Complete Summary

GUIDELINE TITLE

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

BIBLIOGRAPHIC SOURCE(S)

Members of the task force:, Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. Eur J Neurol 2006 Jun;13(6):560-72. [171 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

These recommendations should be updated within 2 years and should be complemented by recommendations for the non-drug treatment of migraine.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- June 15, 2005, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): U.S. Food and Drug Administration (FDA) recommended proposed labeling for both the prescription and over the counter (OTC) NSAIDs and a medication guide for the entire class of prescription products.
- April 7, 2005, Non-steroidal anti-inflammatory drugs (NSAIDS) (prescription and OTC, including ibuprofen and naproxen): FDA asked manufacturers of prescription and non-prescription (OTC) non-steroidal anti-inflammatory drugs (NSAIDs) to revise their labeling to include more specific information about potential gastrointestinal (GI) and cardiovascular (CV) risks.

Additional Notices

- May 2, 2007, Antidepressant drugs: Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.
- July 19, 2006, Triptans: Healthcare professionals and consumers of new safety information regarding taking triptans together with selective serotonin

reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs).

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Migraine

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Pediatrics
Pharmacology
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To give evidence-based recommendations for the drug treatment of migraine attacks and migraine prophylaxis

TARGET POPULATION

Adults, children, and adolescents with migraine

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment/Prevention

1. Analgesics
2. Antiemetics
3. Ergot alkaloids
4. Triptans
5. Treatment of menstrual migraine: naproxen sodium
6. Migraine in pregnancy: paracetamol, NSAIDs
7. Migraine in children and adolescents: ibuprofen, paracetamol, domperidon, sumatriptan nasal spray
8. Prophylaxis of migraine
    - Drugs of first choice (e.g., beta blockers, calcium channel blockers, antiepileptic drugs)
    - Miscellaneous drugs of second and third choice (see the "Major Recommendations" field for details)
    - Prophylaxis of menstrual migraine
    - Prophylaxis in pregnancy: magnesium and metoprolol
    - Prophylaxis in children and adolescents: flunarizine and propranolol

Note: The non-drug management (e.g. behavioral therapy) is not included in this guideline, although it is regarded as an important part of migraine treatment.

MAJOR OUTCOMES CONSIDERED

- Effectiveness of treatment in pain relief, headache recurrence, severity of pain, and analgesic requirements
- Adverse effects of medications used to treat migraine

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A literature search was performed using the reference databases MedLine, Science Citation Index, and the Cochrane Library; the key words used were 'migraine' and 'aura' (last search in January 2005). All papers published in English, German, or French were considered when they described a controlled trial or a case series on the treatment of at least five patients. In addition, a review book and the German treatment recommendations for migraine were considered.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

All authors performed an independent literature search. The first draft of the manuscript was written by the chairman of the task force. All other members of the task force read the first draft and discussed changes by e-mail. A second draft was then written by the chairman which was again discussed by e-mail. All recommendations had to be agreed to by all members of the task force unanimously. The background of the research strategy and of reaching consensus and the definitions of the recommendation levels used in this paper have been described in the European Federation of Neurological Societies (EFNS) recommendations (see the "Availability of Companion Documents" field).

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see "Availability of Companion Documents").

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Drug Treatment of Migraine Attacks

Analgesics

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

Antiemetics

Table. Antiemetics Recommended for the Acute Treatment of Migraine Attacks

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

Ergot Alkaloids

The advantage of ergot alkaloids in some patients is a longer half life time and a lower recurrence rate. Therefore, these substances should be restricted to patients with very long migraine attacks or with regular recurrence. The only compound with sufficient evidence of efficacy is ergotamine tartrate 2 mg (oral or suppositories).

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

Table. Different Triptans for the Treatment of Acute Migraine Attacks (Order in the Time of Marketing). Not all doses or application forms are available in all European countries

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

Migraine Prophylaxis

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

Table. Recommended Substances (Drugs of First Choice) for the Prophylactic Drug Treatment of Migraine

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

Table. Drugs of Second Choice for Migraine Prophylaxis (Evidence of Efficacy, but Less Effective or More Side Effects than Drugs of the Table above)

Substances	Daily Dose	Level
Amitriptyline	50–150	B
Naproxen	2 x 250–500	B
Petasites	2 x 75	B
Bisoprolol	5–10	B

Table. 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 x 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

Migraine in Pregnancy

If migraine occurs during pregnancy, only paracetamol is allowed during the whole period. Non-steroidal anti-inflammatory drugs (NSAIDs) can be given in the second trimester. These recommendations are based on the advices of the regulatory authorities in most European countries. There might be differences in some respect between different countries (in particular, NSAIDs might be allowed in the first trimester).

For migraine prophylaxis, only magnesium and metoprolol are recommended during pregnancy (**level B recommendation**).

Definitions:

Evidence Classification Scheme for a Therapeutic Intervention

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Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate drug treatment and prophylaxis of migraine

POTENTIAL HARMS

Analgesics

- *Acetylsalicylic acid (ASA)* and *non-steroidal anti-inflammatory drugs (NSAIDs)* are associated with gastrointestinal side effects and risk of bleeding.
- *Paracetamol and Phenazon* should be given with caution in liver and kidney failure.
- *Metamizol* is associated with risk of agranulocytosis and hypotension
- In order to prevent drug overuse headache, the intake of simple analgesics should be restricted to 15 days/month and the intake of combined analgesics to 10 days/month.

Antiemetics

- *Metoclopramide* is associated with dyskinesia
- *Domperidon* has less severe side effects compared to metoclopramide and can be given to children.

Ergot Alkaloids

- Major side effects of *ergot alkaloids* include nausea, vomiting, paresthesia, and ergotism.
- Ergot alkaloids can induce drug overuse headache very fast and in very low doses. Therefore, their use must be limited to 10 days/month.

Triptans

- The use of *triptans* is restricted to maximum 10 days/month. Otherwise, the induction of a drug overuse headache is possible for all triptans.
- General side effects for all *triptans*: chest symptoms, nausea, distal paresthesia, fatigue.
- After application of *sumatriptan*, severe adverse events have been reported such as myocardial infarction, cardiac arrhythmias, and stroke.

Antidepressants

In several small studies *amitriptyline* showed central side effects.

Miscellaneous Drugs

Methysergide is recommended for short-term use only (maximum 6 months per treatment period) because of potentially severe side effects

CONTRAINDICATIONS

CONTRAINDICATIONS

- *Metoclopramide* is contraindicated in childhood and pregnancy.
- *Ergot alkaloids* are contraindicated in cardiovascular and cerebrovascular diseases, Raynaud's disease, arterial hypertension, renal failure, and pregnancy and lactation.
- *Triptan* contraindications: arterial hypertension (untreated), coronary heart disease, cerebrovascular disease, Raynaud's disease, pregnancy and

lactation, age under 18 (except sumatriptan nasal spray) and age above 65 years, severe liver or kidney failure.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Members of the task force:, Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. Eur J Neurol 2006 Jun;13(6):560-72. [171 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Jun

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force on the Drug Treatment of Migraine

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The present guidelines were developed without external financial support. The authors report the following financial supports:

Stefan Evers: Salary by the government of the State Northrhine-Westphalia; honoraries and research grants by Almirall, AstraZeneca, Berlin Chemie, Boehringer, GlaxoSmithKline, Ipsen Pharma, Janssen Cilag, MSD, Pfizer, Novartis, Pharm Allergan, Pierre Fabre. Judit Áfra: Salary by the Hungarian Ministry of Health; honoraries by GlaxoSmithKline. Achim Frese: Salary by the government of the State Northrhine-Westphalia; no honoraries. Peter J. Goadsby: Salary by the University College of London; honoraries by Almirall, AstraZeneca, Glaxo-SmithKline, MSD, Pfizer, Medtronic. 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

GUIDELINE STATUS

This is the current release of the guideline.

These recommendations should be updated within 2 years and should be complemented by recommendations for the non-drug treatment of migraine.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site.

Print copies: Available from Stefan Evers, Department of Neurology, University of Münster, Albert-Schweitzer-Str. 33, 48129 Münster, Germany; Phone: +49-251-8348196; Fax: +49-251-8348181; E-mail: everss@uni-muenster.de

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site.
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the European Federation of Neurological Societies Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on April 6, 2007. The information was verified by the guideline developer on May 15, 2007. This summary was updated by ECRI Institute on November 9, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs.

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Date Modified: 10/13/2008