Evidence-based Guidelines Update: Pharmacologic Treatments and NSAIDs and Other Complementary Treatments for Episodic Migraine Prevention in Adults

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Questions or Feedback

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Guideline Endorsement

- Endorsed by the American Osteopathic Association
Presentation Objectives

- To present analysis of the evidence regarding efficacy and safety of pharmacologic treatments and nonsteroidal antiinflammatory drugs (NSAIDs) and other complementary treatments for migraine prevention
- To present evidence-based recommendations
Overview

- Background
- Gaps in care
- American Academy of Neurology (AAN) guideline process
- Analysis if evidence, conclusions, recommendations
- Recommendations for future research
Background

- Epidemiologic studies suggest approximately 38% of migraineurs need preventive therapy, but only 3%–13% currently use it.\(^1\)
- In 2000, the American Academy of Neurology (AAN) published guidelines for migraine prevention.\(^2,3\)
  - Since then, new clinical studies have been published on the efficacy and safety of migraine preventive therapies.
- Separate guidelines are available for botulinum toxin.\(^4\)
  - The 2008 guideline included a Level B recommendation that botulinum toxin was probably ineffective for treatment of episodic migraine.
  - A new guideline is in development.
AAN Guideline Process

- Clinical Question
  - Evidence
    - Conclusions
      - Recommendations
Clinical Questions

- For patients with migraine, which pharmacologic therapies are proven effective for prevention, as measured by reduced migraine attack frequency, reduced number of migraine days, or reduced attack severity?
- For patients with migraine, which anti-inflammatory or complementary treatments are effective for prevention, as measured by reduced migraine attack frequency, reduced number of migraine days, or reduced attack severity?
Literature Search/Review

- Rigorous, Comprehensive, Transparent

Search

Review abstracts

Review full text

Select articles

Relevant

Search
AAN Classification of Evidence

- All studies rated Class I, II, III, or IV
- Five different classification systems
  - Therapeutic
    - Randomization, control, blinding
  - Diagnostic
    - Comparison with gold standard
  - Prognostic
  - Screening
  - Causation
AAN Level of Recommendations

- **A** = *Established* as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population
- **B** = *Probably* effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population
- **C** = *Possibly* effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population
- **U** = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven
  - Note that recommendations can be positive or negative

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Translating Class to Recommendations

- **A** = Requires at least two consistent Class I studies*
- **B** = Requires at least one Class I study or two consistent Class II studies
- **C** = Requires at least one Class II study or two consistent Class III studies
- **U** = Studies not meeting criteria for Class I through Class III

*Class I studies: The highest level of evidence, based on multiple, consistent, high-quality studies.

**Class II studies:** Lower level of evidence, based on fewer, less consistent studies.

**Class III studies:** Lower level of evidence, based on expert opinion or case studies.
Translating Class to Recommendations, cont.

* In exceptional cases, one convincing Class I study may suffice for an “A” recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).
Applying the Process to the Issue

- We will now turn our attention to the guidelines.
Methods

- MEDLINE, PsycINFO, and CINAHL databases identified new studies (published in English).
- Search strategy used the MeSH term “headache” (exploded) and a published search strategy for identifying randomized controlled trials (RCTs) published between June 1999 and May 2007.
Methods, cont.

- At least two authors reviewed each article for inclusion.
- Risk of bias was determined using the classification of evidence scheme for therapeutic articles.
- Strength of recommendations were linked directly to levels of evidence.
- Conflicts of interest were disclosed.
Literature Search/Review

- Rigorous, Comprehensive, Transparent

284 abstracts

Inclusion criteria:
- Studies randomizing adult patients with migraine to the agent under study or a comparator drug (including placebo) and utilized masked outcome assessment
- Studies assessing efficacy of NSAIDs and complementary treatments for prevention of episodic migraine in adults (e.g., 15 days/month)

Exclusion criteria:
- Studies assessing efficacy of therapeutic agents for prevention or treatment of chronic migraine, intractable migraine, tension-type headache, or headache in adolescents or children
- Studies assessing acute migraine treatment, migraine aura treatment or prevention, or nonpharmacologic treatments
- Studies using quality of life measures, disability assessment, or nonstandardized outcomes as primary efficacy endpoints
- NSAIDs/complementary treatments not commonly or readily available in the United States

44 articles
AAN Classification of Evidence for Therapeutic Interventions

- **Class I:** A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:
  - Concealed allocation
  - Primary outcome(s) clearly defined
  - Exclusion/inclusion criteria clearly defined
  - Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
AAN Classification of Evidence for Therapeutic Interventions, cont.

- **Class II:** A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

- **Class III:** All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**
**Class IV:** Studies not meeting Class I, II or III criteria including consensus or expert opinion.

*Note that numbers 1–3 in Class I, item 5 are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.*

**Objective outcome measurement:** an outcome measure that is unlikely to be affected by an observer’s (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).
Clinical Question 1

- For patients with migraine, which pharmacologic therapies are proven effective for prevention, as measured by reduced migraine attack frequency, reduced number of migraine days, or reduced attack severity?
ARBs and ACE Inhibitors: Conclusions

- Lisinopril and candesartan are possibly effective for migraine prevention (1 Class II study each).
- Telmisartan is possibly ineffective for reducing the number of migraine days (1 negative Class II study).
Antiepileptic Drugs: Conclusions

- Divalproex sodium and sodium valproate are established as effective in migraine prevention (multiple Class I studies).
- Data are insufficient to determine the effectiveness of gabapentin (1 Class III study).
- Lamotrigine is established as ineffective for migraine prevention (2 Class I studies).
- Oxcarbazepine is possibly ineffective for migraine prevention (1 Class II study).
Antiepileptic Drugs: Conclusions, cont.

- Topiramate is established as effective for migraine prevention (4 Class I studies, multiple Class II studies; 1 negative Class II study).
- Topiramate is probably as effective for migraine prevention as propranolol (1 Class I study), sodium valproate (1 Class I study), and amitriptyline (2 Class II studies).
Antiepileptic Drugs: Clinical Context

- In most headache trials, patients taking divalproex sodium or sodium valproate reported no more adverse events (AEs) than those on placebo. However, weight gain has been clinically observed with divalproex sodium long-term use.\(^5,6\)

- Treatment with these agents requires careful follow-up and testing because of pancreatitis, liver failure, and teratogenicity risks.\(^7\)
Antidepressants: Conclusions

- There is conflicting Class II evidence for use of fluoxetine.
- Venlafaxine is probably effective for migraine prevention (1 Class I study) and is possibly as effective as amitriptyline in migraine prevention (1 Class II study).
- Amitriptyline is probably effective for migraine prevention (multiple Class II studies); it is probably as effective as topiramate (2 Class II studies) and possibly as effective as venlafaxine (1 Class II study) for migraine prevention.
**Beta-Blockers: Conclusions**

- Metoprolol is established as effective for migraine prevention (2 Class I studies) and is possibly as effective as nebivolol or aspirin for migraine prevention (1 Class II study each).
- Propranolol is established as effective for migraine prevention (multiple Class I studies) and is possibly as effective as cyproheptadine for migraine prevention (1 Class II study).
Calcium-Channel Blockers: Conclusion

- Data from older studies regarding verapamil and nimodipine are insufficient when current AAN classification criteria are applied.
Direct Vascular Smooth Muscle Relaxants: Conclusion

- The efficacy of cyclandelate is unknown (conflicting Class II studies).
Triptans: Conclusions

- Frovatriptan is established as effective for the short-term prevention of menstrually associated migraine (MAMs) (2 Class I studies).
- Zolmitriptan and naratriptan are probably effective for the short-term prevention of MAMs (1 Class I study each).
- The utility of these agents in receiving a separate indication for pure menstrual migraine is currently being deliberated by US regulatory authorities).
Other Pharmacologic Agents: Conclusion

- The efficacy of acetazolamide is unknown at this time (1 Class II study terminated early).
Pharmacologic Recommendations

- **Level A.** The following medications are established as effective and should be offered for migraine prevention:
  - Antiepileptic drugs (AEDs): divalproex sodium, sodium valproate, topiramate
  - Beta-Blockers: metoprolol, propranolol, timolol
  - Triptans: frovatriptan for short-term MAMs prevention

- **Level B.** The following medications are probably effective and should be considered for migraine prevention:
  - Antidepressants: amitriptyline, venlafaxine
  - Beta-Blockers: atenolol, nadolol
  - Triptans: naratriptan, zolmitriptan for short-term MAMs prevention

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Pharmacologic Recommendations, cont.

- **Level C.** The following medications are possibly effective and may be considered for migraine prevention:
  - Antidepressants: amitriptyline, venlafaxine
  - Beta-Blockers: atenolol, nadolol
  - Triptans: naratriptan, zolmitriptan for short-term MAMs prevention

- **Level U.** Evidence is conflicting or inadequate to support or refute the use of the following medications for migraine prevention:
  - AEDs: gabapentin
  - Antidepressants
    - Selective serotonin reuptake inhibitor/selective serotonin-norepinephrine reuptake inhibitors: fluoxetine, fluvoxamine
    - Tricyclics: protriptyline
Pharmacologic Recommendations, cont.

- **Level A Negative.** The following medication is established as ineffective and should not be offered for migraine prevention:
  - Lamotrigine

- **Level B Negative.** The following medication is probably ineffective and should not be considered for migraine prevention:
  - Clomipramine
Pharmacologic Recommendations, cont.

- **Level C Negative.** The following medications are possibly ineffective and may not be considered for migraine prevention:
  - Acebutolol
  - Clonazepam
  - Nabumetone
  - Oxcarbazepine
  - Telmisartan
Pharmacologic Clinical Context

- Evidence to support pharmacologic treatment strategies for migraine prevention indicates which treatments might be effective but is insufficient to establish how to choose an optimal therapy.
- Consequently, although Level A recommendations can be made for pharmacologic migraine prevention, similar evidence is unavailable to help the practitioner choose one therapy over another.
- Treatment regimens, therefore, need to be designed case by case, which may include complex or even nontraditional approaches.
- Moreover, decision-making must remain with the physician and the patient to determine the optimal therapy, accounting for efficacy, AEs, coexisting/comorbid conditions, and personal considerations. Often trial and error is needed.
- Evidence is also unavailable for making broad-range comparisons among multiple agents within a single class; such evidence would provide a more comprehensive understanding of relative efficacy and tolerability profiles across a broader range of therapeutic agents.
- Studies are needed that specifically evaluate when preventive therapy is warranted and how medications should be titrated.
- Table e-1 of the published guideline lists some specific consensus-based clinical circumstances wherein considering preventive therapy would be reasonable.
A shortcoming of migraine prevention clinical studies is the relatively brief treatment duration (often only 12–16 weeks). Long-term assessment of the efficacy and safety of migraine preventive treatments is needed. Additionally, overall cost is a consideration when prescribing medications; cost may influence compliance, especially long-term.

It seems reasonable that a clinician be mindful of comorbid and coexistent conditions in patients with migraine, to maximize potential treatment efficacy and minimize AE risk.

Table e-2 of the published guideline identifies which therapies to consider or avoid when common migraine coexisting conditions are present.

Because migraine is frequent in women of childbearing age, the potential for adverse fetal effects related to migraine prevention strategies is particularly concerning.

Evidence from the 2 Class I frovatriptan studies meets the AAN threshold for a Level A recommendation for short-term use to prevent menstrual migraine (reduction in MAM headache incidence by 26% on 2.5 mg BID).

However, the Food and Drug Administration questions whether the benefit demonstrated is clinically meaningful and has not approved frovatriptan for this indication.
Clinical Question 2

- For patients with migraine, which anti-inflammatory or complementary treatments are effective for prevention, as measured by reduced migraine attack frequency, reduced number of migraine days, or reduced attack severity?
Histamines/antihistamines/
leukotriene receptor antagonists:
Conclusions

- Histamine SC is established as probably effective (3 Class II studies) for migraine prevention.
- Cyproheptadine is possibly effective for migraine prevention and possibly as effective as propranolol for migraine prevention (single Class II study).
- Montelukast is probably ineffective for migraine prevention (1 Class I study; see table 1 of the published guideline).
NSAIDS: Conclusion

- The efficacy of aspirin for migraine prevention is unknown (conflicting Class II studies; see table 1 of the published guideline).
NSAIDs: Clinical Context

- Regular or daily use of selected NSAIDs for the treatment of frequent migraine attacks may exacerbate headache because of development of a condition called medication overuse headache.\(^8\)

- Therefore, use of aspirin, selected analgesics, and NSAIDs may exacerbate headache; use of these agents in migraine prevention studies may confound the clinical interpretation of the study results.
Herbal Preparations, Vitamins, Minerals, and Other Interventions: Conclusions

- Petasites is established as effective for migraine prevention (2 Class I studies).
- Riboflavin is probably effective for migraine prevention (1 Class I trial and 1 imprecise Class II study).
- Co-Q10 is possibly effective for migraine prevention (1 Class II study).
- A combination of soy isoflavones (60 mg), dong quai (100 mg), and black cohosh (50 mg) is possibly effective for migraine prevention (1 Class II study).
Herbal Preparations, Vitamins, Minerals, and Other Interventions: Conclusions, cont.

- Percutaneous estradiol is possibly effective for migraine prevention (1 Class II study); however, there is an increased risk of migraine recurring after estradiol patch discontinuation.
- Magnesium is probably effective for migraine prevention (multiple Class II trials). MIG-99 (feverfew) is probably effective for migraine prevention (1 Class I study, 1 positive Class II study, and 1 underpowered negative Class II study).
- The efficacy of HBO for migraine prevention is unclear (1 imprecise negative Class II study).
- The efficacy of omega-3 for migraine prevention is unclear (1 imprecise Class I study).
Complementary Recommendations

- **Level A.** The following therapy is established as effective and should be offered for migraine prevention:
  - Petasites (butterbur)

- **Level B.** The following therapies are probably effective and should be considered for migraine prevention:
  - NSAIDS: fenoprofen, ibuprofen, ketoprofen, naproxen, naproxen sodium
  - Herbal therapies, vitamins, and minerals: riboflavin, magnesium, MIG-99 (feverfew)
  - Histamines: histamine SC
Complementary Recommendations, cont.

- **Level C.** The following therapies are possibly effective and may be considered for migraine prevention:
  - NSAIDs: flurbiprofen, mefenamic acid
  - Herbal therapies, vitamins, and minerals: Co-Q10, estrogen
  - Antihistamines: cyproheptadine

- **Level U.** Evidence is inadequate or conflicting to support or refute the use of the following therapies for migraine prevention:
  - NSAIDs: aspirin, indomethacin
  - Herbal therapies, vitamins, and minerals: omega-3
  - Other: HBO

- **Level B Negative.** The following therapy is probably ineffective and should not be considered for migraine prevention:
  - Leukotriene receptor antagonists: montelukast
Complementary Clinical Context

- In a previous epidemiologic study, 38.7% of study participants had ever used a migraine preventive treatment, of which only 12.4% were current users and 17.2% were coincident users (taking a migraine preventive treatment for other reasons).
- The proportion of those who use NSAIDs or individual complementary treatments specifically for migraine prevention is unclear at this time, and is a topic which warrants further study.
- Additionally, the treatments reviewed herein are those available in the United States.
- In other countries, treatments may not be available commercially or may be available in other dosages or in other preparations or combinations. Therefore, the results from this and other guidelines are limited to those treatments available in the United States.
- Additionally, studies assessing the efficacy of NSAIDs and complementary treatments for migraine prevention are limited and should be considered relative to other available pharmacologic therapies reviewed in a separate guideline.
- Silberstein and colleagues report divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, and timolol are effective for migraine prevention and should be offered to patients with migraine to reduce migraine attack frequency and severity (Level A).
Complementary Clinical Context, cont.

- Additionally, the clinical evidence for NSAIDs and complementary treatments for migraine prevention should be reviewed with caution because there are clear discrepancies in how patients were selected for study inclusion; how severe, frequent, or disabling their attacks were; and how severity was assessed.
- Also, these treatments are unregulated. There are few or no studies on how these medications should be taken—specifically relative to dosing strategies and coadministration with other prescription pharmacologic treatments.
- When patients are instructed or choose to take NSAIDs or complementary treatments for migraine prevention, it is important that they be followed over the course of treatment so dosing and titration modifications and AE risk can be monitored.
- Prospective long-term safety of many of these agents is not well studied specifically regarding their use as preventive migraine treatments.
- It is reasonable also for clinicians to inquire about the doses being used and frequency of use of NSAIDs and complementary treatments.
- Frequent medication use or high dose levels may increase the risk of headache progression or medication overuse, which may lead to other secondary health complications (e.g., gastrointestinal upset/bleeding with aspirin or NSAIDs or headache rebound with discontinuation of feverfew).
Complementary Clinical Context, cont.

- Complete review and disclosure of coexisting conditions are warranted, as complementary or pharmacologic therapies taken for coexisting conditions (e.g., depression) may exacerbate headache.

- Because migraine is frequent in women of childbearing age, the potential for adverse fetal effects related to migraine prevention strategies is of particular concern.

- Little has been done to establish the long-term safety and efficacy of these agents during pregnancy or breastfeeding.

- Additionally, when patients have unlimited access to over-the-counter medications, they may be unaware of the continued need for routine physician follow-up for a chronic illness such as migraine, as illness severity may progress or improve, often warranting medication changes (see table e-1 of the published guideline).

- It also is important for patients to understand the magnitude of benefit that can be expected from preventive migraine therapies; moreover, patient education about migraine and appropriate management is important in successful patient care.
Complementary Clinical Context, cont.

- For some patients, a 35% reduction in headache frequency or intensity may be deemed an insufficient level of improvement, thus leading them to risk dose escalation.
- Additionally, patients with migraine may need to be educated about appropriate use and risks of these agents.
- Finally, recent studies suggest that some medications used for migraine may offer long-term protection against headache progression whereas other agents may elevate progression risk.
- Specifically, one epidemiologic study assessing medication use in the general migraine population reports that aspirin or ibuprofen use may protect against progression from episodic to chronic headache conditions.\(^\text{11}\)
- In contrast, opioid use was positively associated with chronic headache conditions. Although conclusions are preliminary regarding the benefits and risks of selected agents for long-term use, studies suggest that these agents may play a significant role in headache progression and patterns, lending further emphasis to the importance of following patients closely, including regular assessment of NSAIDs, and other complementary treatments for migraine prevention.
Pharmacologic Future Research Recommendations

- Although many preventive therapies reviewed herein are rated as Level C or U on the basis of the quality of evidence available, for some treatments extensive clinical experience supports a possible role in migraine prevention.
- Many of the older approaches to treating episodic migraine lack the financial justification for high-quality clinical study because they are not currently patentable drugs or otherwise do not promise a financial return for the cost of a major study.
- Until such treatments can be accurately studied, practitioners are cautioned not to discount these agents because Class I prospective clinical studies are lacking.
- A case-by-case evaluation of these agents as treatment options is prudent. Future directions should include validating these initial clinical observations in scientifically sound randomized controlled trials.
Complementary Future Research Recommendations

- Little is known about many of the NSAIDs and complementary treatments reviewed in this guideline; therefore, additional studies are needed to further understand the optimal doses of these migraine prevention treatments.
- Additionally, many of these treatments are readily available but not for migraine prevention, so little is known about increased AE risks when treatments are used one or more times daily for migraine prevention.
- More studies are needed that further assess the relative efficacy of these treatments in relation to other pharmacologic therapies.
- Other shortcomings of the existing evidence became apparent during this review and analysis, and several areas worthy of future investigation may include the following:
  - Acceptability, long-term use, safety, and effectiveness of specific preventive therapies
  - Use of combination therapies, including drug therapy with behavioral treatment or combinations of 2 or more drugs
Complementary Future Research Recommendations, cont.

- Best duration for giving preventive treatment and how to discontinue treatment
- Predictors of remission with or response to preventive treatment
- Treatment of migraine and associated common comorbidities (e.g., depression, obesity, epilepsy, hypertension) and use of specific monotherapies or combination therapies in these patient subpopulations
- Development of stepped care and other treatment strategies for particular migraine headache types or particular migraine patient subgroups
- Compliance with preventive therapies
- Value of follow-up and patient education in disease management
- Use of preventive therapies to prevent illness progression (to chronic migraine)
- Effect of preventive treatments on acute therapy effectiveness
Complementary Future Research Recommendations, cont.

- The role of acute medication overuse in limiting the therapeutic efficacy of migraine preventive therapies
- Prospective trials that investigate standardized outcomes
References


References, cont.


For a complete list of references, please access the full guideline at guidelines@aan.com.
Question-and-Answer Period

- Questions/comments?
Closing

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