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Research Submissions

The 2012 AHS/AAN Guidelines for Prevention of Episodic Migraine: A Summary and Comparison With Other Recent Clinical Practice Guidelines

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Background.—Updated guidelines for the preventive treatment of episodic migraine have been issued by the American Headache Society (AHS) and the American Academy of Neurology (AAN). We summarize key 2012 guideline recommendations and changes from previous guidelines. We review the characteristics, methods, consistency, and quality of the AHS/AAN guidelines in comparison with recently issued guidelines from other specialty societies.

Methods.—To accomplish this, we reviewed the AHS/AAN guidelines and identified comparable recent guidelines through a systematic MEDLINE search. We extracted key data, and summarized and compared the key recommendations and assessed quality using the Appraisal of Guidelines Research and Evaluation-II (AGREE-II) tool. We identified 2 additional recent guidelines for migraine prevention from the Canadian Headache Society and the European Federation of Neurological Societies. All of the guidelines used structured methods to locate evidence and linked recommendations with assessment of the evidence, but they varied in the methods used to derive recommendations from that evidence.

Results.—Overall, the 3 guidelines were consistent in their recommendations of treatments for first-line use. All rated topiramate, divalproex/sodium valproate, propranolol, and metoprolol as having the highest level of evidence. In contrast, recommendations diverged substantially for gabapentin and feverfew. The overall quality of the guidelines ranged from 2 to 6 out of 7 on the AGREE-II tool.

Conclusion.—The AHS/AAN and Canadian guidelines are recommended for use on the basis of the AGREE-II quality assessment. Recommendations for the future development of clinical practice guidelines in migraine are provided. In particular, efforts should be made to ensure that guidelines are regularly updated and that guideline developers strive to locate and incorporate unpublished clinical trial evidence.

Key words: migraine, guidelines, prevention, prophylaxis, quality, AGREE-II

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INTRODUCTION

The American Headache Society (AHS) and the American Academy of Neurology (AAN) have issued updated guidelines for pharmacologic preventive treatment of episodic migraine.[1,2] Migraine is a common, disabling, and costly disorder. There is no cure, but preventive treatment to decrease the number and severity of headache attacks improves health outcomes and quality of life.[3] It also reduces disability and costs.[4]

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Conflict of Interest: PR and RB have no conflicts of interest relevant to this paper. EL is a member of the dissemination committee for the 2012 AHS/AAN Guidelines but was not involved in their development. She is the president-elect of the American Headache Society, which was a partner in the development of the guidelines and endorsed the completed guidelines.

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The AHS/AAN guidelines are the result of a systematic search, expert review, and synthesis of relevant evidence for preventive treatments of episodic migraine. The evidence identified in formulating the previous guidelines in 2000 was supplemented with evidence from a new search that extended through mid 2009.

Despite the availability of such up-to-date, evidence-based recommendations, research suggests that a majority of migraine sufferers who would benefit from prevention therapies do not receive them.[5,6] Possible barriers to the adequate preventive treatment of migraine may be lack of physician awareness of the contents of clinical practice guidelines or a lack of confidence in the methodology and quality of such guidelines.[7-9] Variability in guideline quality and consistency has been demonstrated in other therapeutic areas.[10-12] One recent study on clinical practice guideline quality concluded that the quality of clinical practice guidelines improved only slightly over the past 2 decades.[13]

We sought to summarize the key recommendations of the 2012 AHS/AAN guidelines and identify areas of change from the 2000 guidelines that they replace. In addition, we systematically review the quality and consistency of these guidelines in comparison with 2 other recent migraine prevention clinical practice guidelines.

METHODS

All authors read the 2012 AHS/AAN guidelines for migraine prevention, and EL summarized key concepts and changes from the 2000 guidelines. These were reviewed with PR and RB, and agreement on the summary was reached by consensus. Although these guidelines were published as 2 separate papers, 1 covering traditional pharmacologic agents for migraine prophylaxis and the other covering non-steroidal anti-inflammatory drugs (NSAIDs), complementary treatments and other miscellaneous treatments, for the purposes of this review, we consider the guidelines as a whole and refer to the contents of the 2 documents as "the AHS/AAN guidelines." Although the 2012 guidelines incorporate drugs used for short-term prophylaxis of menstrually triggered migraine attacks among the other treatments, for this review, we consider them separately to facilitate comparison with other guidelines, which generally do not consider such short-term treatments to be comparable with daily, long-duration preventive treatment.

An additional caveat, conspicuous by its absence from the guidelines presented here is onabotulinumtoxinA. OnabotulinumtoxinA has been extensively studied for treatment of episodic migraine and found to be ineffective. It was not included in the current AHS/AAN guidelines for preventive treatment of episodic migraine because it is covered in another AAN guideline, where it is identified as ineffective for episodic migraine. OnabotulinumtoxinA was, however, approved by the Food and Drug Administration for the treatment of *chronic* migraine in October 2010, and at this writing is the only treatment specifically indicated for that migraine variant. Its exclusion reflects simply that the guidelines we review and summarize pertain to the treatment of *episodic* migraine (ie, migraine with a headache burden of <15 days/month). A discussion of *chronic* migraine and its treatment would be timely (and clinically relevant) but lies beyond the scope of the present paper.

For the systematic review portion of this study, we searched for clinical practice guidelines for the preventive treatment of migraine in adults 18 or older. We included only guidelines based on a systematic review and synthesis of evidence, and graded recommendations linked to evidence quality. Guidelines had to be written in English and endorsed by a national or international professional organization. We excluded guidelines that focused solely on the treatment of specific subgroups of migraineurs, eg, pregnant women or children. To ensure that the clinical practice guidelines included in this review are relevant to contemporary medical practice, inclusion was limited to guidelines published from January 2008 through April 2012.

We searched MEDLINE from January 2008 to April 2012 using the text words and Medical Subject Heading terms of "migraine" and "guidelines." The electronic database search was supplemented by searching websites that list guidelines. The search strategy is contained in Appendix II. EL screened the search results for inclusion. Full-text papers were

retrieved for potentially relevant clinical practice guidelines and reviewed against inclusion criteria. The included clinical practice guidelines were summarized descriptively by EL and reviewed by RB according to pharmacologic and other preventive treatment options. For each treatment, we noted whether the respective guideline recommended that treatment, the level of evidence assigned to it, and the appraised quality of studies supporting the recommendation.

We compared treatment ratings among the included guidelines. Because each guideline used different methods to rate and assign treatments to categories, we assumed that the top tier in each rating system was comparable with the top tier in the other guidelines, and so on. Thus, Level A in the AHS/AAN guidelines was considered equivalent to the "High" level of evidence category in the Canadian guidelines (regardless of the strength of the recommendation to use or not use, which was based on judgments about the balance of harms to benefits) and the "drugs of first choice" category in European Federation of Neurological Societies (EFNS). Similarly, Level B was considered equivalent to the "Moderate" level of evidence category in the Canadian guidelines and the "drugs of second choice" category in the EFNS guidelines. Finally, Level C in the AHS/AAN guidelines was considered equivalent to the "Low" level of evidence category in the Canadian guidelines and to the "drugs of third choice" category in the EFNS guidelines.

All authors independently scored retrieved guidelines according to the Appraisal of Guidelines for Research and Evaluation (AGREE) II criteria. The AGREE criteria are widely used to assess the quality of clinical practice guidelines. They provide a list of specific information that should be reported in guideline publications. Specifically, the AGREE-II assessment instrument contains 23 items distributed among 6 quality domains, along with 2 global quality ratings.[14]

The 6 domains and the guideline characteristics assessed within each domain are: (1) Scope and Purpose, which assesses the overall aim of the guideline and target groups for whom the guideline is intended; (2) Stakeholder Involvement, which evaluates the extent to which appropriate stakeholders were involved in developing the guideline and whether it represents the views of its intended users; (3) Rigor of Development, which appraises the process of gathering and summarizing the evidence and methods used to develop recommendations; (4) Clarity of Presentation, which evaluates the language, structure, and format of the guideline; (5) Applicability, which evaluates potential barriers and facilitators to implementation and strategies to improve uptake as well as resources needed to implement the guideline; and (6) Editorial Independence, which evaluates biases because of competing interests. The overall assessment includes rating the overall quality of the guideline and stating whether the guideline is recommended for use in practice.

Each item within a domain is rated on a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree). A score of 1 indicates that there is no information on that item or that it is very poorly reported. A score of 7 indicates that criteria for the item delineated in the AGREE-II user manual have been met and that the reporting is complete and clear. A quality score for each of the 6 domains is calculated, in addition to a global assessment of overall guideline quality and recommendations for clinical use. The AGREE-II developers recommend that guideline quality should be assessed by 2-4 reviewers.

RESULTS

Summary of AHS/AAN Migraine Prevention Guideline Recommendations.—Tables 1–3 summarize key recommendations of the AHS/AAN 2012 guidelines for preventive treatment of migraine. The new guidelines assign treatments to 1 of 5 levels based on the strength of evidence for their efficacy: Level A, Level B, Level C, Level U, and an "Other" group. The last contains drugs that are established as, or probably or possibly ineffective. This method of categorizing treatments is based entirely on assessments of the strength of scientific evidence of drug efficacy and does not incorporate evidence about side effects or qualitative clinical impressions.

This differs from the method used to classify treatments in the 2000 guidelines.[15] In the 2000 guidelines, treatments were assigned to 1 of 5 groups, with group 1 indicating the highest level of recommendation and

Table 1.—AHS/AAN Migraine Prevention Guidelines
Drugs Recommended for Use

Drug	Examples of Studied Doses
Level A: established as effective	
Should be offered to patients requiring migraine prophylaxis	
Divalproex/sodium valproate	400-1000 mg/day
Metoprolol	47.5-200 mg/day
Petasites (butterbur)	50-75 mg bid
Propranolol	120-240 mg/day
Timolol	10-15 mg bid
Topiramate	25-200 mg/day
Level B: probably effective	
Should be considered for patients requiring migraine prophylaxis	
Amitriptyline	25-150 mg/day
Fenoprofen	200-600 mg tid
Feverfew	50-300 mg bid; 2.08-18.75 mg tid for MIG-99 preparation
Histamine	1-10 ng subcutaneously twice a week
Ibuprofen	200 mg bid
Ketoprofen	50 mg tid
Magnesium	600 mg trigmagnesium dicitrate qd
Naproxen/naproxen sodium	500-1100 mg/day for naproxen 550 mg bid for naproxen sodium
Riboflavin	400 mg/day
Venlafaxine	150 mg extended release/day
Atenolol	100 mg/day
Level C: possibly effective	
May be considered for patients requiring migraine prophylaxis	
Candesartan	16 mg/day
Carbamazepine	600 mg/day
Clonidine	0.75-0.15 mg/day; patch formulations also studied
Guanfacine	0.5-1 mg/day
Lisinopril	10-20 mg/day
Nebivolol	5 mg/day
Pindolol	10 mg/day
Flurbiprofen	200 mg/day
Mefenamic acid	500 mg tid
Coenzyme Q10	100 mg tid
Cyproheptadine	4 mg/day

Based on Silberstein et al[2] and Holland et al.[1] Studied dose information abstracted from these guidelines and Agency for Health Care Policy and Research technical review (http://www.ncbi.nlm.nih.gov/books/NBK45457/pdf/TOC.pdf). Intended solely to give an idea of tested doses and not as a recommendation for treatment.
All drugs given orally unless otherwise noted.
AAN = American Academy of Neurology; AHS = American Headache Society; bid = twice a day; qd = daily; tid = 3 times a day.

group 5 the lowest. The group assignment, however, was based on a combination of the quality of clinical trial evidence but also incorporated clinical judgments of efficacy and evidence concerning potential adverse effects. This change in rating method should be borne in mind when the reader compares the ratings of drugs between the 2 guidelines.

Level A Drugs.—Three beta-blockers (metoprolol, propranolol, and timolol), several antiepileptic drugs (topiramate, and divalproex or sodium valproate), as well as the herbal drug Butterbur are rated as Level A drugs in the 2012 guidelines. This rating is given to treatments for which there are at least 2 high-quality randomized, controlled trials (RCTs) demonstrating efficacy. The guideline authors suggest that Level A drugs should be offered to patients who require prophylaxis for migraine. In the 2000 guidelines, only 4 drugs were placed in group 1: amitriptyline, divalproex, propranolol, and timolol. Of note, 3 of those 4 drugs retain the highest rating in

Table 2.—AHS/AAN Migraine Prevention Guidelines
Drugs Recommended for Short-Term Prevention of Migraine Associated With Menstruation

Drug	Dose or Dose Range	Comment
Level A: established as effective		
Should be offered to patients requiring prophylaxis		
Frovatriptan	2.5 mg bid perimenstrually	A loading dose was used
Level B: probably effective		
Should be considered for patients requiring prophylaxis		
Naratriptan	1 mg bid for 5 days perimenstrually	No loading dose
Zolmitriptan	2.5 mg bid or tid perimenstrually	No loading dose
Level C: possibly effective		
May be considered for patients requiring prophylaxis		
Estrogen	1.5 mg estradiol in gel qd × 7 days perimenstrually	

Based on Silberstein et al[2] and Holland et al.[1] Studied dose information abstracted from these guidelines and intended solely to give an idea of tested doses and not as a recommendation for treatment.
All drugs given orally unless otherwise noted.
AAN = American Academy of Neurology; AHS = American Headache Society; bid = twice a day; qd = daily; tid = 3 times a day.

the updated guidelines. Amitriptyline has been downgraded to Level B in the new guidelines.

Level B Drugs.—The 2012 AHS/AAN guidelines assign 10 drugs to Level B, which is reserved for treatments for which there is only 1 high-quality RCT, or 2 or more less rigorous studies suggesting efficacy. The guideline authors suggest that Level B drugs should be considered for patients who require prophylaxis

Table 3.—AHS/AAN Migraine Prevention Guidelines
Drugs and Treatments With Conflicting or Inadequate Evidence of Efficacy or With Evidence Indicating Lack of Efficacy

Drug or Treatment	
Level U: conflicting or inadequate evidence	
Insufficient data to support or refute use for migraine prophylaxis	
Acenocoumarol	Hyperbaric oxygen
Acetazolamide	Indomethacin
Aspirin	Nicardipine
Bisoprolol	Nifedipine
Coumadin	Nimodipine
Cyclandelate	Omega-3
Fluoxetine	Picotamide
Fluvoxamine	Proptriptyline
Gabapentin	Verapamil
Medications or treatments established as possibly or probably ineffective for migraine prophylaxis	
Should not be offered or considered for migraine prophylaxis†	
Acebutolol	Montelukast
Clomipramine	Nabumetone
Clonazepam	Oxcarbazepine
Lamotrigine	Telmisartan

Based on Silberstein et al[2] and Holland et al.[1]
†The evidence supporting designation of a treatment as ineffective was subcategorized as established, probable, or possible. For this chart, we have collapsed those categories.

for migraine. The Level B group includes amitriptyline as well as the herbal treatment feverfew, several NSAIDs, riboflavin (vitamin B2), venlafaxine, and subcutaneous histamine.

In the 2000 guidelines, 17 drugs were placed in the second highest group (group 2). These included atenolol, metoprolol, nadolol, gabapentin, verapamil, fluoxetine, fenoprofen, ketoprofen, naproxen and naproxen sodium, feverfew, magnesium, and vitamin B2. In contrast with the drugs in the highest rating category in 2000, there has been considerable change in the ratings assigned to drugs in the former group 2. Roughly 50% of them have been upgraded or downgraded. For example, gabapentin, verapamil, and fluoxetine are assigned to Level U in the 2012 guidelines, a substantial downgrade from their former rating that indicates a changed assessment of the quality or the inclusion of new evidence for these drugs. At least for gabapentin, this judgment is in line with recent evidence that has surfaced of serious problems with the reporting of clinical trial results.[16] In contrast, metoprolol has been upgraded to Level A from its former position in group 2.

Level C Drugs.—The 2012 AHS/AAN guidelines assign 11 drugs to Level C, which contains drugs for which there is a single less rigorous study indicating efficacy. The guideline authors suggest that Level C treatments "may" be considered for patients requiring migraine prophylaxis. Level C includes 2 drugs making new appearances in the guidelines: lisinopril and candesartan. It also includes clonidine, cyproheptadine, coenzyme Q10, and several NSAIDs.

In the 2000 guidelines, 16 drugs were placed in group 3. These included 10 drugs that are not listed in the updated 2012 guidelines: buproprion, doxepin, imipramine, mirtazapine, nortriptyline, paroxetine, sertraline, trazodone, diltiazem, and phenelzine. Of the remaining 6 drugs that appeared in group 3 in the 2000 guidelines, 2 (fluvoxamine and protriptyline) have been downgraded to Level U in the 2012 guidelines, while cyproheptadine remains in the roughly comparable Level C group, and ibuprofen and venlafaxine have been upgraded to Level B. Thus, only 1 drug in the third tier in 2000 has remained in that tier in 2012.

Level U Drugs.—Fourteen drugs are assigned to Level U, a category reserved for treatments that have "insufficient data to support or refute use for migraine prophylaxis." This may mean that studies were judged to have substantial methodological shortcomings or that there are conflicting results from multiple studies. In addition to gabapentin, verapamil, and fluoxetine, this group contains the tricyclic antidepressant proptriptyline and the carbonic anhydrase inhibitor acetazolamide.

Ineffective Drugs.—The 2012 AHS/AAN guidelines also list 8 medications for which evidence is considered to show that they are established as, or possibly or probably ineffective for migraine prophylaxis. The authors suggest that these should not be offered or considered for patients requiring migraine prophylaxis. These include the anti-epileptic drug lamotrigine, the leukotriene inhibitor montelukast, oxcarbazepine, and telmisartan.

In the 2000 guidelines, 8 drugs were placed in the lowest group 5, 3 of which (indomethacin, nicardipine, and nifedipine) now are in Level U in the new guidelines. Three drugs included in group 5 in 2000 have been upgraded to Level C in the current guidelines (carbamazepine, pindolol, and clonidine), while 2 (clomipramine and clonazepam) are now considered likely to be ineffective.

Drugs for Menstrually Triggered Attacks of Migraine.—For short-term prevention of menstrually triggered migraine attacks, frovatriptan is assigned to Level A, and naratriptan and zolmitriptan to Level B, while estrogen is in Level C.

Comparison of the 2012 AHS/AAN Migraine Prevention Guidelines With Other Contemporary Migraine Prevention Clinical Practice Guidelines.— Our search and abstract screen identified 5 additional contemporary clinical practice guidelines relevant to migraine prevention in adults and published since 2008. Three were excluded, 2 because they were not published in English and 1 because it did not link recommendations to a formal appraisal of evidence.[17-19] The 2 guidelines that met criteria for inclusion in this review were guidelines published in 2012 by the Canadian Headache Society (referred to herein as the "Canadian guidelines") and guidelines published in 2008 by the EFNS (referred to herein as the "EFNS guidelines").[20,21] Table 4 displays the characteristics and methods of the 3 guidelines.

Table 4.—Characteristics and Methods Used For Developing the 3 Migraine Prevention Clinical Practice Guidelines

	American Headache Society (AHS)/American Academy of Neurology (AAN) Guideline	Canadian Guideline	European Federation of Neurological Societies (EFNS) Guideline
Status (new or updated)	Updated	New	New
Organization(s) participating in guideline development	AAN; AAN	Canadian Headache Society	EFNS
Organization(s) endorsing guideline	AAN; AAN; American Osteopathic Association	Canadian Headache Society	EFNS
Funding/sponsorship source(s)	AAN; AAN	Canadian Headache Society	EFNS
Dates of search	Built on MEDLINE search done for previous guidelines, updated with information from June 1999 through May 2009	MEDLINE, EMBASE, Cochrane Library inception -April 2008; Updated in June 2011. Search limited to "those agents commonly used in clinical practice." They provide a list of target drugs.	"A literature search was performed using the reference databases MEDLINE, Science Citation Index, and the Cochrane Library . . . last search in January 2009." States that "all authors performed an independent literature search."
Attempts reported to locate unpublished evidence or verify full study reporting? For example, search of the grey literature, manufacturer databases, regulatory documents, or trial registries.	No	No	No
Study inclusion criteria	". . . randomized adult patients with migraine to the agent under study or a comparator drug (including placebo) and utilized masked outcome assessment"	". . . required to be prospective, randomized, double-blind, controlled trials of drug treatments used to prevent the occurrence of migraine attacks." Studies had to include adults who met accepted criteria for migraine or provide "sufficient detail" to support a migraine diagnosis.	"All papers published in English, German or French were considered when they described a controlled trial or a case series on the treatment of at least five patients. In addition a review book and the German treatment recommendations for migraine were considered."
Study exclusion criteria	Assessed for headaches other than episodic migraine; assessed acute treatment, aura treatment, nonpharmacologic treatment; used quality of life, disability or nonstandardized outcomes; tested drugs not available in the United States.	Excluded studies of patients with headache 15 or more days per month, transformed migraine, or chronic tension-type headache. Excluded studies of agents not "commonly used in clinical practice."	Not explicitly stated.
Methods of classifying treatments	AAN therapeutic classification of evidence scheme. Each drug assigned one of the following ratings Level A (medications with established efficacy, greater than or equal to 2 Class I trials); Level B (medications are probably effective [3 Class I or 2 Class II studies]); Level C (medications are possibly effective [3 Class II studies]); Level U (inadequate or conflicting data to support or refute use); or other (medications that are established as possibly or probably ineffective)	Treatment classified based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. Each drug was assigned 1 of 4 levels of evidence: high, moderate, low, or very low. The recommendation was then further graded as strong or weak based on assessment of the balance of benefits and harms. Developers note that this can result in a "strong" recommendation for a therapy that is only modestly effective or has a low level of evidence, if it is well tolerated and safe.	"The definitions of the recommendation levels follow the EFNS criteria." Each drug assigned a rating of A ("drugs of first choice"), B ("drugs of second choice") . . . evidence of efficacy but less effective or more side-effects than level A drugs), or C ("drugs of third choice"), only probable efficacy.
Methods of deriving recommendations (evidence linked with formal consensus method; evidence linked with informal consensus method; consensus method with no detailed description; not described	Evidence linked with informal consensus method: "At least 2 panelists independently reviewed each study and rated it . . . Differences in ratings were resolved by author panel discussion."	Evidence linked with informal consensus method	Consensus method with no detailed description
Assessed included studies based on disease-specific recommendations for outcome measures, trial conduct, and adverse event reporting recommended by professional society guidelines	In part: used 50% responder rates as measure of success	In part	Not stated
Year of publication of previous version	2000	Not applicable	Not applicable
Year planned for next update	Not reported	"At least every two years."	"Should be updated within three years"

Table 5.—Areas of Apparent Agreement on Evidence Quality for Drugs Rated by at Least 2 of 3 Migraine Prevention Guidelines

	AHS/AAN Guidelines	Canadian Guidelines	EFNS Guidelines
Coenzyme Q10	C	Strong, low-quality evidence	C
Divalproex	A	Weak, high-quality evidence	A
Flunarazine	Not rated	Weak, high-quality evidence	A
Lisinopril	C	Weak, low-quality evidence	C
Metoprolol	A	Strong, high-quality (but not reviewed for guidelines, instead rating based on Cochrane review)	A
Nadolol	B	Strong, moderate	Not rated
Naproxen	B	Not rated	B
Pizotifen	Not rated	Weak, high-quality evidence	Not rated
Propranolol	A	Strong, high-quality evidence	A
Topiramate	A	Strong, high-quality evidence	A

Assuming that Level A = high-quality evidence = first-line (A) drugs; Level B = moderate-quality evidence = second-line (B) drugs; Level C = low-quality evidence = third-line (C) drugs; Level U and established as, or possibly or probably ineffective = do not use (no comparable rating in EFNS guidelines).
AAN = American Academy of Neurology; AHS = American Headache Society; EFNS = European Federation of Neurological Societies.

All were sponsored, funded, and carried out by professional societies devoted to the study of neurology or headache. Only the AHS/AAN guidelines, however, were endorsed by other specialty groups. All of the guidelines reported that a systematic search for evidence was conducted, although the dates and breadth of the searches varied. The search for the AHS/AAN guidelines extended only through May 2009, while the search for the Canadian guidelines extends through June 2011.

The inclusion and exclusion criteria differed among the guidelines, with the result that the AHS/ANS guidelines consider a larger number of drugs, while the Canadian guidelines rate only a previously agreed-upon list of medications in common use. All of the guidelines used structured methods to appraise retrieved evidence. None, however, reported making any attempts to identify unpublished or incompletely reported evidence for the treatments reviewed. The 3 guidelines also used different methods of appraising and classifying the evidence that was retrieved. Two of the guidelines mentioned the use of a 50% responder rate as a measure of treatment efficacy, as recommended by International Headache Society clinical trial guidelines for migraine-preventive therapies. None, however, reported basing other assessments of study quality on the disease-specific recommendations for other outcome measures, adverse event reporting, or trial methods that have been developed by professional societies, such as the International Headache Society recommendations about the clinical conduct of preventive trials and adverse event reporting.[22,23]

As previously mentioned, the 2012 AHS/AAN guidelines assign treatments to Levels based on assessment of the strength and quality of evidence of efficacy. Adverse effects, contraindications to use, and other clinical considerations are reviewed but are not incorporated in the assignment of drugs to a particular level. In contrast, both the Canadian and EFNS incorporate an assessment of the balance of benefits and harms for a drug into their categorization schemes.

Areas of apparent agreement among the guideline ratings are summarized in Table 5. These must be interpreted in light of the imperfect correspondence among the various categories, as described earlier. It is notable, however, that there is considerable consensus among the guidelines about drugs that are placed in the highest tier, with divalproex, metoprolol, propranolol, and topiramate assigned to the top category in all 3 of the guidelines. Similarly, all of the guidelines place coenzyme Q10 and linsinopril

Table 6.—Areas of Apparent Divergence About Evidence Quality for Drugs Rated by at Least 2 Guidelines for Migraine Prevention

	AHS/AAN Guidelines	Canadian Guidelines	EFNS Guidelines
Amitriptyline	B	Strong, high-quality evidence	B
Aspirin	U	Not rated	C
Bisoprolol	U	Not rated	B
Candesartan	C	Strong, moderate-quality evidence	C
Feverfew	B	Do not use	C
Gabapentin	U	Strong, moderate-quality evidence	C
Magnesium	B	Strong, low-quality evidence	C
Petasites	A	Strong, moderate-quality evidence	B
Riboflavin	B	Strong, low-quality evidence	C
Venlafaxine	B	Weak, low-quality evidence	B
Verapamil	U	Weak, low-quality evidence	N/A

Assuming that Level A = high-quality evidence = first-line (A) drugs; Level B = moderate-quality evidence = second-line (B) drugs; Level C = low-quality evidence = third-line (C) drugs; Level U and established as, or possibly or probably ineffective = do not use (no comparable rating in EFNS guidelines).
AAN = American Academy of Neurology; AHS = American Headache Society; EFNS = European Federation of Neurological Societies.

in their third category. Some drugs were rated in only 2 guidelines, and in those cases, there was also concordance for naproxen and nadolol, which were placed in the second tier. Drugs rated by only 1 guideline are listed in Appendix III. The majority of those were rated in the AHS/AAN guidelines, which cast a wider net for evidence than the Canadian and EFNS guidelines.

Table 6 identifies areas of apparent divergence among the guidelines. In general, the divergence is not substantial. For 6 of the 11 treatments (amitriptyline, candesartan, magnesium, petasites, riboflavin, and venlafaxine), there is only a difference of a single category up or down for one of the guidelines, while the other 2 guidelines place the drug in similar tiers. For 2 drugs, however, the differences in classification are more substantial. Gabapentin is placed in Level U (conflicting or insufficient evidence to support or refute efficacy) whereas in the 2012 AHS/AAN guidelines, while the Canadian guidelines rate it as having "moderate-quality evidence" and make a strong recommendation for its use based on the combination of possible efficacy and good tolerability. The EFNS guidelines consider it a "third choice" drug. For feverfew, the Canadian guidelines recommend against use based on an interpretation of the trial evidence as negative overall, while the AHS/AAN guidelines include it in Level B (probably effective, should be considered) and the EFNS guidelines consider it a "third choice" treatment.

AGREE-II Appraisal Results.—Table 7 shows the results of the quality rating using the AGREE-II tool for assessing clinical practice guideline quality. In general, the Canadian and the AHS/AAN guidelines received higher scores for quality in all domains, with the Canadian guidelines achieving the highest overall assessment of quality. The AHS/AAN guidelines received their highest score in Domain 1, which scores the reporting of the scope and purpose of the guidelines, and their lowest score in stakeholder involvement, which appraises the extent to which stakeholders such as patients and nonspecialist clinicians were involved in guideline development. The Canadian guidelines also received their highest score in Domain 1 and their lowest in Domain 6, which rates the reporting of factors associated with editorial independence.

The EFNS guidelines had consistently low scores in all domains with the exception of Domain 6, editorial independence, where they achieved their highest score. They were rated lowest in Domain 4, Clarity of Presentation. Based on an overall assess-

Table 7.—Overall Assessment and Domain Scores for the 3 Migraine Prevention Clinical Practice Guidelines Using the AGREE-II Instrument

	AHS/AAN Raw Score (percentage of possible score†)	Canadian Raw Score (percentage of possible score†)	EFNS Raw Score (percentage of possible score†)	Best Possible Score
Domain 1: Scope and Purpose	17.6 (84%)	20.7 (99%)	7 (33%)	21
Domain 2: Stakeholder Involvement	6 (29%)	18.3 (87%)	5.3 (25%)	21
Domain 3: Rigor of Development	32 (57%)	52 (93%)	19.6 (35%)	56
Domain 4: Clarity of Presentation	15.6 (74%)	19.3 (92%)	1.3 (6%)	21
Domain 5: Applicability	10 (36%)	24.7 (88%)	5.6 (20%)	28
Domain 6: Editorial Independence	8.3 (59%)	11.3 (81%)	9.6 (69%)	14
Overall Assessment (scale of 1-7)	4.3 (61%)	6 (86%)	2 (29%)	7
Recommended for use?	Yes	Yes	No	Yes

†Raw score is the average of the scores of 3 independent reviewers, rounded to 1 decimal place. Percentages are rounded to the nearest whole number.
AAN = American Academy of Neurology; AGREE-II = Appraisal of Guidelines Research and Evaluation-II; AHS = American Headache Society; EFNS = European Federation of Neurological Societies.

ment of guideline quality by the 3 reviewers, the AHS/AAN and the Canadian guidelines were recommended for use, while the EFNS guidelines were not. Appendix IV provides the ratings for each component of the 6 domains.

DISCUSSION

The 2012 AHS/AAN guidelines for episodic migraine prevention provide a welcome summary of the evidence that underpins commonly used treatments for migraine. Most of the drugs deemed to have the highest level of evidence in the 2000 guidelines remain in that category in 2012. Although the methods used to locate and appraise evidence and link it to recommendations varied among the 3 guidelines we reviewed, there was remarkable consistency in the ratings of drugs for first-line use.

In contrast, recommendations diverged substantially for gabapentin and feverfew. This divergence is potentially confusing for clinicians and patients.[7] It may be related to differences in search strategies or methods for selecting the evidence. In our view, however, it is most likely due to the way in which recommendations were formulated. The AHS/AAN ratings were assigned solely on the basis of an assessment of efficacy, while the Canadian and EFNS categorizations sought to balance efficacy and side effects. In the case of gabapentin, which is widely believed to be well tolerated, it is therefore not surprising that the Canadian and EFNS guidelines place the drug in their second and third tiers, respectively, while the AHS/AAN guidelines downgrade the drug because of conflicting and poor-quality evidence of efficacy.

We believe this example points out a serious shortcoming in rating methods that seek to incorporate both benefits and harms. First, although willingness to use treatments is influenced by both benefits and harms, ratings assigned by others can never hope to correctly capture the views of different patients. Second, it is well known that potential harm and adverse events are not systematically sought or reported in clinical trials, so that published evidence of harms is likely to be an underestimate.[24] And finally, it is questionable whether a drug with low or uncertain efficacy should be recommended for widespread use on the basis of tolerability when more effective drugs are available. The quality and credibility of clinical trial evidence for gabapentin has recently been called into considerable question.[16,25] This evidence quality problem is better addressed by methods that use a purer approach in generating recommendations, one that is based principally on assessments of efficacy.

On the other hand, a pure efficacy-based system of recommendations raises the question of what constitutes a clinically meaningful treatment effect,

especially in relation to side effects. Some drugs that have statistically significant evidence of benefit in well-designed and conducted trials may nonetheless provide very marginal benefits when applied to routine clinical practice. An example of this situation is frovatriptan, where the magnitude of clinical benefit is quite small in comparison with treatment burden and cost.[26] One compromise might be to present information about both efficacy and side effects but to refrain from incorporating them in a composite measure. This allows clinicians using the guidelines to individualize treatment decisions based on both efficacy and patient preferences regarding specific risks.

The quality of the AHS/AAN and Canadian guidelines, as assessed with the AGREE-II tool, was better than that of guidelines in other specialties, which is heartening.[13] Both are recommended for use on the basis of the AGREE-II quality assessment. It is likely that the Canadian guidelines scored particularly high on the AGREE measure because they were developed in accordance with AGREE recommendations. In contrast, the EFNS guidelines do not appear to meet widely accepted standards for guideline quality and are not recommended for use.

Future efforts are needed to ensure that guidelines are regularly updated and that guideline developers make use of methods to locate and incorporate unpublished clinical trial evidence.[27] There are many reasons that it can be difficult to locate clinical trial evidence. Some have to do with problems in tagging studies as RCTs in MEDLINE or the need to condense information to meet word limits imposed by medical journals.[28,29] It is clear, however, that much clinical trial evidence has never been published or has been incompletely reported.[30] Unfortunately, there is substantial reason to believe that this problem of missing or manipulated evidence affects the clinical evidence when one evaluates migraine therapy.[22,31-33] The incorporation of unpublished evidence into meta-analyses has been shown to alter conclusions about treatment efficacy. To ensure the integrity, validity, and credibility of migraine clinical practice guidelines, developers should make strenuous efforts to locate all relevant evidence.[34] This and other recommendations for the development of future migraine clinical practice guidelines are listed in Box 1.

Box 1.—Seven recommendations for the development of clinical practice guidelines for migraine treatment.

- Ensure that guideline processes conform to authoritative recommendations about ideal guideline development and reporting, such as the Appraisal of Guidelines Research and Evaluation (AGREE) measures
- Provide explicit definitions for terms such as "acute" or "preventive/prophylactic" treatment
- Avoid limiting the initial evidence search to familiar or widely used treatments in order to minimize the chance of missing important new research and developments
- Make and document attempts to locate unpublished and missing clinical trial evidence, for example by searching the grey literature, manufacturer web sites, and clinical trial registration and reporting sites such as clinicaltrials.gov
- Assess trial quality against headache-specific recommendations for outcome measures, quality of adverse event collection and reporting, and trial conduct. See in particular the International Headache Society guidelines for the conduct of controlled trials of migraine prophylaxis and adverse event reporting in migraine trials
- Present separate assessments and recommendations regarding the efficacy and side effects of treatments. Avoid the use of composite recommendations that seek to balance efficacy and tolerability because the quality and completeness of evidence for side effects is known to be poor
- Present and adhere to a timeline for regular updates and modifications to guidelines

In summary, the 2012 updated AHS/AAN guidelines for preventive treatment of episodic migraine provide a welcome and comprehensive overview of the breadth and quality of existing evidence. They

confirm the benefits of many widely used therapies, identify drugs that should be avoided, and remind clinicians of emerging evidence for a wide array of newer treatment choices.

APPENDIX I: SEARCH STRATEGY

MEDLINE Search Strategy:

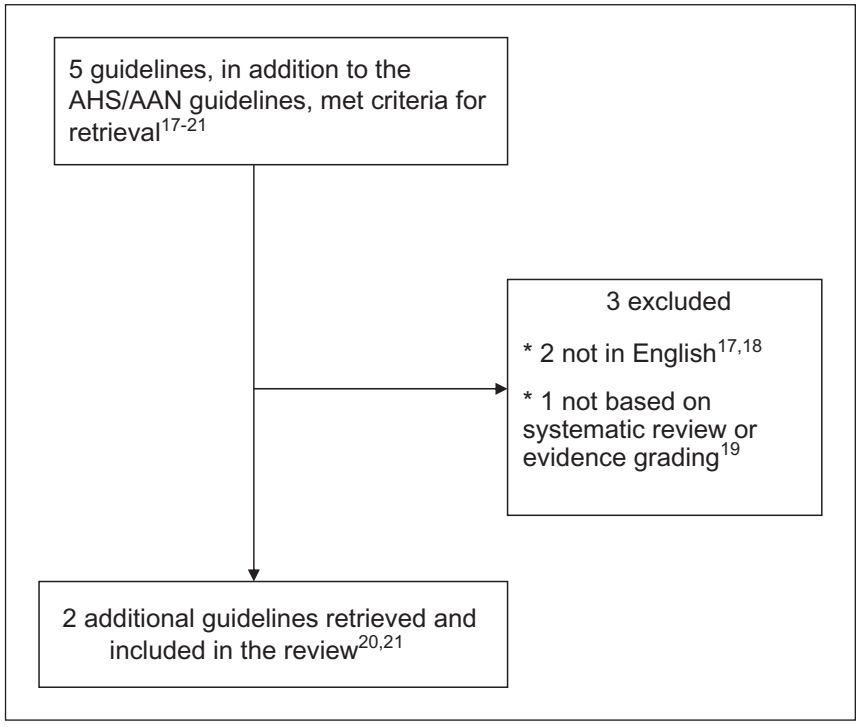
Database: Ovid MEDLINE(R) <1950 to April Week 3 2012>

1. guideline.pt.
2. practice guideline.pt.
3. Health Planning Guidelines/
4. Consensus Development Conference/
5. (guideline or guidelines).m_titl.
6. *Clinical Protocols/
7. or/1-6
8. exp migraine/
9. "migraine".tw.
10. or/8-10
11. 7 and 10
12. limit 11 to yr="2008-Current"

Guideline website search strategy:

We searched the website of the National Guideline Clearinghouse maintained by the United States Agency for Health Care Quality. The search was conducted at http://www.guideline.gov/search/search.aspx?term=migraine using the keyword "migraine" on April 17, 2012.

APPENDIX II: FLOW OF GUIDELINES THROUGH THE REVIEW



APPENDIX III: RATINGS OF DRUGS EVALUATED IN ONLY 1 GUIDELINE

	AHS/AAN Guideline	Canadian Guideline	EFNS Guideline
Acebutolol	Possibly not effective	Not rated	Not rated
Acenocoumadin	U	Not rated	Not rated
Acetazolamide	U	Not rated	Not rated
Atenolol	B	Not rated	Not rated
Carbamazepine	C	Not rated	Not rated
Clomipramine	Probably not effective	Not rated	Not rated
Clonazepam	Possibly not effective	Not rated	Not rated
Clonidine	C	Not rated	Not rated
Coumadin	C	Not rated	Not rated
Cyclandelate	U	Not rated	Not rated
Cyproheptadine	C	Not rated	Not rated
Estrogen	C	Not rated	Not rated
Fenoprofen	B	Not rated	Not rated
Fluoxetine	U	Not rated	Not rated
Flurbiprofen	C	Not rated	Not rated
Fluvoxamine	U	Not rated	Not rated
Frovatriptan	A	Not rated	Not rated
Guanfacine	C	Not rated	Not rated
Histamine SC	B	Not rated	Not rated
Hyperbaric oxygen	U	Not rated	Not rated
Ibuprofen	B	Not rated	Not rated
Indomethacin	U	Not rated	Not rated
Ketoprofen	B	Not rated	Not rated
Lamotrigine	Established as ineffective	Not rated	Not rated
Mefenamic acid	C	Not rated	Not rated
Montelukast	Probably not effective	Not rated	Not rated
Nabumetone	Possibly not effective	Not rated	Not rated
Naproxen sodium	B	Not rated	Not rated
Naratriptan	B	Not rated	Not rated
Nebivolol	C	Not rated	Not rated
Nicardipine	U	Not rated	Not rated
Nimodipine	U	Not rated	Not rated
Omega 3	U	Not rated	Not rated
Oxcarbazepine	Possibly not effective	Not rated	Not rated
Picotamide	U	Not rated	Not rated
Pindolol	C	Not rated	Not rated
Pitzotifen	Not rated	Weak, high-quality evidence	Not rated
Protriptyline	U	Not rated	Not rated
Telmisartan	Possibly not effective	Not rated	Not rated
Timolol	A	Not rated	Not rated
Zolmitriptan	B	Not rated	Not rated

APPENDIX IV: QUALITY OF THE 3 MIGRAINE PREVENTION GUIDELINES FOR THE 6 DOMAINS OF THE AGREE-II INSTRUMENT

Guideline:		AHS/AAN	Canadian	EFNS
Item number		Average of 3 reviewer ratings; possible score of 7		
Domain 1: Scope and Purpose	1. The overall objective(s) of the guideline is (are) specifically described.	6.7	6.7	3.6
	2. The health question(s) covered by the guideline is (are) specifically described.	6	7	1.7
	3. The population (patients, public, etc) to whom the guideline is meant to apply is specifically described.	5	7	1.7
Domain 2: Stakeholder Involvement	4. The guideline development group includes individuals from all relevant professional groups.	2.7	6.3	2.7
	5. The views and preferences of the target population (patients, public, etc) have been sought.	1	5	1
	6. The target users of the guideline are clearly defined.	3.7	7	2.3
Domain 3: Rigor of Development	7. Systematic methods were used to search for evidence.	4.6	6.7	2.6
	8. The criteria for selecting the evidence are clearly described.	4.1	6.7	2.7
	9. The strengths and limitations of the body of evidence are clearly described.	4.6	6.3	1.7
	10. The methods for formulating the recommendations are clearly described.	4.3	6.3	2.6
	11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	3.3	6.7	2
	12. There is an explicit link between the recommendations and the supporting evidence.	6.7	7	2
	13. The guideline has been externally reviewed by experts prior to its publication.	5.3	6.3	1.7
	14. A procedure for updating the guideline is provided.	2	6.3	5.7
Domain 4: Clarity of Presentation	15. The recommendations are specific and unambiguous.	4.7	6.3	3.3
	16. The different options for management of the condition or health issue are clearly presented.	5	6	3
	17. Key recommendations are easily identifiable.	6	7	1.7
Domain 5: Applicability	18. The guideline describes facilitators and barriers to its application.	2	6.7	1
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	4.3	6.7	1
	20. The potential resource implications of applying the recommendations have been considered.	2.7	6	1
	21. The guideline presents monitoring and/or auditing criteria.	1.7	5.6	2.3
Domain 6: Editorial Independence	22. The views of the funding body have not influenced the guideline (explicit statement).	5	7	7
	23. Competing interests of guideline development group members have been recorded and addressed.	3.7	4.3	2.7

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table 1. AHS/AAN Migraine Prevention Guidelines Drugs Recommended for Use.

Table 2. AHS/AAN Migraine Prevention Guidelines, Drugs Recommended for Short-Term Prevention of Migraine Associated With Menstruation.

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