Pharmacologic treatment of migraine in children and adolescents: A systematic review and guideline development protocol

Proposal of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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DISCLOSURE

Dr. Yolanda Holler-Managan has received funding for travel from the AAN. She is on the editorial advisory board of *Neurology Now*.

Dr. Maryam Oskoui has received funding for travel from the AAN and Isis Pharmaceuticals. She has received research support from Isis Pharmaceuticals, FRQS (Quebec), CIHR (Canada), and the McGill University Research Institute.

Dr. David Gloss is an evidence-based medicine consultant for the AAN. He has served as associate editor for risk of bias classifications for the journal *Neurology*.

Dr. Andrew Hershey has served on a scientific advisory board for Allergan, XOC Pharma, and Amgen. He has served as an editor for *Headache, Cephalalgia*, and the *Journal of Headache and Pain*. He has received research support from Allergan and Teva. He has received grants from the NIH and serves as a board member of the American Headache Society.

Dr. Nicole Licking reports no disclosures.

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Dr. Michael Sowell received funding from the Southern Headache Society to speak at their fourth annual meeting in Ashville, NC, from September 27-29, 2014. He has served as manuscript editor for the journal *Headache*, on a speakers' bureau for Allergan, and as an interviewer for *Neurology* podcasts. He received honoraria in May 2014 from the 6th Annual

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Dr. Christine Victorio is the site primary investigator for an NIH-funded childhood migraine and prevention study, which is contracted through Akron Children's Hospital.

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Dr. Marcy Yonker has served on a scientific advisory board for AMGEN. She has served as a reviewer for the journals *Cephalalgia*, *Headache,* and the *Journal of the Child Neurology Society*. She has received research support as a primary investigator from AstraZeneca, Allergan, and NINDS.

INTRODUCTION

Since the 2004 publication of the American Academy of Neurology (AAN) practice parameter "Pharmacological treatment of migraine headache in children and adolescents,[1]" there have been several major studies published regarding acute and preventive treatments for migraine headache. At the time of the last guideline, there were very few controlled and randomized trials to support recommendations. Currently there are randomized controlled trials that address acute and preventive pharmacologic and nonpharmacologic management of migraine headache. Since the clinical problem of migraine headache is so prevalent in children and adolescents, an update is warranted.

Migraine is common in pediatric patients, with a prevalence of 1%–3% in 3- to 7-year-olds, 4%–11% in 7- to 11-year-olds, and 8%–23% by age 15 years.[2] The definition of migraine is according to the International Classification of Headache Disorders, 3rd edition.[3] In comparison to adults, migraine headache in children and adolescents is more often bilateral and of shorter duration.[3] Migraine is typically diagnosed by obtaining a thorough history and performing an examination without neuroimaging. Management of pediatric headache consists of acute and preventive treatments. Treatments are chosen according to headache type and frequency, type of symptoms present, adverse effect profile, and comorbidities present.[4]

It is imperative to determine the most effective treatment of pediatric headache because there is a great cost to headaches, including a personal and financial burden. In adults and children, the estimated annual cost for migraine-associated emergency department (ED) visits was $700 million in the United States in 2010.[5] In children and adolescents, an estimated 250,000 annual

visits are related to headache, 2.1% of total visits.[6] Among children presenting to the ED for headache, two-thirds have tried abortive medication at home prior to their visit.[2] Therefore, effective treatment of pediatric headache should decrease the financial burden of frequent ED visits, the personal burden of persistent headache in the child, and the family burden of taking the child to the ED.

Rationale for this guideline

Because migraine is common in pediatric patients, it has a large impact on the quality of life of the child or adolescent. Recurrent headaches can impact a child's life by affecting school, leisure, and family activities. In one study, children with migraine missed an average of 23.9 days of school activities, household tasks, and leisure activities over 3 months.[7] In another, children with migraines reported a similar pattern of disability as children with rheumatoid disease or cancer. These findings suggest that children with migraines can experience comparable or more severe impairments as children with other serious chronic illnesses.[8]

The purpose of this guideline is to systemically assess all randomized clinical trials and nonrandomized studies that evaluate acute and preventive pharmacologic and nonpharmacologic treatment of migraine headache. The goal is to provide patients and their providers with a reference regarding appropriate treatment that will reduce headache frequency and duration and improve the patient's quality of life. The guideline seeks to answer the following clinical questions:

Clinical Questions

1. In children and adolescents with migraine headaches, do acute treatments, compared with no treatment, reduce headache duration and associated symptoms (especially nausea and vomiting) and maintain headache freedom?

2. In children and adolescents with migraine headaches, do preventive treatments, compared with no treatment, reduce headache frequency?

3. In children and adolescents with migraine headaches, do complementary and alternative medicine therapies, compared with no treatment, reduce headache frequency?

Question (type)	Patient population	Intervention	Comparative intervention	Outcome
1 (therapeutic)	Children and adolescents with migraine headaches	Acute treatments	No treatment	Headache duration, associated nausea and vomiting, number who remain headache free
2 (therapeutic)	Children and adolescents with migraine headaches	Preventive treatments	No treatment	Headache frequency
3(therapeutic)	Children and adolescents with migraine headaches	Nonpharmacologic treatments	No treatment	Headache frequency

Rationale for clinical questions

Treatment modalities must be carefully selected based on a patient's headache pattern and changing frequency.[1] The first step is to prevent migraines with lifestyle modifications such as sleep hygiene and diet. However, when migraines occur, there must be a plan to treat acute

symptoms (Question 1). For frequent headaches that interfere with functioning, preventive treatments can be initiated (Question 2). And when the medicine cabinet is not effective, we should evaluate alternatives that exist beyond traditional pharmaceuticals (Question 3).

SYSTEMATIC REVIEW PROTOCOL

Composition of the author panel

This guideline will be developed according to the process described in the 2011 AAN guideline development process manual (as amended),[9] and is in compliance with the Institute of Medicine Standards for Systematic Reviews[10]. In January 2015, a multidisciplinary panel consisting of 12 AAN physician members and 3 patient representative members were recruited to develop this systematic review. The physicians included content experts (A.H., K.M..S., C.V., M.Y.), a methodology expert (D.G.), and Guideline Development, Dissemination, and Implementation (GDDI) Committee members (Y.H.-M., M.O., N.L.). The patient representatives (E.G., E.L., H.Z) included 2 adolescents and 1 adult who had experienced migraine headache in childhood. The physicians and patient representatives were required to submit an online conflict of interest (COI) form and a copy of their curriculum vitae (CV). The panel leadership, consisting of the lead author (Y.H.-M.), the AAN methodologist (D.G.), and the AAN staff person (T.G., S.M.), reviewed the COI forms and CVs for financial and intellectual COI. These documents were specifically screened to exclude both those individuals with a clear financial conflict and those whose profession and intellectual bias would diminish the credibility of the review in the eyes of the intended users. Per AAN Policy, the lead author (Y.H.-M.) has no COIs. Four of the 10 authors were determined to have COIs which were judged to be not significant enough to

preclude them from authorship (A.H., M.S., C.V., M.Y.). All authors determined to have COI's will not be permitted to review or rate the evidence. These individuals will be used in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and help with the identification of seminal articles to validate the literature search. Panel members with COIs will be allowed to participate in the recommendation development process. The panel was recommended to the AAN GDDI leadership, who reviewed the author panel constitution and provided final approval. This panel was solely responsible for the final decisions about the design, analysis, and reporting of the review, which was then submitted for approval to the AAN GDDI.

Study screening and selection criteria

We included randomized clinical trials, nonrandomized studies, case reports, meta-analyses, and the grey literature.

Types of participants

Children and adolescents from birth to age 18 years were included. Special populations included sexually active adolescents who are of childbearing age.

Types of intervention

The review will include all interventions for the treatment of migraine headache. Interventions may include pharmacologic therapy or nonpharmocologic therapy. Treatment will include acute treatment of a migraine attack as well as preventive treatment of migraine.

Comparison group

The comparator group is children and adolescents who did not receive any treatment for their migraine headaches.

Types of outcome measures

The outcomes include (1) reduction of headache frequency by use of preventive medications and nonpharmacologic measures such as complementary and alternative medicine, lifestyle changes, and behavioral modification; (2) reduction of headache duration and associated symptoms and attainment of headache freedom by use of acute treatment; and (3) reduction of headache frequency by use of nonpharmacologic treatments.

The outcomes for acute therapy include headache improvement (typically >50%) and headache freedom at a defined time point after intervention (typically 2 hours).

The outcomes for preventive therapy include change in headache frequency (defined as number of migraine days per month) and headache severity (defined by visual analog scale, PedMIDAS scores, or another established metric).

The outcomes for nonpharmacologic therapy include change in headache frequency (defined as number of migraine days per month) and headache severity (defined by visual analog scale, PedMIDAS scores, or another established metric).

Study selection

A medical librarian performed a comprehensive literature search to obtain the relevant studies. The panel developed the search terms described below based on the proposed clinical questions and the research librarian performed literature searches of the MEDLINE and Cochrane databases and the grey literature using the following search strategy:

1. migraine headache AND
2. ibuprofen
3. acetaminophen (US)/paracetamol (international)
4. triptans: sumatriptan, rizatriptan, zolmitriptan, naratriptan, almotriptan, frovatriptan, eletriptan
5. DHE (dihydroergotamine)
6. ketorolac
7. diclofenac
8. gabapentin
9. antihistamines: diphenhydramine
10. caffeine
11. dopamine agonists: chlorpromazine/metoclopramide
12. cyproheptadine
13. beta blockers (propranolol)
14. calcium channel blockers (flunarizine)
15. alpha agonists (clonidine)
16. TCA (tricyclic antidepressant): amitriptyline, protriptyline, and nortryptiline

17. SNRI (serotonin-norepinephrine reuptake inhibitor): venlafaxine
18. tetracyclic antidepressant (trazodone)
19. serotonin agonist/antihistamine (pizotifen, hydroxyzine)
20. anticonvulsant (divalproex sodium, topiramate, levetiracetam, zonisamide)
21. Botox
22. butterbur/petadolex
23. feverfew extract
24. coenzyme q10
25. vitamins: riboflavin, ergocalciferol
26. magnesium
27. melatonin
28. biofeedback
29. cognitive-behavioral therapy
30. music therapy
31. Internet self-help
32. acupuncture
33. transcutaneous electrical nerve stimulation (TENS) unit (Cefaly)

Timeline

The tentative timeline for the systematic review will be as follows:

Review of abstracts: Completed by May 2015

Protocol posted for public comment: June 5, 2015 to July 5, 2015

Screening of full-text articles: Completed by September 2015

Review of full-text articles and data extraction: Completed by November 2015

Evidence tables: Completed by December 2015

First draft of systematic review: Completed and presented to the GDDI April 2016

Systematic review draft manuscript posted for public comment: May 9 2016 to June 9 2016

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews and other guidance published by the American Academy of Neurology and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information: 1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; 2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

CONFLICT OF INTEREST

The American Academy of Neurology is 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 keeps 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 limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN 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. For complete information on this process, access the 2011 AAN process manual.[9]

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