Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults : Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

S. Holland, S.D. Silberstein, F. Freitag, et al.

Neurology 2012;78;1346
DOI 10.1212/WNL.0b013e3182535d0c

SPECIAL ARTICLE

Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

S. Holland, PhD
S.D. Silberstein, MD, FACP
F. Freitag, DO
D.W. Dodick, MD
C. Argoff, MD
E. Ashman, MD

Correspondence & reprint requests to American Academy of Neurology: guidelines@aan.com

ABSTRACT

Objective: To provide updated evidence-based recommendations for the preventive treatment of migraine headache. The clinical question addressed was: Are nonsteroidal anti-inflammatory drugs (NSAIDs) or other complementary treatments effective for migraine prevention?

Methods: The authors analyzed published studies from June 1999 to May 2009 using a structured review process to classify the evidence relative to the efficacy of various medications for migraine prevention.

Results: The author panel reviewed 284 abstracts, which ultimately yielded 49 Class I or Class II articles on migraine prevention; of these 49, 15 were classified as involving nontraditional therapies, NSAIDs, and other complementary therapies that are reviewed herein.

Recommendations: Petasites (butterbur) is effective for migraine prevention and should be offered to patients with migraine to reduce the frequency and severity of migraine attacks (Level A). Fenoprofen, ibuprofen, ketoprofen, naproxen, naproxen sodium, MIG-99 (feverfew), magnesium, riboflavin, and subcutaneous histamine are probably effective for migraine prevention (Level B). Treatments considered possibly effective are cyproheptadine, Co-Q10, estrogen, mefenamic acid, and flurbiprofen (Level C). Data are conflicting or inadequate to support or refute use of aspirin, indomethacin, omega-3, or hyperbaric oxygen for migraine prevention. Montelukast is established as probably ineffective for migraine prevention (Level B). *Neurology*® 2012;78:1346–1353

GLOSSARY

AAN = American Academy of Neurology; **AE** = adverse effect; **CI** = confidence interval; **HBO** = hyperbaric oxygen; **NSAID** = nonsteroidal anti-inflammatory drug; **OR** = odds ratio; **RR** = relative risk.

See page 1337

Supplemental data at www.neurology.org

Supplemental Data

Podcast

CME

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. This guideline seeks to assess this new evidence to answer the following clinical question: 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? This article addresses the efficacy and safety of histamines/antihistamines; nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics; and several herbal, vitamin, and mineral preparations, whereas a companion article addresses standard pharmacologic treatments for migraine prevention.[4]

DESCRIPTION OF THE ANALYTIC PROCESS

The AAN and the American Headache Society participated in the development process. An author

From the Armstrong Atlantic State University (S.H.), Savannah, GA; Thomas Jefferson University (S.D.S.), Jefferson Headache Center, Philadelphia, PA; Comprehensive Headache Center (F.F.), Baylor University Headache Medicine Center, Dallas, TX; Mayo Clinic (D.D.), Scottsdale, AZ; New York University School of Medicine (C.A.), Albany; and Elmendorf Air Force Base (E.A.), AK.

Appendices e-1–e-5 and tables e-1 and e-2 are available on the *Neurology*® Web site at www.neurology.org.

Approved by the Quality Standards Subcommittee on February 19, 2011; by the Practice Committee on June 19, 2011; by the AHS Board of Directors on March 29, 2012; and by the AAN Board of Directors on November 7, 2011.

Study funding: This guideline was developed with financial support from the American Academy of Neurology and the American Headache Society. None of the authors received reimbursement, honoraria, or stipends for their participation in the development of this guideline.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.

Table 1 Classification of migraine preventive therapies (available in the United States)

Level A: Medications with established efficacy (≥2 Class I trials)	Level B: Medications are probably effective (1 Class I or 2 Class II studies)	Level C: Medications are possibly effective (1 Class II study)	Level U: Inadequate or conflicting data to support or refute medication use	Other: Medications that are established as possibly or probably ineffective
Herbal preparations, vitamins, minerals, and other	NSAIDs	NSAIDs	NSAIDs	Probably not effective
Petasites	Fenoprofen[a]	Flurbiprofen[a]	Aspirin	Leukotriene receptor antagonist
	Ibuprofen[a]	Mefenamic acid[a]	Indomethacin[a]	Montelukast
	Ketoprofen[a]	Herbal preparations vitamins, minerals, and other	Herbal preparations vitamins, minerals, and other	
	Naproxen[a]	Co-Q10	Omega-3	
	Naproxen sodium[a]	Estrogen	Other	
	Herbal preparations, vitamins, minerals, and other	Antihistamine	Hyperbaric oxygen	
	Magnesium	Cyproheptadine		
	MIG-99 (feverfew)			
	Riboflavin			
	Histamines			
	Histamine SC			

Abbreviation: NSAID = nonsteroidal anti-inflammatory drug.
[a] Indicates classification based on original guideline and new evidence not found for this report.

panel of headache and methodologic experts was assembled to review the evidence.

Computerized searches of the MEDLINE, PsycINFO, and CINAHL databases identified new studies. The search strategy used the MeSH term "headache" (exploded) and a published search strategy for identifying randomized controlled trials in adults that were published in English between June 1999 and May 2007. Additional MEDLINE searches revealed studies published through May 2009, which were reviewed and are included as supplemental articles.

Studies of NSAIDs and complementary treatments available in the United States were included in the analysis if they randomized patients with migraine to the agent under study or a comparator treatment (including placebo) and utilized masked (blinded) outcome assessment. At least 2 panelists independently reviewed each selected study and rated it using the AAN therapeutic classification of evidence scheme (appendix e-3 on the *Neurology*® Web site at www.neurology.org). Differences in ratings were resolved by author panel discussion.

ANALYSIS OF EVIDENCE The original search identified 179 articles and included pharmacologic and complementary treatments and NSAIDs. The supplemental search from 2007 to 2009 yielded an additional 105 articles. Of the total 284 articles, 15 were classified as Class I or Class II and identified as relating to NSAIDs and complementary treatments; they are reviewed herein. Clinical studies reviewed were limited to those assessing efficacy of NSAIDs and complementary treatments for prevention of episodic migraine in adults (e.g., <15 days/month). Studies were excluded if they assessed the efficacy of therapeutic agents for prevention or treatment of chronic migraine, intractable migraine, tension-type headache, or headache in adolescents or children. Also excluded were studies that assessed 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 were not included. NSAIDs and complementary treatments not commonly or readily available in the United States are not reviewed in this guideline.

Since the 2000 guideline publication, the AAN revised its evidence classification criteria to include study completion rates. Studies whose completion rates are below 80% were downgraded.

We found no additional Class I or Class II studies published since the original guideline for fenoprofen, ibuprofen, ketoprofen, naproxen, naproxen sodium, or indomethacin. Recommendations regarding these treatments are based on the evidence reviewed in the original guideline (denoted in table 1).

Following is a summary of Class I and Class II evidence for the efficacy of NSAIDs and comple-

mentary treatments for migraine prevention. Assessment of relative safety and tolerability of these agents as compared with placebo or other active treatments falls outside the scope of this efficacy assessment, but general information regarding safety and tolerability is included. Additionally, efficacy results from the summarized trials may be dependent on study design, including study duration (8 weeks vs 6 months), medication doses (low vs high), and dosing regimens and titrations—all of which may influence efficacy onset, relative efficacy, and quality of the evidence.

Histamines/antihistamines/leukotriene receptor antagonists. In the 2000 guideline, there were no studies of histamines, antihistamines, or leukotriene receptor antagonists for migraine prevention. Since that publication, several studies of histamine, cyproheptadine, and montelukast have been performed.

Histamine. Three Class II single-center studies (all from the same center) show the efficacy of histamine for migraine prevention.[5–7] N-alpha-methyl histamine (1–10 ng 2 times/week) SC injections reduced attack frequency from baseline as compared with placebo.[5] Headache frequency at 4 weeks was reduced from 3.8 to 0.5 in the histamine group, as compared with reduction from 3.6 to 2.9 attacks for placebo ($p < 0.0001$). Histamine was statistically superior to placebo at all treatment visits through 12 weeks for reduction in migraine frequency, severity, and duration ($p < 0.0001$). Transient itching at the injection sites was the only reported adverse effect (AE), but it did not reach significance.

In a second Class II study, histamine was shown to be as effective as sodium valproate in reducing attack frequency and better than sodium valproate in reducing headache duration and intensity.[6] Specifically, both sodium valproate 500 mg/day and histamine (1–10 ng 2 times/week) SC injections improved headache frequency, duration, and intensity as early as 8 weeks following treatment when compared with baseline ($p < 0.05$). No patients on histamine presented with AEs. Conversely, 37% of patients on sodium valproate experienced nausea, 34% had tremor, 24% had weight gain, and 12% had alopecia.

A third study reported the efficacy of histamine in migraine prevention as compared with topiramate. Topiramate 100 mg/day was compared with histamine (1–10 ng 2 times/week SC), and both active treatments showed improvement over baseline measures for attack frequency, intensity, and use of rescue medication.[7] Eleven percent (5/45) of subjects treated with histamine withdrew from the histamine group because they were not satisfied with the speed of results, although no AEs were reported. Few subjects reported transitory burning and itching at the injection site. Similar AEs and withdrawal rates (for slow reaction speed) were reported for the sodium valproate study.[6] Histamine SC was associated with transitory burning and itching at the injection site.

Cyproheptadine. A single Class II study (described in the companion guideline) showed cyproheptadine (4 mg/day) was as effective as propranolol (80 mg/day) in reducing migraine frequency and severity.[8]

Montelukast. One Class I study of montelukast (20 mg) for migraine prevention reported no significant difference between treatments in the percentage of patients with a ≥50% decrease in migraine attack frequency per month (15.4% for montelukast vs 10.3% for placebo [odds ratio (OR) = 1.64; confidence interval (CI) 0.64–4.20]).[9] As compared with the placebo group, the montelukast group reported no differences in incidence, frequency, or severity of AEs in this 3-month treatment phase.

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; table 1).

NSAIDs. The efficacy of NSAIDs for migraine prevention was reported in the original guideline, including 23 controlled trials of 10 different NSAIDs that showed a modest but significant benefit for naproxen sodium, with similar trends for flurbiprofen, ketoprofen, and mefenamic acid. In the absence of new clinical reports, recommendations for NSAID use for migraine prevention are based on data from the original guideline. Regarding aspirin, new clinical evidence is available and included herein.

Aspirin. In the original guideline, studies of aspirin were found to have conflicting results. Since the original report, 2 additional Class II studies have been reported. As summarized in the companion article, aspirin was found to be as effective as metoprolol for migraine prevention.[10] In a second study, aspirin 100 mg in combination with vitamin E 600 IU every other day was compared with placebo in combination with vitamin E.[11] No differences were noted between aspirin and placebo treatments for migraine frequency or severity at 12 months or 36 months.

Conclusions. The efficacy of aspirin for migraine prevention is unknown (conflicting Class II studies; table 1).

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.[12] 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. Since the original guideline, additional studies have been identified that assess the efficacy of Co-Q10, estrogen, hyperbaric oxygen (HBO), magnesium, MIG-99, omega-3, Petasites, and riboflavin for migraine prevention.

Co-Q10 (water-soluble disbursable form of Co-Q10). One small Class II study showed that Co-Q10 100 mg TID was significantly more effective than placebo in reducing attack frequency from baseline to 4 months following treatment.[13] The 50% responder rate for attack frequency (≥50% reduction) was 47.6% for CoQ10 vs 14.3% for placebo ($p = 0.02$). The actual reduction in attack frequency was -1.9 ± 1.9 for CoQ10 and 0.09 ± 1.9 for placebo ($p = 0.05$). One patient withdrew from the Co-Q10 treatment group because of cutaneous allergy.

Estrogen. A combination of soy isoflavones (60 mg), dong quai (100 mg), and black cohosh (50 mg) (each component standardized to its primary alkaloid) reduced migraine attack frequency vs placebo in a small Class II study.[14] The mean frequency of menstrually associated migraine attacks during weeks 9–24 was reduced from 10.3 ± SEM 2.4 in patients treated with placebo to 4.7 ± SEM 1.8 ($p < 0.01$) in patients treated with the phytoestrogen preparation.

In a second Class II trial, percutaneous estradiol was applied 6 days before the first full day of bleeding up to and including the second full day of menstruation.[15] Estradiol 1.5 mg (gel patch applied to the upper thigh or arm) was associated with a 22% reduction in migraine days (estradiol = 133 migraine days, placebo = 171 migraine days; relative risk [RR] 0.78; CI 0.62–0.99, $p = 0.04$). This improvement was temporary, as subjects reported a 40% increase in migraine days in the 5 days following treatment (RR 1.40; CI 1.03–1.92, $p = 0.03$). No serious AEs were otherwise reported, although common risks associated with estrogen supplementation are well documented throughout the literature. Limited studies are available regarding estrogen's safety specifically for long-term use in migraine prevention.

Hyperbaric oxygen. In a single Class II study, no differences were found between the HBO group (3 30-minute treatments/week) and control group, but an increase in headache hours was experienced by both groups vs the pretreatment level.[16] Corrected for the number of days, the increase was 6.9 hours/week for HBO vs 4.7 hours/week for controls. This study reports no assessment of tolerability or safety of HBO vs control for migraine prevention.

Magnesium. In the original guideline, magnesium was found to be probably effective for migraine prevention on the basis of 2 positive Class II studies and 1 negative Class III study. Since the 2000 report, 1 additional Class II study compared the combination of magnesium (300 mg), riboflavin (400 mg), and MIG-99 (100 mg) with placebo (25 mg of riboflavin, which was thought to be a subtherapeutic dose but sufficient to provide urine discoloration to prevent unblinding of the study).[17] Both treatment groups showed improvement over baseline, but no between-group differences were noted (42% responders [defined as ≥50% reduction in attacks] in treatment group and 44% in placebo group; $p = 0.87$). The study was not powered to show between-group differences and involved administration of magnesium only as combination therapy; thus, the results cannot be clearly interpreted regarding the efficacy of magnesium for migraine prevention. AEs were not reported.

MIG-99. MIG-99 is a relatively new stable extract of tanacetum parthenium (feverfew), which is reproducibly manufactured with supercritical CO_2 from feverfew. In the original guideline, 3 positive studies and 1 negative study (feverfew given as alcohol extract) are reviewed that suggest possible efficacy for migraine prevention. Since the original guideline, 3 new studies on MIG-99 for migraine prophylaxis have been published. In 1 Class I study, the migraine frequency decreased from 4.76 by 1.9 attacks/month in the MIG-99 group and by 1.3 attacks in the placebo group ($p < 0.05$). A logistic regression analysis of responder rates showed an OR of 3.4 in favor of MIG-99 ($p < 0.005$).[18] AEs reported were similar to those from placebo, the most common being gastrointestinal system disorders or respiratory system disorders.

In a Class II dose-finding study, MIG-99 6.25 mg TID (other doses tested: 2.08 and 18.75 mg TID) was effective in reducing migraine frequency by 1.8 attacks/month (baseline = 4.5 ± 0.8 to 3.0 ± 1.5 attacks at week 12). The placebo group reduced migraine frequency by 0.3 attacks/month (baseline = 4.9 ± 0.9 to 4.6 ± 2.2 attacks at week 12; $p = 0.02$, CI 1.07–2.49).[19]

In a second Class II study, described above for magnesium, the efficacy of the combination of magnesium (300 mg), riboflavin (400 mg), and MIG-99 (100 mg) was not shown in comparison with a placebo (25 mg of riboflavin).[17]

Omega-3. One Class I study assessed the efficacy of omega-3 polyunsaturated fatty acids (3 g BID) vs placebo and found no difference in mean number of attacks during the last 4 weeks of the study (month 4), but the total number of attacks in 4 months was

lower in the omega-3 treatment group.[20] A very strong placebo effect was observed in this trial: 45% reduction of attacks between run-in and 4-month treatment period for placebo as compared with 55% in the omega-3 group ($p = 0.058$). AEs associated with omega-3 treatment included significantly more frequent eructation (8%) than with placebo (1%); otherwise, no differences in AEs between treatments were reported.

Petasites. Petasites is a purified extract from the butterbur plant. Two Class I studies show Petasites (50–75 mg BID) to be effective in reducing migraine attack frequency.[21,22] In the first study, the frequency of migraine attacks decreased by a maximum of 60% vs baseline, and the reduction in the number of migraine attacks vs placebo was significant ($p \leq 0.05$).[21] Petasites reduced the frequency of attacks from 3.3 ± 1.5 to 1.8 ± 0.8 attacks/month after 4 weeks, to 1.3 ± 0.9 attacks/month after 8 weeks, and to 1.7 ± 0.9 attacks/month after 12 weeks ($p \leq 0.05$). Following placebo, attack frequency decreased from 2.9 ± 1.2 to 2.2 ± 0.7 after 4 weeks ($p \leq 0.05$), to 2.4 ± 0.8 after 8 weeks ($p \leq 0.05$), and to 2.6 ± 1.1 after 12 weeks ($p \leq 0.05$). No AEs were reported.

In the second Class I study, migraine attack frequency was reduced by 48% for Petasites extract 75 mg BID ($p = 0.0012$ vs placebo), by 36% for Petasites extract 50 mg BID ($p = 0.127$ vs placebo), and by 26% for the placebo group.[22] The incidence of burping increased for Petasites extract 75 mg or 50 mg vs placebo. Importantly, safety of prolonged use of Petasites is not established by the short-term studies included in this review.

Riboflavin. In the original guideline, 1 Class I trial reported riboflavin to be superior to placebo, suggesting probable efficacy for migraine prevention. Since then, 1 additional Class II study (reviewed above) failed to show the efficacy of the combination of magnesium (300 mg), riboflavin (400 mg), and MIG-99 (100 mg) vs 25 mg of riboflavin.[16]

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). 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).

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

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

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).[23] 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.[4] 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).

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). 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). 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. 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.[24] 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.

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

AUTHOR CONTRIBUTIONS

Dr. Holland: manuscript preparation, drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Silberstein: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. Dr. Freitag: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Dodick: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Argoff: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Ashman: drafting/revising the manuscript, analysis or interpretation of data.

DISCLOSURE

Dr. Holland (formerly Dr. Pearlman) receives consulting income from Map Pharmaceuticals and the American Headache Society and research support from Albert Einstein College of Medicine. Dr. Silberstein is on the advisory panel of and receives honoraria from AGA, Allergan, Amgen, Capnia, Coherex, Colucid, Cydex, GlaxoSmithKline, Lilly, MAP, Medtronic, Merck, Minster, Neuralieve, NINDS, NuPathe, Pfizer, St. Jude Medical, and Valeant. He is on the speakers' bureau of and receives honoraria from Endo Pharmaceuticals, GlaxoSmithKline, and Merck. He serves as a consultant for and receives honoraria from Amgen and Novartis. His employer receives research support from AGA, Allergan, Boston Scientific, Capnia, Coherex, Endo Pharmaceuticals, GlaxoSmithKline, Lilly, MAP, Medtronic, Merck, NINDS, NuPathe, St. Jude Medical, and Valeant Pharmaceuticals. Dr. Freitag has served on the scientific advisory boards of Zogenix Pharmaceuticals, Allergan Pharmaceuticals, Nautilus, MAP Pharmaceuticals, and Nupathe; has received travel expenses and or honoraria from GlaxoSmithKline, Zogenix, Merck, Nautilus, Allergan, Diamond Headache Clinic Research and Educational Foundation (not for profit), and the American Headache Society (travel). Dr. Freitag is a member of the Board of Directors of the National Headache Foundation. Dr. Dodick, within the past 3 years, serves on advisory boards and has consulted for Allergan, Alder, Pfizer, Merck, Coherex, Ferring, Neurocore, Neuralieve, Neuraxon, NuPathe Inc., MAP, SmithKlineBeecham, Boston Scientific, Medtronic, Inc., Nautilus, Eli Lilly & Company, Novartis, Colucid, GlaxoSmithKline, Autonomic Technologies, MAP Pharmaceuticals, Inc., Zogenix, Inc., Impax Laboratories, Inc., Bristol Myers Squibb, Nevro Corporation, Atlas, Arteaus, and Alder Pharmaceuticals. Within the past 3 years, Dr. Dodick has received funding for travel, speaking, or editorial activities from CogniMed, Scientiae, Intramed, SAGE Publishing, Lippincott Williams & Wilkins, Oxford University Press, Cambridge University Press, Miller Medical, Annenberg for Health Sciences; he serves as Editor-in-Chief and on the editorial boards of *The Neurologist*, *Lancet Neurology*, and *Postgraduate Medicine*; and has served as Editor-in-Chief of *Headache Currents* and as an Associate Editor of *Headache*; he receives publishing royalties for *Wolff's Headache, 8th edition* (Oxford University Press, 2009) and *Handbook of Headache* (Cambridge University Press, 2010). Within the past 3 years, Dr. Dodick has received research grant support from Advanced Neurostimulation Systems, Boston Scientific, St Jude Medical, Inc., Medtronic, NINDS/NIH, Mayo Clinic. Dr. Argoff has served on a scientific advisory board for the Department of Defense and DSMB for the NIH; has received funding for travel and/or speaking and/or has served on a speakers' bureau for Pfizer (King), Janssen (Pricara), Millennium Laboratories, Neurogesx, Forest Laboratories, Eli Lilly, Covidien, and Endo Pharmaceuticals; has received research support from Endo Pharmaceuticals, Forest Laboratories, Eli Lilly, Neurogesx, Pfizer, and SBRT funded by the NIH; and has received stock/stock options from Pfizer. Dr. Ashman is the Level of Evidence editor for *Neurology* and serves on the AAN Guideline Development Subcommittee. He reports no other disclosures. **Full disclosures were provided at the time of Board approval. Go to Neurology.org for full disclosures.**

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology and the American Headache Society. It is based on as assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN and the AHS recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

CONFLICT OF INTEREST

The American Academy of Neurology and the American Headache Society are committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and AHS keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN and AHS limit the participation of authors with substantial conflicts of interest. The AAN and AHS forbid commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN and AHS committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

Received June 27, 2011. Accepted in final form October 26, 2011.

REFERENCES

1. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF; The American Migraine Prevalence and Prevention Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007; 68:343–349.

2. Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. Available at: http://www.aan.com/professionals/practice/pdfs/gl0090.pdf. Accessed April 10, 2010.
3. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55:754–762.
4. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78:1337–1345.
5. Millán-Guerrero RO, Isais-Millán R, Benjamín TH, Tene CE. N-alpha-methyl histamine safety and efficacy in migraine prophylaxis: phase III study. Can J Neurol Sci 2006;33:195–199.
6. Millán-Guerrero RO, Isais-Millán R, Barreto-Vizcaíno S, et al. Subcutaneous histamine versus sodium valproate in migraine prophylaxis: a randomized, controlled, double-blind study. Eur J Neurol 2007;14:1079–1084.
7. Millán-Guerrero RO, Isais-Millán R, Barreto-Vizcaíno S, et al. Subcutaneous histamine versus topiramate in migraine prophylaxis: a double-blind study. Eur Neurol 2008;59:237–242.
8. Rao BS, Das DG, Taraknath VR, Sarma Y. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. Neurol India 2000;48:223–226.
9. Brandes JL, Visser WH, Farmer MV, et al. Montelukast for migraine prophylaxis: a randomized, double-blind, placebo-controlled study. Headache 2004S;44:581–586.
10. Diener HC, Hartung E, Chrubasik J, et al; Study group. A comparative study of oral acetylsalicylic acid and metoprolol for the prophylactic treatment of migraine: a randomized, controlled, double-blind, parallel group phase III study. Cephalalgia 2001;21:120–128.
11. Benseñor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE. Low-dose aspirin for migraine prophylaxis in women. Cephalalgia 2001;21:175–183.
12. Silberstein SD, Olesen J, Bousser MG, et al; International Headache Society. The International Classification of Headache Disorders, 2nd Edition (ICHD-II): revision of criteria for 82 Medication-overuse headache [erratum in 2006;26:360]. Cephalalgia 2005;25:460–465.
13. Sandor PS, Di Clemente L, Coppola G, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology 2005;64:713–715.
14. Burke BE, Olson RD, Cusack BJ. Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine. Biomed Pharmacother 2002;56:283–288.
15. 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.
16. Eftedal OS, Lydersen S, Helde G, White L, Brubakk AO, Stovner LJ. A randomized, double blind study of the prophylactic effect of hyperbaric oxygen therapy on migraine. Cephalalgia 2004;24:639–644.
17. Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. Headache 2004;44:885–890.
18. Pfaffenrath V, Diener HC, Fischer M, Friede M, Henneicke-von Zepelin HH. 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.
19. Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-von Zepelin HH. Efficacy and safety of 6.25 mg tid feverfew CO2-extract (MIG-99) in migraine prevention–a randomized, double-blind, multicentre, placebo-controlled study. Cephalalgia 2005;25:1031–1041.
20. Pradalier A, Bakouche P, Baudesson G, et al. Failure of omega-3 polyunsaturated fatty acids in prevention of migraine: a double-blind study versus placebo. Cephalalgia 2001;21:818–822.
21. Grossman W, Schmidramsl H. An extract of Petasites hybridus is effective in the prophylaxis of migraine. Altern Med Rev 2001;6:303–310.
22. Lipton RB, Gobel H, Einhaupl KM, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. Neurology 2004;63:2240–2244.
23. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache 2007;47:355–363.
24. Scher AI, Lipton RB, Stewart WF, Bigal M. Patterns of medication use by chronic and episodic headache sufferers in the general population: results from the frequent headache epidemiology study. Cephalalgia 2010;30:321–328.

Endorsed by the American Osteopathic Association on March 22, 2012.

Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults : Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

S.D. Silberstein, S. Holland, F. Freitag, et al.

Neurology 2012;78;1337
DOI 10.1212/WNL.0b013e3182535d20

SPECIAL ARTICLE

Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society

S.D. Silberstein, MD, FACP
S. Holland, PhD
F. Freitag, DO
D.W. Dodick, MD
C. Argoff, MD
E. Ashman, MD

Correspondence & reprint requests to American Academy of Neurology: guidelines@aan.com

ABSTRACT

Objective: To provide updated evidence-based recommendations for the preventive treatment of migraine headache. The clinical question addressed was: What pharmacologic therapies are proven effective for migraine prevention?

Methods: The authors analyzed published studies from June 1999 to May 2009 using a structured review process to classify the evidence relative to the efficacy of various medications available in the United States for migraine prevention.

Results and Recommendations: The author panel reviewed 284 abstracts, which ultimately yielded 29 Class I or Class II articles that are reviewed herein. 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). Frovatriptan is effective for prevention of menstrual migraine (Level A). Lamotrigine is ineffective for migraine prevention (Level A). *Neurology*® 2012;78:1337–1345

GLOSSARY

AAN = American Academy of Neurology; **AE** = adverse event; **CI** = confidence interval; **ER** = extended-release; **MAM** = menstrually associated migraine; **PMP** = perimenstrual period; **RCT** = randomized controlled trial.

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. This guideline seeks to assess this new evidence to answer the following clinical question: 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? This article addresses the safety and efficacy of pharmacologic therapies for migraine prevention.

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. An updated guideline on nonsteroidal anti-inflammatory drugs[5] and complementary alternative treatments has been approved for publication as a companion to this guideline.[5]

DESCRIPTION OF THE ANALYTIC PROCESS

The AAN and the American Headache Society participated in the development process. An author panel of headache and methodologic experts was assembled to review the evidence. Computerized searches of the MEDLINE, PsycINFO, and CINAHL databases identified new studies (published in English). The 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. Additional MEDLINE searches revealed studies published through May

See page 1346

Supplemental data at www.neurology.org

Supplemental Data

Podcast

CME

From Thomas Jefferson University (S.D.S.), Jefferson Headache Center, Philadelphia, PA; the Armstrong Atlantic State University (S.H.), Savannah, GA; Comprehensive Headache Center (F.F.), Baylor University Headache Medicine Center, Dallas, TX; Mayo Clinic (D.D.), Scottsdale, AZ; New York University School of Medicine (C.A.), Albany; and Elmendorf Air Force Base (E.A.), AK.

Appendices e-1–e-5, reference e1, and tables e-1 and e-2 are available on the *Neurology*® Web site at www.neurology.org.

Approved by the Quality Standards Subcommittee on February 19, 2011; by the Practice Committee on June 19, 2011; by the AHS Board of Directors on March 29, 2012; and by the AAN Board of Directors on January 27, 2012.

Study funding: This guideline was developed with financial support from the American Academy of Neurology and the American Headache Society. None of the authors received reimbursement, honoraria, or stipends for their participation in development of this guideline.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.

Table 1 Classification of migraine preventive therapies (available in the United States)

Level A: Medications with established efficacy (≥2 Class I trials)	Level B: Medications are probably effective (1 Class I or 2 Class II studies)	Level C: Medications are possibly effective (1 Class II study)	Level U: Inadequate or conflicting data to support or refute medication use	Other: Medications that are established as possibly or probably ineffective
Antiepileptic drugs	Antidepressants/ SSRI/SSNRI/TCA	ACE inhibitors Lisinopril	Carbonic anhydrase inhibitor	Established as not effective
Divalproex sodium	Amitriptyline	Angiotensin receptor blockers	Acetazolamide	Antiepileptic drugs
Sodium valproate	Venlafaxine	Candesartan	Antithrombotics	Lamotrigine
Topiramate	β-Blockers	α-Agonists	Acenocoumarol	Probably not effective
β-Blockers	Atenolol[a]	Clonidine[a]	Coumadin	Clomipramine[a]
Metoprolol	Nadolol[a]	Guanfacine[a]	Picotamide	Possibly not effective
Propranolol	Triptans (MRM[b])	Antiepileptic drugs	Antidepressants SSRI/SSNRI	Acebutolol[a]
Timolol[a]	Naratriptan[b]	Carbamazepine[a]	Fluvoxamine[a]	Clonazepam[a]
Triptans (MRM[b])	Zolmitriptan[b]	β-Blockers	Fluoxetine	Nabumetone[a]
Frovatriptan[b]		Nebivolol	Antiepileptic drugs	Oxcarbazepine
		Pindolol[a]	Gabapentin	Telmisartan
		Antihistamines	TCAs	
		Cyproheptadine	Protriptyline[a]	
			β-Blockers	
			Bisoprolol[a]	
			Ca++ blockers	
			Nicardipine[a]	
			Nifedipine[a]	
			Nimodipine	
			Verapamil	
			Direct vascular smooth muscle relaxants	
			Cyclandelate	

Abbreviations: ACE = angiotensin-converting-enzyme; MRM = menstrually related migraine; SSNRI = selective serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
[a] Classification based on original guideline and new evidence not found for this report.
[b] For short-term prophylaxis of MRM.

2009, which were reviewed and included as supplemental articles.

Studies of pharmacologic agents available in the United States were included in the analysis if they randomized adult patients with migraine to the agent under study or a comparator drug (including placebo) and utilized masked outcome assessment. At least 2 panelists independently reviewed each study and rated it according to the AAN therapeutic classification of evidence scheme (appendix e-3 on the *Neurology*® Web site at www.neurology.org). Differences in ratings were resolved by author panel discussion.

ANALYSIS OF EVIDENCE The original search identified 179 articles. A supplemental search (2007–2009) yielded 105 additional articles. Of the total 284 articles, 29 were classified as Class I or Class II and are reviewed herein. Studies were excluded if they:

- Assessed the efficacy of therapeutic agents for headache other than episodic migraine in adults
- Assessed acute migraine treatment, migraine aura treatment/prevention, or nonpharmacologic treatments (e.g., behavioral approaches)
- Used quality of life measures, disability assessment, or nonstandardized outcomes as primary efficacy endpoints
- Tested the efficacy of drugs not available in the United States

Since the 2000 guideline publication, the AAN revised its evidence classification criteria to include study completion rates. Studies with completion rates below 80% were downgraded; several studies in the original guideline have thus been downgraded.

We found no new Class I or II studies published for acebutolol, atenolol, bisoprolol, carbamazepine,

clonazepam, clonidine, clomipramine, fluvoxamine, guanfacine, nabumetone, nadolol, nicardipine, nifedipine, or protriptyline. Recommendations for these agents are based on the evidence reviewed in the original guideline (see table 1). Currently, no Class I or Class II studies exist for anticoagulants (limited Class III and IV studies were identified; table 1 includes anticoagulants).

Angiotensin receptor blockers and angiotensin-converting-enzyme inhibitors. In the 2000 guideline, there were no studies testing the efficacy of angiotensin receptor blockers or angiotensin-converting-enzyme (ACE) inhibitors for migraine prevention. Since that publication, 3 reports have been published.

Candesartan. In a Class II crossover study (12-week treatment separated by 4-week washout), the mean number of headache days was 18.5 with placebo (26.3% reduction from baseline) vs 13.6 with candesartan (45.6% reduction from baseline; $p = 0.001$).[6] Selected secondary endpoints also favored candesartan: headache hours (139 vs 95; $p < 0.001$), migraine days (12.6 vs 9.0; $p < 0.001$), migraine hours (92.2 vs 59.4; $p < 0.001$), and headache severity index (293 vs 191; $p < 0.001$). No serious adverse events (AEs) occurred. The most common AEs were dizziness (31%), "symptoms of the musculoskeletal system" (21%), and fatigue (14%); none occurred significantly more often than with placebo.

Lisinopril. One Class II study reported significant reduction in all 3 primary endpoints with lisinopril vs placebo (headache hours: 129 vs 162 [mean change in hours 20, confidence interval (CI) 5–36]; headache days: 19.7 vs 23.7 [20, CI 5–30]; migraine days: 14.5 vs 18.5 [21, CI 9–34]).[7] AEs included cough (26%; 10% discontinued treatment due to cough), dizziness (23%), and "tendency to faint" (10%). No serious AEs were reported.

Telmisartan. In a single Class II placebo-controlled trial, telmisartan 80 mg did not show a significant difference from placebo for reduction in migraine days (−1.65 vs −1.14).[8]

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. ***Divalproex.*** The original guideline found strong, consistent support (5 studies) for the efficacy of divalproex sodium and its corresponding compound, sodium valproate, for migraine prevention.

Since the 2000 publication, 1 double-blind, randomized, Class I placebo-controlled 12-week trial showed extended-release (ER) divalproex sodium 500–1,000 mg/day had a mean reduction in 4-week migraine headache rate from 4.4/week (baseline) to 3.2/week (−1.2 attacks/week) in the ER divalproex sodium group and from 4.2/week to 3.6/week (−0.6 attacks/week) in the placebo group (CI 0.2–1.2; $p = 0.006$).[9] No significant differences were detected between groups in the number of treatment-emergent AEs.

Clinical context. In most headache trials, patients taking divalproex sodium or sodium valproate reported no more AEs than those on placebo. However, weight gain has been clinically observed with divalproex sodium long-term use.[9,10] Treatment with these agents requires careful follow-up and testing because of pancreatitis, liver failure, and teratogenicity risks.[11]

Gabapentin. Since the 2000 publication, a Class III study[12] reported that a stable gabapentin dose (4-week titration phase to 2,400 mg/day; 8-week maintenance phase) significantly reduced the median monthly migraine rate vs placebo on the basis of a modified intention-to-treat analysis.

Lamotrigine. The original guideline reported a single Class I lamotrigine study[13] that failed to show a significant effect for migraine prevention. A second, new Class I study comparing lamotrigine 50 mg/day with placebo or topiramate 50 mg/day reported lamotrigine was not more effective than placebo (for both primary endpoints) and was less effective than topiramate in reducing migraine frequency and intensity.[14] The primary outcome measure (responder rate: ≥50% monthly migraine frequency reduction) was 46% for lamotrigine vs 34% for placebo ($p = 0.093$, CI 0.02–0.26) and 63% for topiramate vs 46% for lamotrigine ($p = 0.019$, CI 0.03–0.31). Treatment-related AEs (rash, giddiness, sleepiness, and gastrointestinal intolerance) occurred in 10% of patients on lamotrigine.

Oxcarbazepine. One Class II trial evaluated the efficacy of oxcarbazepine (1,200 mg/day) vs placebo.[15] There was no difference between oxcarbazepine (−1.30 [SE 0.282]) and placebo for mean change in number of migraine attacks from baseline during the last 28 days of the double-blind 15-week treatment phase (−1.74 [SE 0.283]; $p = 0.2274$).

Topiramate. Four Class I studies[14,16–18] and 7 Class II studies[19–25] report topiramate (50–200 mg/day) is effective in migraine prevention.

In a Class I placebo-controlled study (mean topiramate dose 125 mg/day [range 25–200 mg/day]), patients given topiramate experienced a significantly lower 28-day migraine frequency vs with placebo (3.31 ± 1.7 vs 3.83 ± 2.1; $p = 0.002$).[18] In a second placebo-controlled Class I double-crossover study (reviewed above), topiramate was more effective than

placebo and lamotrigine for primary efficacy measures.[14] In the topiramate groups, 15% of patients experienced AEs, most commonly paresthesias, sleepiness, and gastrointestinal intolerance. The placebo group reported gastrointestinal intolerance (3%) and anorexia (3%).

Two additional Class I studies report topiramate is as effective as propranolol[16] or sodium valproate,[17] drugs previously established as effective for migraine prevention. In the first study, subjects given topiramate 50 mg/day had reduced mean migraine frequency (episodes/month) from baseline (6.07 ± 1.89 to 1.83 ± 1.39; $p < 0.001$) at 8 weeks, decreased headache intensity VAS score from 7.1 ± 1.45 to 3.67 ± 2.1 ($p < 0.001$), and decreased headache duration from 16.37 ± 7.26 hours to 6.23 ± 5.22 hours ($p < 0.001$).[16] Subjects given topiramate reported paresthesias (23%), weight loss (16%), and somnolence (13%). In patients treated with propranolol 80 mg/day, mean headache frequency (episodes/month) decreased from 5.83 ± 1.98 to 2.2 ± 1.67 ($p < 0.001$) at 8 weeks, headache intensity VAS score decreased from 6.43 ± 1.6 to 4.13 ± 1.94 ($p < 0.001$), and headache duration decreased from 15.10 ± 6.84 hours to 7.27 ± 6.46 hours ($p < 0.001$). Although monthly headache frequency, intensity, and duration decreased in both groups, the topiramate group reported significantly greater mean reduction (topiramate frequency decrease 4.23 ± 1.2 vs propranolol 3.63 ± 0.96 [$p = 0.036$; CI 0.39–1.16]; topiramate intensity decrease 3.43 ± 1.38 vs propranolol 2.3 ± 1.2 [$p = 0.001$; CI 0.46–1.8]; topiramate duration decrease 10.1 ± 4.3 vs propranolol 7.83 ± 4.5 [$p = 0.048$; CI 0.17–4.6]).

In a crossover Class I trial (2-month washout between therapies) comparing topiramate 50 mg/day with sodium valproate 400 mg/day, both groups showed improvement from baseline in headache frequency, intensity, and duration.[17] Average monthly migraine frequency decreased by 1.8 times with sodium valproate (baseline 5.4 ± 2.5; posttreatment 3.6 ± 2.1; CI 1.0–2.6; $p < 0.001$), as compared with a 3-time reduction with topiramate (baseline 5.4 ± 2.0; posttreatment 2.4 ± 2.4; CI 2.1–3.9; $p < 0.001$). Headache intensity decreased by 3.7 with sodium valproate (baseline 7.7 ± 1.2; treatment 4.0 ± 2.1; CI 2.9–4.6; $p < 0.001$), as compared with a reduction of 3.6 with topiramate (baseline 6.9 ± 1.2, treatment phase 3.3 ± 1.5; CI 2.9–4.3; $p < 0.001$). The average headache episode duration decreased by 13.4 hours from baseline with sodium valproate (baseline 21.3 ± 14.6; treatment 7.9 ± 7.7; CI 7.5–19.3; $p < 0.001$) as compared with an 11.9-hour reduction with topiramate (baseline 17.3 ± 8.4; treatment 5.4 ± 6.4; CI 8.2–15.6; $p < 0.001$). The overall analysis of repeated-measures analysis of variance demonstrated no differences in monthly headache frequency, intensity, or duration after the first or second treatment rounds. Topiramate AEs were weight loss (18.8%), paresthesias (9.4%), or both (25%). Sodium valproate AEs were weight gain (34.5%), hair loss (3.1%), and somnolence (3.1%).

Results of 5 Class II studies support those of the Class I studies showing topiramate as effective for migraine prevention.[19–25] Four studies demonstrated significant improvement over placebo[19,20,23,24]; one included an active comparator arm, suggesting equivalence of topiramate (100, 200 mg/day) and propranolol (160 mg/day).[20] Two studies comparing topiramate and amitriptyline (25–150 mg/day) reported no difference in efficacy for primary endpoints; however, amitriptyline was associated with a significant AE increase, and the amitriptyline-topiramate combination suggested improvement in depression scores vs monotherapy.[21,22] In one of these studies,[21] the most common AEs were similar to those previously reported. One Class II placebo-controlled 24-week pilot study failed to show a difference in efficacy between topiramate 200 mg and placebo.[26]

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). 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).

Antidepressants. ***Fluoxetine.*** In the original guideline, 1 Class II study[27] showed fluoxetine (racemic) was significantly better than placebo for migraine prevention, but the results were not duplicated in a second study.[28]

Since the original guideline, a Class II study has shown fluoxetine 20 mg/day was more effective than placebo in reducing total pain index scores (calculated as [Dl × 1] + [D2 × 2] + [D3 × 3], where D1, D2, and D3 represent headache hours calculated in a month, with pain intensity shown by 1, 2, 3) at 6 months.[29] After the 6 months, pain index scores for the fluoxetine group decreased from 135 (baseline) to 41.3 (SD ± 63.8; $p = 0.001$). The placebo group pain index was 98 at baseline and 61.1 at 6 months (SD ± 57.7; $p = 0.07$); however, differences were noted between treatment groups for baseline measures.

Venlafaxine. In a Class I study, venlafaxine XR 150 mg significantly reduced the number of headache days (median reduction in days: venlafaxine 150 mg −4 days; venlafaxine 75 mg −2 days; placebo −1 day; Kruskal-Wallis = 10.306, $df = 2$; $p < 0.006$).[30] All 3 groups showed decreased headache severity and duration from baseline; no differences were observed between treatment groups for these endpoints. The most common AEs were nausea (41%), vomiting (27%), and drowsiness (27%). Fourteen percent of patients receiving venlafaxine withdrew because of AEs.

A Class II trial assessed the efficacy of venlafaxine vs amitriptyline; both were effective in reducing attack frequency (venlafaxine: baseline = 4.15 [SD ± 2.24] vs 12 weeks = 1.77 [SD ± 1.39; $p < 0.001$]; amitriptyline: baseline = 3.27 [SD ± 1.61] vs 12 weeks 1.54 [SD ± 1.54; $p < 0.001$]).[31] Patients taking venlafaxine experienced nausea/vomiting (23%) and tachycardia (15%); 1 patient withdrew because of AEs. Patients taking amitriptyline reported hypersomnolence (80%), dry mouth (69%), and concentration difficulties (54%).

Tricyclic antidepressants. The original guideline concluded amitriptyline was established as effective for migraine prevention; that evidence has since been downgraded to Class II (all 3 studies had >20% dropout rates). Comparative studies of amitriptyline with topiramate[21,22] and venlafaxine[31] (reviewed above) report similar efficacy at the doses tested.

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.

β-Blockers. ***Metoprolol.*** The original guideline concluded metoprolol was probably effective in migraine prevention. We reclassified these studies as Class I using the revised AAN criteria.

One new Class II study reported metoprolol (200 mg/day) was more effective than aspirin (300 mg/day) in achieving 50% migraine frequency reduction (responder rate metoprolol = 45.2%; aspirin = 29.6%; mean difference 15.65; CI 4.43–26.88).[32] Attack frequencies (attacks/month) at placebo run-in and week 20 are 3.36 to 2.37, respectively, for aspirin and 3.55 to 1.82, respectively, for metoprolol. No significant AEs were reported.

A small Class II study reported metoprolol (47.5–142.5 mg/day) had similar efficacy to nebivolol 5 mg/day for migraine prevention (assessed by a decrease in mean migraine attacks).[33]

Propranolol. The original guideline concluded propranolol was established as effective for migraine prevention.

In a Class II study, propranolol (80 mg/day) was more effective than placebo and as effective as cyproheptadine (4 mg/day) in reducing migraine frequency, duration, and attack severity.[34] The difference in attack frequency reduction was significant between treatments: propranolol −2.85 ± 0.2 (SEM) vs cyproheptadine −3.09 ± 0.31 vs combination 3.12 ± 0.1 vs placebo −1.77 ± 0.44 (all $p <$ 0.05 vs placebo). For attack frequency reduction, combination therapy was more effective than monotherapy ($p < 0.05$). AEs were drowsiness, sleep disturbance, weight gain, fatigue, and dry mouth; percentages of patients affected were not reported.

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. The original guideline concluded that verapamil and nimodipine were probably effective for migraine prevention. The original studies on verapamil and nimodipine were found to have conflicting Class III evidence on the basis of current classification criteria and were downgraded accordingly, yielding Level U recommendations.

Conclusions. Data from older studies regarding verapamil and nimodipine are insufficient when current AAN classification criteria are applied.

Direct vascular smooth muscle relaxants. The original guideline concluded cyclandelate was probably effective for migraine prevention.

Cyclandelate. Two new Class II studies reported conflicting results. The first study showed cyclandelate to be no more effective than placebo in reducing migraine days, attacks, or duration.[35] The second study (smaller, underpowered; n = 25) found cyclandelate significantly reduced the number of migraine days and duration (assessed using a contingent negative variation measure).[36]

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

Triptans. Since the original guideline, new Class I studies have assessed the efficacy of frovatriptan,[37,38] naratriptan,[39] and zolmitriptan[40] for short-term prevention of menstrually associated migraine (MAM).

Frovatriptan. Frovatriptan 2.5 mg BID/qd was more effective than placebo in reducing migraine fre-

quency.[37] The mean number of headache-free perimenstrual periods (PMPs) per patient (primary endpoint) was higher in the 2 frovatriptan groups (2.5 mg qd = 0.69 [SD ± 0.92; CI 1.14–2.73; p = 0.0091] vs 2.5 mg BID = 0.92 [SD 1.03; CI 1.84–4.28; $p < 0.0001$] vs placebo = 0.42 [SD ± 0.78]), representing 64% (2.5 mg/day) and 119% (5 mg/day) increases in the mean number of headache-free PMPs per patient over placebo. A second Class I study[38] also reports the MAM headache incidence during the 6-day PMP was 67% for placebo, 52% for frovatriptan 2.5 mg QD ($p < 0.0001$ vs placebo), and 41% for frovatriptan 2.5 mg BID ($p < 0.0001$ vs placebo; $p < 0.0001$ vs QD regimen). The AE incidence and type for both regimens were similar to those for placebo. The overall AE incidence for frovatriptan was 4.1% (2.5 mg BID) and 2.7% (2.5 mg qd) higher than during placebo treatment.

Naratriptan. In a Class I study, 1 mg BID (given for 5 days, starting 2 days before menses onset) reduced the number of perimenstrual migraine attacks and migraine days.[39] Patients treated with naratriptan 1 mg experienced more headache-free PMPs than those on placebo (50% vs 25%, p = 0.003). Naratriptan 1 mg reduced the number of MAMs (2.0 vs 4.0, $p < 0.05$) and MAM days (4.2 vs 7.0, $p < 0.01$) vs placebo. The AE incidence and severity were similar to those of placebo; <10% of patients experienced dizziness, chest pain, or malaise.

Zolmitriptan. One Class I study reported the efficacy of zolmitriptan 2.5 BID/TID vs placebo. Both zolmitriptan regimens demonstrated superior efficacy vs placebo: the proportion of patients with a ≥50% MAM attack frequency reduction (zolmitriptan 2.5 mg TID [58.6%], $p = 0.0007$ vs placebo; zolmitriptan 2.5 mg BID [54.7%], $p = 0.002$ vs placebo; placebo 37.8%).[40] AEs were considered possibly treatment-related in 28 patients (33.3%) in the zolmitriptan 2.5 mg TID group, 29 (36.3%) in the zolmitriptan 2.5 mg BID group, and 18 (22.0%) in the placebo group. The most common AEs were asthenia, headache, dizziness, and nausea.

Conclusions. Frovatriptan is established as effective for the short-term prevention of 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 agents. Since the original guideline, additional studies have been identified that assess the efficacy of a carbonic anhydrase inhibitor and a neurokinin inhibitor for migraine prevention.

Carbonic anhydrase inhibitor. In a single Class II study, acetazolamide 250 mg BID was no more effective than placebo in reducing migraine frequency, duration, and severity.[e1] This trial (n = 53) was stopped prematurely because of a high number of withdrawals (34%), primarily due to acetazolamide-associated AEs, including paresthesias and asthenia.

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

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
- β-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
- β-Blockers: atenolol, nadolol
- Triptans: naratriptan, zolmitriptan for short-term MAMs prevention

Level C. The following medications are possibly effective and may be considered for migraine prevention:

- ACE inhibitors: lisinopril
- Angiotensin receptor blockers: candesartan
- α-Agonists: clonidine, guanfacine
- AEDs: carbamazepine
- β-Blockers: nebivolol, pindolol

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
- Antithrombotics: acenocoumarol, Coumadin, picotamide
- β-Blockers: bisoprolol
- Calcium-channel blockers: nicardipine, nifedipine, nimodipine, verapamil
- Acetazolamide
- Cyclandelate

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

Level C negative. The following medications are possibly ineffective and may not be considered for migraine prevention:

- Acebutolol
- Clonazepam
- Nabumetone
- Oxcarbazepine
- Telmisartan

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 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 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.

RECOMMENDATIONS FOR FUTURE RESEARCH 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 RCTs.

AUTHOR CONTRIBUTIONS

Dr. Silberstein: manuscript preparation, drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Holland: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Freitag: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Dodick: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Argoff: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Ashman: drafting/revising the manuscript, analysis or interpretation of data.

DISCLOSURE

Dr. Silberstein is on the advisory panel of and receives honoraria from AGA, Allergan, Amgen, Capnia, Coherex, Colucid, Cydex, GlaxoSmithKline, Lilly, MAP, Medtronic, Merck, Minster, Neuralieve, NINDS, NuPathe, Pfizer, St. Jude Medical, and Valeant. He is on the speakers' bureau of and receives honoraria from Endo Pharmaceuticals, GlaxoSmithKline, and Merck. He serves as a consultant for and receives honoraria from Amgen and Novartis. His employer receives research support from AGA, Allergan, Boston Scientific, Capnia, Coherex, Endo Pharmaceuticals, GlaxoSmithKline, Lilly, MAP, Medtronic, Merck, NINDS, NuPathe, St. Jude Medical, and Valeant Pharmaceuticals. Dr. Holland (formerly Dr. Pearlman) receives consulting income from Map Pharmaceuticals and the American Headache Society and research support from Albert Einstein College of Medicine. Dr. Freitag has served on the scientific advisory boards of Zogenix Pharmaceuticals, Allergan Pharmaceuticals, Nautilus, MAP Pharmaceuticals, and Nupathe; has received travel expenses and or honoraria from GlaxoSmithKline, Zogenix, Merck, Nautilus, Allergan, Diamond Headache Clinic Research and Educational Foundation (not for profit), and the American Headache Society (travel). Dr. Freitag is a member of the Board of Directors of the National Headache Foundation. Dr. Dodick, within the past 3 years, serves on advisory boards and has consulted for Allergan, Alder, Pfizer, Merck, Coherex, Ferring, Neurocore, Neuralieve, Neuraxon, NuPathe Inc., MAP, SmithKlineBeecham, Boston Scientific, Medtronic, Inc., Nautilus, Eli Lilly & Company, No-

vartis, Colucid, GlaxoSmithKline, Autonomic Technologies, MAP Pharmaceuticals, Inc., Zogenix, Inc., Impax Laboratories, Inc., Bristol Myers Squibb, Nevro Corporation, Atlas, Arteaus, and Alder Pharmaceuticals. Within the past 3 years, Dr. Dodick has received funding for travel, speaking, or editorial activities from CogniMed, Scientiae, Intramed, SAGE Publishing, Lippincott Williams & Wilkins, Oxford University Press, Cambridge University Press, Miller Medical, Annenberg for Health Sciences; he serves as Editor-in-Chief and on the editorial boards of *The Neurologist*, *Lancet Neurology*, and *Postgraduate Medicine*; and has served as Editor-in-Chief of *Headache Currents* and as an Associate Editor of *Headache*; he receives publishing royalties for *Wolff's Headache, 8th edition* (Oxford University Press, 2009) and *Handbook of Headache* (Cambridge University Press, 2010). Within the past 3 years, Dr. Dodick has received research grant support from Advanced Neurostimulation Systems, Boston Scientific, St Jude Medical, Inc., Medtronic, NINDS/NIH, Mayo Clinic. Dr. Argoff has served on a scientific advisory board for the Department of Defense and DSMB for the NIH; has received funding for travel and/or speaking and/or has served on a speakers' bureau for Pfizer (King), Janssen (Pricara), Millennium Laboratories, Neurogesx, Forest Laboratories, Eli Lilly, Covidien, and Endo Pharmaceuticals; has received research support from Endo Pharmaceuticals, Forest Laboratories, Eli Lilly, Neurogesx, Pfizer, and SBRT funded by the NIH; and has received stock/stock options from Pfizer. Dr. Ashman is the Level of Evidence editor for *Neurology* and serves on the AAN Guideline Development Subcommittee. He reports no other disclosures. **Full disclosures were provided at the time of Board approval. Go to Neurology.org for full disclosures.**

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology and the American Headache Society. It is based on as assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN and the AHS recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

CONFLICT OF INTEREST

The American Academy of Neurology and the American Headache Society are committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and AHS keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN and AHS limit the participation of authors with substantial conflicts of interest. The AAN and AHS forbid commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN and AHS committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

Received June 27, 2011. Accepted in final form January 25, 2012.

REFERENCES

1. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF; The American Migraine Prevalence and Prevention Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007; 68:343–349.
2. Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. Available at: http://www.aan.com/professionals/practice/pdfs/gl0090.pdf. Accessed April 10, 1010.
3. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55: 754–762.
4. Naumann M, So Y, Argoff C, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Subcommittee of the American Academy of Neurology. Neurology 2008;70:1707–1714.
5. Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78: 1346–1353.
6. Tronvik E, Stovner LJ, Helde G, Sant T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA 2003; 289:65–69.
7. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ 2001;322:19–22.
8. Diener HC, Gendolla A, Feuersenger A, et al. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia 2009;29:921–927.
9. Freitag FG, Collins SD, Carlson HA, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology 2002;58:1652–1659.
10. Silberstein SD, Collins SD. Safety of divalproex sodium in migraine prophylaxis: an open-label, long-term study: long-term safety of Depakote in Headache Prophylaxis Study Group. Headache 1999;39:633–643.
11. Harden CL, Meador KJ, Pennell PB, et al; American Academy of Neurology; American Epilepsy Society. Practice parameter update: management issues for women with epilepsy–focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:133–141.
12. Mathew NT, Rapoport A, Saper J, et al. Efficacy of gabapentin in migraine prophylaxis. Headache 2001;41:119–128.
13. Steiner TJ, Findley LJ, Yuen AW. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia 1997;17:109–112.
14. Gupta P, Singh S, Goyal V, Shukla G, Behari M. Low-dose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp study). Headache 2007;47:402–412.
15. Silberstein SD, Saper J, Berenson F, Somogyi M, McCague MA, D'Souza JD. Oxcarbazepine in migraine headache: a double-blind, randomized, placebo-controlled study. Neurology 2008;70:548–555.

16. Ashtari F, Shaygannejad V, Akbari M. A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis. Acta Neurol Scand 2008;118:301–305.
17. Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V. Comparison of the effect of topiramate and sodium valproate in migraine prevention: a randomized blinded crossover study. Headache 2006;46:642–648.
18. Storey JR, Calder CS, Hart DE, Potter DL. Topiramate in migraine prevention: a double-blind, placebo-controlled study. Headache 2001;41:968–975.
19. Brandes JL, Saper JR, Diamond M, et al; MIGR-002 Study Group. Topiramate for migraine prevention: a randomized controlled trial. JAMA 2004;291:965–973.
20. Diener HC, Matias-Guiu J, Hartung E, et al. Topiramate in migraine prophylaxis–results from a placebo-controlled trial with propranolol as an active control. J Neurol 2004; 251:943–950.
21. Dodick DW, Freitag F, Banks J, et al; CAPSS-277 Investigator Group. Topiramate versus amitriptyline in migraine prevention: a 26-wk, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clin Ther 2009;31:542–559.
22. Keskinbora K, Aydinli I. A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine. Clin Neurol Neurosurg 2008;110:979–984.
23. 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.
24. Silberstein SD, Neto W, Schmitt J, Jacobs D; MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol 2004;61:490–495.
25. Millán-Guerrero RO, Isais-Millán R, Barreto-Vizcaíno S, et al. Subcutaneous histamine versus topiramate in migraine prophylaxis: a double-blind study. Eur Neurol 2008;59:237–242.
26. Silberstein SD, Hulihan J, Karim MR, et al. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. Clin Ther 2006;28:1002–1011.
27. Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. Headache 1992;32:101–104.
28. Saper JR, Silberstein SD, Lake AE III, Winters ME. Double-blind trial of fluoxetine: chronic daily headache and migraine. Headache 1994;34:497–502.
29. 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.
30. 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.
31. 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.
32. Diener HC, Hartung E, Chrubasik J, et al. A comparative study of oral acetylsalicylic acid and metoprolol for the prophylactic treatment of migraine: a randomized, controlled, double-blind, parallel group phase III study. Cephalalgia 2001;21:120–128.
33. Schellenberg R, Lichtenthal A, Wöhling H, Graf C, Brixius K. Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? Headache 2008;48: 118–125.
34. Rao BS, Das DG, Taraknath VR, Sarma Y. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. Neurol India 2000;48:223–226.
35. Diener HC, Krupp P, Schmitt T, Steitz G, Milde K, Freytag S; on behalf of the Study Group. Cyclandelate in the prophylaxis of migraine: a placebo-controlled study. Cephalalgia 2001;21:66–70.
36. 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.
37. 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.
38. Brandes JL, Poole A, Kallela M, et al. Short-term frovatriptan for the prevention of difficult-to-treat menstrual migraine attacks. Cephalalgia 2009;29:1133–1148.
39. Newman L, Mannix LK, Landy S, et al. Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. Headache 2001;41:248–256.
40. Tuchman MM, Hee A, Emeribe U, Silberstein S. Oral zolmitriptan in the short-term prevention of menstrual migraine: a randomized, placebo-controlled study. CNS Drugs 2008;22:877–886.

Endorsed by the American Osteopathic Association on March 22, 2012.