment of migraine in children. A comparative review. *Paediatr Drugs* 1999; **1:** 7–18.
207. Winner P, Lewis D, Visser H, *et al*. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double-blind, placebo-controlled study. *Headache* 2002; **42:** 49–55.
208. Solomon GD, Cady RK, Klapper JA, Earl NL, Saper JR, Ramadan NM. Clinical efficacy and tolerability of 2,5 mg zolmitriptan for the acute treatment of migraine. *Neurology* 1997; **49:** 1219–1225.
209. Tepper SJ, Donnan GA, Dowson AJ, *et al*. A long-term study to maximise migraine relief with zolmitriptan. *Curr Med Res Opin* 1999; **15:** 254–271.
210. Evers S, Rahmann A, Kraemer C, *et al*. Treatment of childhood migraine attacks with oral zolmitriptan and ibuprofen. *Neurology* 2006; **67:** 497–499.
211. Lewis DW, Winner P, Hershey AD, Wasiewski WW, Adolescent Migraine Steering Committee. Efficacy of zolmitriptan nasal spray in adolescent migraine. *Pediatrics* 2007; **120:** 390–396.
212. Ahonen K, Hämäläinen ML, Eerola M, Hoppu K. A randomized trial of rizatriptan in migraine attacks in children. *Neurology* 2006; **67:** 1135–1140.
213. Lewis D, Ashwal S, Hershey A, *et al*. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology* 2004; **63:** 2215–2224.
214. Winner P, Pearlman EM, Linder SL, Jordan DM, Fisher AC, Hulihan J. Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. *Headache* 2005; **45:** 1304–1312.
215. Winner P, Gendolla A, Stayer C, *et al*. Topiramate for migraine prevention in adolescents: a pooled analysis of efficacy and safety. *Headache* 2006; **46:** 1503–1510.

