Practice guideline update:

Pharmacologic treatment for pediatric migraine prevention

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society

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AUTHOR CONTRIBUTIONS

Dr. Oskoui: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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Dr. Powers: drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

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Dr. Hershey: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

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L. Billinghurst has no relevant disclosures for this guideline. D. Gloss has no relevant disclosures for this guideline.

A. Hershey has served on a scientific advisory board for Allergan, XOC Pharma, and Amgen; served as an editor for *Headache*, *Cephalalgia*, and the *Journal of Headache and Pain*; has received compensation from Allergan and MAP Pharma and currently receives compensation from Alder, Amgen, Avanir, Curelator, Depomed, Impax, Lilly, Supernus, and Upsher-Smith for serving on speakers' bureaus and as a medical consultant; has received research support from GlaxoSmithKline for serving as a Local Site P.I. on a study on pediatric migraine treatment, from the Migraine Research Foundation and Curelator, Inc. for serving as a principal investigator on studies on migraine genomics and diagnosis, and from the National Headache Foundation for serving as a coinvestigator on a study on migraine prognosis; has received grants from the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) for serving as a coinvestigator on a study on migraine management, studies on treatment, prognosis, and diagnosis of pediatric chronic migraine and headache, and for serving as a dual principal investigator on a study on amitriptyline and topiramate in the prevention of childhood migraine; and serves as a board member of the American Headache Society.

N. Licking has no relevant disclosures for this guideline.

M. Sowell has received compensation for serving on a speakers' bureau for Amgen/Novartis Pharmaceuticals; has served as manuscript editor for the journal *Headache* and the *Journal of Child Neurology*, on a speakers' bureau for Allergan, and as an interviewer for *Neurology* podcasts; served as site principal investigator for the CHAMP (Childhood and Adolescent Migraine Prevention) study, for which he received research support from NINDS; and receives research support from Impax Pharmaceuticals.

M. C. Victorio is the site primary investigator for a childhood and adolescent migraine prevention study funded by the National Institutes of Health and site investigator for a pediatric migraine treatment study funded by Impax Laboratories, both studies were contracted through Akron Children's Hospital; has received funding for travel to meetings of the Registry Committee and Quality and Safety Subcommittee by the AAN; has received honoraria for authoring and coauthoring chapters in the *Merck Manual* and for authoring an article in *Pediatric Annals*; performs the following clinical procedures in her practice: onabotulinumtoxinA injection for chronic migraine (2%), peripheral nerve block injections (2%).E. Gersz reports no relevant disclosures.

E. Leininger reports no relevant disclosures.

H. Zanitsch has received financial compensation from the Patient-Centered Outcomes Research Institute and Peer Reviewed Medical Research Program and serves as a volunteer advocate for the National Headache Foundation.

M. Yonker has served on a scientific advisory board for AMGEN and for Upsher-Smith Pharmaceuticals; has served as a reviewer for the journals *Cephalalgia*, *Headache*, *Pediatrics*, and the *Journal of the Child Neurology Society*; has received research support as a primary investigator from AstraZeneca, Allergan, Avanir, and NINDS; has received funding for travel from the American Headache Society for serving as a presenter at the Scottsdale Headache Symposium; and serves as a consultant to Impax.

Dr. Kenneth Mack has served as an advisor for AMGEN; receives publishing royalties from UpToDate; performs botulinum toxin injections for headache treatment as 5% of his clinical effort; and serves as a member of the *Neurology*® editorial board.

S. Powers has received funding from the NIH, Migraine Research Foundation, and National Headache Foundation; has served as a manuscript reviewer for *Headache*, *Cephalalgia*, *Pain*, *Journal of Pain*, *JAMA Pediatrics*, and *Pediatrics*.

. ABBREVIATIONS

AAN: American Academy of Neurology

CBT: cognitive behavioral therapy

CI: confidence interval

COI: conflict of interest

DVPX ER: extended-release divalproex sodium

GABA: γ-aminobutyric acid

FDA: Food and Drug Administration

PedMIDAS: Pediatric Migraine Disability Assessment

RR: risk ratio

SMD: standard mean differences

ABSTRACT

Objective: To provide updated evidence-based recommendations for migraine prevention using pharmacologic treatment with or without cognitive behavioral therapy in the pediatric population.

Methods: The authors systematically searched the literature from January 2003 to August 2017 using a structured review process to classify the evidence and develop practice recommendations using the American Academy of Neurology 2011 classification process, as amended.

Results: Fifteen class I-III studies on migraine prevention in children in adolescents met inclusion criteria. There is insufficient evidence to determine if children and adolescents receiving divalproex, onabotulinumtoxinA, amitriptyline, nimodipine and flunarizine are more or less likely than those receiving placebo to have a reduction in headache frequency. Children with migraine receiving propranolol are possibly more likely than those receiving placebo to have an at least 50% reduction in headache frequency. Children and adolescents receiving topiramate and cinnarizine are probably more likely than those receiving placebo to have a decrease in headache frequency. Children with migraine receiving amitriptyline plus cognitive behavioral therapy are more likely than those receiving amitriptyline plus headache education to have a reduction in headache frequency.

Recommendations: The majority of randomized controlled trials studying the efficacy of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. Recommendations for the prevention of migraine in children include counseling on lifestyle and behavioral factors that influence headache frequency, and assessment and management of comorbid disorders associated with headache persistence. Clinicians should engage in shared

decision making with patients and caregivers regarding the use of preventive treatments for migraine, including discussion of the limitations in the evidence to support pharmacologic treatments.

INTRODUCTION

This publication is an update of the American Academy of Neurology (AAN) "Practice parameter: Pharmacological treatment of migraine headache in children and adolescents."[1] At the time of the 2004 practice parameter, there were few randomized controlled studies to support recommendations. Since then, new studies have been published on the efficacy and safety of migraine prevention treatments. This guideline systematically evaluates this new evidence to answer the following clinical question: In children and adolescents with migraines, do preventive pharmacologic treatments, with or without cognitive behavioral therapy (CBT), compared with placebo, reduce headache frequency?

Migraine is common in children and adolescents, with a prevalence of 1% to 3% in 3- to 7-year-olds, 4% to 11% in 7- to 11-year-olds, and 8% to 23% by age 15 years.[2] Diagnosis of primary headache disorders is based on clinical criteria by the *International Classification of Headache Disorders*, 3rd edition by the International Headache Society.[3] Most children benefit from acute migraine treatments along with behavioral and lifestyle changes for headache prevention and do not require additional pharmacologic or biobehavioral preventive treatment.[4] Additional migraine prevention should be considered when headaches occur with sufficient frequency and severity and result in migraine related disability. The Pediatric Migraine Disability Assessment (PedMIDAS) is a 6-question self-administered scale developed and validated in children and adolescents to measure functional impact of pediatric migraine during a 3-month period.[5] A score of 0 to 10 indicates little to no disability, 11 to 30 indicates mild disability, 31 to 50 indicates moderate disability, and a score greater than 50 indicates severe disability.

DESCRIPTION OF ANALYTIC PROCESS

This guideline was developed according to the process described in the 2011 AAN guideline development process manual, as amended[6] and is in compliance with the National Academy of Medicine (formerly Institute of Medicine) Standards for Systematic Reviews.[7] A multidisciplinary author panel, consisting of headache experts, child neurologists, clinical psychologists, methodologists and patients, was assembled by the Guideline Development, Dissemination, and Implementation Subcommittee of the AAN (Appendices e-1and e-2) to write this guideline. The patient representatives (E.G., E.L., H.Z) included 2 adolescents and 1 adult who had experienced migraine in childhood. All authors were required to submit an online conflict of interest (COI) form and a copy of their curriculum vitae. Five of the 10 authors were determined to have COIs that were judged to be not significant enough to preclude them from authorship (A.H., K.M., M.S., C.V., M.Y., S.P.). All authors determined to have COIs were not permitted to review or rate the evidence. These individuals were used in an advisory capacity to help with the validation of the key questions and the scope of the literature search as well as help with the identification of seminal articles to validate the literature search and participate in the recommendation development process. This panel was solely responsible for the final decisions about the design, analysis, and reporting of the guideline. The study protocol was posted for public comment according to the 2011 process manual as amended.

The authors included randomized clinical trials of migraine prevention in children aged 3 to 18 years and considered studies published in English and in other languages. The subject's headache disorders in these studies were classified according to either the *International Classification of*

Headache Disorders, 2nd edition[8] or the *International Classification of Headache Disorders*, 3rd edition (beta version).[9] Special populations included sexually active adolescents who were of childbearing age. Patients with episodic syndromes that may be associated with migraine, including cyclic vomiting, abdominal migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis were excluded. The systematic review included all pharmacologic interventions for the preventive treatment of migraine as well as the use of CBT in combination with pharmacologic therapy, with placebo used as the comparator. The outcome measures included change in headache frequency (defined as the reduction in number of migraine days per month, reduction of number of headache days per month, or 50% reduction in these frequencies), headache severity (defined by visual analog scale or numerical rating scale) and associated disability (PedMIDAS).

The authors performed an initial English language literature search from December 1, 2003, to February 15, 2015 of the following databases: MEDLINE, Cochran, CINAHL, EMBASE, CDSR, DARE, CENTRAL and an updated literature search of the same databases from January 1, 2015, to August 25, 2017. Appendix e-3 presents the complete search strategy, which was validated by its ability to pick up key articles as determined by content experts. The search was conducted to find articles on both acute and preventive treatment of migraine in children and adolescents, although only trials evaluating preventive therapies were included in this systematic review. Two authors independently reviewed all abstracts and full-text articles for relevance. Articles were included if (1) 90% of participants were aged 3 to 18 years, (2) participants had a diagnosis of migraine, (3) the article included at least 20 subjects, and (4) comparison was with placebo. The initial literature search included both pharmacologic and nonpharmacologic interventions, but due to a large number of included studies, the inclusion criteria were narrowed

to only prescription pharmacologic intervention alone or in combination with CBT. Nonpharmacologic interventions, such as behavioral interventions alone or nutraceuticals, are not addressed by this guideline.[10-13] Differences were reconciled by discussion; where disagreements arose, a methodologist on the panel (DG) adjudicated. In addition, all Class I and II studies included in the 2004 guideline were also included. Following full-text screening, all included articles were reviewed independently by 2 authors who extracted key data from each article and determined the article's class using a standardized data extraction form that was developed for each clinical question by the AAN methodologists (TP, DG) with input from the author panel.

The author panel reviewed the results of a comprehensive literature search (1994 total abstracts) and identified published studies relevant to the clinical questions (the full texts of 313 articles were reviewed), which were then classified according to the AAN's 2011 evidence-based methodology, as amended (detailed in appendices e-4 through e-9). From this search and classification strategy, 11 articles ranked as Class I, II, or III were included. In addition, the 7 prevention studies from the 2004 guideline that were previously rated as Class I or II were reclassified using the 2011 process manual, as amended, and 4 rated as Class III or higher were included in the current review (figure 1). All 4 articles were downgraded to Class II or III when graded according to the 2011 process as amended, typically because of failure to specify concealed allocation and state a primary outcome.[14-18] The author panel based the strength of the recommendations on the grading of evidence, with consideration of costs, risks, and feasibility as well as the AAN's modifications to the Grade of Recommendations, Assessment, Development, and Evaluation. Risk ratios (RR) and standardized mean differences (SMD) and the 95% confidence interval (CI) for the outcomes of interest were calculated. For the headache responder

rate outcome (proportion of participants with a 50% reduction or greater in headache frequency from baseline), we calculated the RR. We prespecified a minimal clinically important difference of 1.25 between treatment and placebo; an RR less than 1.10 was determined to be clinically unimportant. For continuous headache frequency outcomes, including the number of headache days, the number of migraine days, and migraine-related disability at endpoint, we examined the SMD. We prespecified a minimal clinically important difference in the SMD of 0.20; an SMD less than 0.1 was determined to be clinically unimportant.[19]

The panel formulated practice recommendations based on the strength of evidence and other factors, including axiomatic principles of care, the magnitude of anticipated health benefits relative to harms, financial burden, availability of interventions, and patient preferences. The panel assigned levels of obligation (A, B, C, U, R) to the recommendations, using a modified Delphi process. Considerations for future research and recommendations were also developed, and this guideline will be reassessed over time for currency and potential updates, according to the published AAN Guideline Development, Dissemination, and Implementation process.

ANALYSIS OF EVIDENCE

In children and adolescents with migraine, do preventive pharmacologic treatments, compared with placebo, reduce headache frequency?

Antiepileptic drugs

Topiramate

Four Class I studies were identified. Topiramate has a broad spectrum of action, including blockade of voltage-gated sodium channels, inhibition of high-voltage-gated calcium channels, inhibition of glutamate-mediated neurotransmission, and enhanced transmission of γ-aminobutyric acid (GABA) receptor-mediated chloride flux, which are postulated to contribute to migraine pathophysiology.

In the first Class I double-blind placebo-controlled study,[20] adolescents aged 12 to 17 years with a history of migraines longer than 6 months were randomized to receive topiramate, 50 mg/d, divided twice daily (n=35); topiramate, 100 mg/d, divided twice daily (n=35); or placebo (n=33). Topiramate was introduced at 25 mg/d, titrated over 4 weeks to the target dose or maximal tolerated dose, and maintained for 12 weeks. The daily topiramate dose during the study period, including the titration and maintenance phase, (mean, SD) was 40.9 SD 10.1 mg/d in the 50-mg/d group and 73.6 SD 18.7 mg/d in the 100-mg/d group. The primary efficacy outcome was the percentage of reduction in the rate of monthly migraine attacks during the last 12 weeks of the double-blind treatment phase compared with the prospective baseline period, with the use of the 48-hour rule. The 48-hour rule defined a single migraine episode as all recurrences of migraine symptoms within 48 hours after onset. Children who received 100 mg/d of topiramate, but not those who received 50-mg/d, had a lower mean number of migraine attacks per month during the last 4 weeks of treatment compared with children who received placebo (topiramate 100 mg vs placebo, SMD 0.56, [95% CI, 0.07 to 1.04]; topiramate 50 mg vs placebo, SMD 0.10, [95% CI, -0.38 to 0.58]). Children who received 100 mg/d of topiramate, but not those who received 50 mg/d, were more likely than children who received placebo to achieve a at least a 50% reduction in monthly migraine attack frequency (topiramate 100 mg vs placebo, RR 1.82 [95% CI, 1.25 to 2.81]; topiramate 50 mg/d vs placebo, RR 1.01 [95% CI, 0.60 to 1.68]). More

than one treatment-emergent adverse event was seen in 74% of the topiramate group and 48% of the placebo group. The most common adverse events were upper respiratory tract infection (21%), paresthesia (17%), anorexia (10%), and fatigue (5%). Renal calculus leading to withdrawal was reported in 1 subject in the topiramate 100-mg/d group. The percentage weight change from baseline for the placebo, topiramate 50-mg/d, and topiramate 100-mg/d groups were 0.8kg (SD 2.3), -0.1kg (SD 1.6), and -0.3kg (SD 3.2), respectively.

In the second Class I study,[21] children and adolescents aged 8 to 17 years with migraine and a frequency of at least 4 headache days over 28 days were randomized to receive amitriptyline 1 mg/kg/d (N=132), topiramate 2 mg/kg/d (N=130), or placebo (N=66), with a 16-week maintenance phase. The primary endpoint was reduction in headache days (defined as any headache within a 24-hour period, midnight to midnight) of at least 50%. No efficacy over placebo was shown in the primary or secondary outcomes. The average daily topiramate dose during the study period was 1.93 mg/kg/d (SD 0.18 mg/kg/d). The percentage of children with at least 50% reduction in headache days was 55% in the topiramate group and 61% in the placebo group, RR 0.91 (95% CI, 0.72 to 1.19). The mean number of headache days per month at the end of treatment was 4.6 (SD 5.3) for the topiramate group and 5.2 (SD 6.5) for the placebo group, standardized mean difference 0.11 (95% CI, -0.19 to 0.40). Headache disability (measured by PedMIDAS score) at end of treatment was 14.4 (SD 17.3) in the topiramate group and 19.4 (SD 20.8) in the placebo group, SMD 0.27 (95% CI, -0.03 to 0.57). There was 1 serious adverse event in the topiramate group (suicide attempt) not seen in the placebo group. Adverse events that occurred significantly more often in the topiramate group than in the placebo group were paresthesia (31% vs 8%, $P<0.001$) and decreased weight (8% vs 0%, $P=0.02$). Other adverse events more frequently observed in the topiramate group included fatigue (25% vs 14%), dry

mouth (18% vs 12%), memory impairment (17% vs 10%), aphasia (16% vs 10%), and cognitive disorder (16% vs 11%).

In the third Class I, double-blind, placebo-controlled parallel group study, children aged 6 to 15 years with migraine headaches 3 to 10 times per month for at least 3 months were randomized to receive topiramate (n=112) or placebo (n=50).[22] Topiramate was initiated at 15 mg/d and titrated over 8 weeks to 2 to 3 mg/kg/d or maximal tolerated dose (maximum allowed dose 200 mg/d) and maintained for 12 weeks of treatment. The primary efficacy variable was the change in mean number of migraine days per month (28 days) during the double-blind phase, relative to the 4-week prospective baseline phase for each treatment group. The mean number of migraine attacks during the last 28 days of treatment was 2.3 (SD 1.7) in the topiramate group and 3.1 (SD 2.0) in the placebo group, with a SMD of 0.45 (95% CI, 0.10 to 0.79). A 50% reduction or greater in migraine days per month was not more likely observed with topiramate compared with placebo (55% vs 47%, respectively; RR 1.16 [95% CI, 0.85 to 1.67]). The most common adverse events in the topiramate group included upper respiratory tract infection (19%), anorexia (13%), weight decrease (10%), gastroenteritis (9%), paresthesia (8%), and somnolence (8%). Serious adverse events were infection (n=2), severe migraine (n=1), and suicidal ideation (n=1). The mean change from baseline in body weight was -0.7 SD 3.9 kg for children receiving topiramate and 1.4 SD 2.6 kg for children receiving placebo.

The last Class I study was a double-blind placebo-controlled trial in children aged 8 to 14 years with 2 or more migraine headaches per month for 3 months who were randomized to receive topiramate (n=22) or placebo (n=22).[23] Topiramate was introduced at 25 mg/d and titrated

weekly by 25-mg increments to 100 mg/d, in 2 divided doses, or the maximum tolerated dose and maintained for 12 weeks of treatment. The first 28 days of the study treatment period was used as the comparative "baseline." The primary outcome measures were the reduction in mean migraine frequency and severity. There was a lower mean number of migraine attacks per month during the last 4 weeks of the double-blind phase in the topiramate group (4.27 SD 1.95) compared with the placebo group (7.48 SD 5.94), SMD 0.73 (95% CI, 0.10 to 1.35).[23] Children treated with topiramate were more likely than those receiving placebo to achieve at least a 50% reduction in migraine frequency (95% vs 52%; RR 1.82, [95% CI, 1.25 to 2.95]). Headache disability at end of treatment (as measured by PedMIDAS score) was 10.42 (SD 6.39) in the topiramate group and 23.7 (SD 19.1) in the placebo group, SMD 0.932 (95% CI, 0.30 to 1.57). There was no statistically significant difference in mean migraine severity (*P*=0.44), no other data were provided. Commonly reported adverse events in the topiramate group included weight loss (81%), loss of appetite (24%), decreased concentration in school (19%), sedation (19%), paresthesias (24%), and abdominal pain (14%). The mean body weight of children treated with topiramate decreased from 30.0 kg (SD 8.13) at baseline to 29.7 kg (SD 6.94), compared with children treated with placebo (baseline 29 kg [SD 6.57] to 29.5 kg [SD 6.71], *P*=0.001).

Conclusion

Children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a decrease in the frequency of migraine or headache days (moderate confidence in the evidence, 4 Class I studies[20-23]; random effect model SMD 0.391; 95% CI, 0.127 to 0.655; confidence in the evidence downgraded due to imprecision). There is insufficient evidence to determine whether children with migraine receiving topiramate are more or less

likely than those receiving placebo to have at least a 50% reduction in headache frequency (very low confidence in the evidence; RR 1.330 [95% CI, 0.933 to 1.894]; confidence in the evidence downgraded due to imprecision). Children with migraine receiving topiramate are possibly no more likely than those receiving placebo to have a decrease in migraine-related disability (low confidence in the evidence, 2 Class I studies[21, 23]; SMD 0.538 [95% CI, -0.097 to 1.174]; confidence in the evidence downgraded due to imprecision).

Extended-release divalproex sodium

The mechanism of action of valproate is not fully understood but may relate to enhanced GABA neurotransmission. A single Class II study was identified (lack of allocation concealment).[24] In a double-blind placebo-controlled parallel group study in 12 to 17 year olds with >1-year history of migraines (2004 ICHD criteria), subjects were randomized to receive 250 mg (n=81), 500 mg (n=74), or 1,000 mg (n=73) daily of extended-release divalproex sodium (DVPX ER) or placebo (n=71) for 12 weeks. There was no change from baseline in number of migraines per week during the last 4 weeks of treatment for each group treated with DVPX ER compared with placebo (DVPX ER 250 mg/d vs placebo SMD 0.1 [95% CI, -0.22 to 0.42]; DVPX ER 500 mg/d vs placebo SMD -0.05 [95% CI, -0.38 to 0.28]; DVPX ER 1,000 mg/d vs placebo SMD 0.05 [95% CI, -0.28 to 0.38]). There was no difference in number of children with a 50% reduction or greater in 4-week migraine rate in any of the treatment groups compared with placebo (DVPX ER 250 mg/d RR 0.88 [95% CI, 0.61 to 1.26]; DVPX ER 500 mg/d RR 0.79 [95% CI, 0.53 to 1.15]; DVPX ER 1,000 mg/d RR 1.11 [95% CI, 0.79 to 1.55]). Adverse events that occurred were observed equally between the placebo group and groups treated with DVPX ER (58% vs 67%, respectively), with the most common being upper respiratory tract infection (20%), nausea

(8%), nasopharyngitis (6%), weight gain (5%), somnolence (4%). The amount of weight gain observed from baseline to endpoint was greater in the groups treated with DVPX ER (1.86 kg [250 mg/d group, 2.22 kg [1,000 mg/d group]) compared with the group treated with placebo (0.88 kg), $P<0.05$. An increase in ammonia level was seen in all treatment groups (5 in placebo group, 4 in DVPX ER 250 mg/d group, 2 in DVPX ER 500 mg/d group, and 8 in DVPX ER 1,000 mg/d group), leading to study drug discontinuation in 3 subjects in the DVPX ER 1,000 mg/d group. In these 3 subjects, ammonia levels normalized upon discontinuation of DVPX ER. There was a dose-related decrease in platelet counts and increase in uric acid levels noted in all treatment groups. The mean change from baseline in platelet count was 4.6 $x10^9$/L in the placebo group, -2.6 $x10^9$/L in the DVPX ER 250-mg/d group, -16.6 $x10^9$/L in the DVPX ER 500 mg/d group, and -27.5 in the DVPX 1,000 mg/d group. None of these changes led to study drug discontinuation. Among postmenarchal female subjects who were not taking hormonal contraceptives or steroids, there was a dose-related increase in sex hormone-binding globulin.

Conclusion

There is insufficient evidence to determine whether children with migraine who are receiving DVPX ER (250, 500, or 1,000 mg/d) are more or less likely than those receiving placebo to have a reduction in headache frequency (very low confidence in evidence, 1 Class II study[24] downgraded for imprecision). There is insufficient evidence to determine whether children with migraine who are receiving DVPX ER are more or less likely than those receiving placebo to have at least a 50% reduction in headache frequency (very low confidence in the evidence; 1 Class II study downgraded for imprecision; RR 0.92 [95% CI, 0.70 to 1.24]).

Antidepressant drugs

Amitriptyline

Amitriptyline acts primarily as a serotonin-norepinephrine reuptake inhibitor, but has other pharmacologic activity, including antagonism at histamine, muscarinic, α_1-adrenergic, and serotonin receptors. A single Class I study described previously was identified.[21] In this study, children and adolescents aged 8 to 17 years with migraine and a frequency of at least 4 headache days over 28 days were randomized to receive amitriptyline 1 mg/kg/d, topiramate 2 mg/kg/d or placebo, with a 16-week maintenance phase. The average daily amitriptyline dose during the study period was 0.99 mg/kg/d (SD 0.4). Amitriptyline was not more effective than placebo in primary or secondary outcomes measured. The percentage of children with at least 50% reduction in headache frequency was 52% in the amitriptyline group and 61% in the placebo group, RR 0.86 (95% CI, 0.68 to 1.13). The mean number of headache days per month during the last 4 weeks of double-blind phase was not significantly different between amitriptyline and placebo, with an SMD of 0.11 (95% CI, -0.18 to 0.41). Headache disability (measured by PedMIDAS score) at the end of treatment was 18.8 (SD 25.3) in the amitriptyline group and 19.4 (SD 20.8) in the placebo group, SMD 0.03 (95% CI, -0.27 to 0.32). Adverse events that occurred significantly more often in the amitriptyline group than the placebo group were fatigue (14% vs 3%, *P*=0.01) and dry mouth (25% vs 12%, *P*=0.03). There were 4 serious adverse events in the participants treated with amitriptyline: 1 with syncope and 3 with altered mood.

Conclusion

There is insufficient evidence to determine whether children with migraine receiving amitriptyline are more or less likely than those receiving placebo to have a decrease in the number of headache days per month, to have at least a 50% reduction in headache frequency, or to have a reduction in migraine-related disability (very low confidence the in evidence, 1 Class I study,[21] confidence the in evidence downgraded for imprecision).

Beta-blockers

Propranolol

Two Class III studies were identified. Propranolol is a nonselective β-blocker. In a double-blind crossover design study (downgraded for unspecified concealed allocation, no primary outcome, and 74% study completion rate), children aged 9 to 15 years with migraine (no criteria specified) were randomized to receive propranolol, 40 mg twice per day, (n=22) or placebo (n=17) for 12 weeks, with a 2-week washout period followed by a crossover.[25] There was no effect of propranolol in reducing headache frequency or duration or associated nausea or vomiting compared with placebo (no raw data provided). Adverse events were seen equally in both groups (12 in the propranolol group). The most common adverse events with treatment were increased appetite (3), abdominal pain (2), amenorrhea (2), and weight gain (2). In a double-blind Class III crossover design study (unspecified concealed allocation, no primary outcome), 28 children aged 7 to 16 years with migraine (1962 diagnostic criteria[26] used) were randomized to placebo or propranolol (20 mg, three times per day, in those weighing less than 35 kg; 40 mg, three times per day, in those weighing more than 35 kg) for 13 weeks.[27] Response to treatment was defined as excellent if no headaches or negligible symptoms were experienced and good if the frequency

of attacks was reduced to less than one third. In period 1, children who received propranolol were more likely than those who received placebo to achieve an excellent or good response (11 of 13 vs 2 of 15; RR 6.35 [95% CI, 2.06 to 22.72]). In period 2, the same efficacy was observed (12 of 15 vs 2 of 13; RR 5.20 [95% CI, 1.74 to 18.59]). Two children reported difficulty falling asleep while taking propranolol. No other adverse events were noted.

Conclusion

Children with migraine receiving propranolol are possibly more likely than those receiving placebo to have at least a 50% reduction in headache attacks (low confidence in the evidence, 1 Class III study[27]; RR 5.20 [95% CI, 1.59 to 17.00]; confidence in evidence upgraded due to magnitude of effect).

Calcium channel blockers

Flunarizine

Flunarizine is a calcium channel blocker not available in the United States but available in Canada. One Class III study was identified. In a double-blind placebo-controlled crossover design study (no carryover or period effects analyzed, unspecified allocation concealment), children aged 5 to 11 years with 3 or more migraine (Vahlquist's criteria[28]) attacks per month in a period of 3 months were randomized to receive 5 mg/day of flunarizine (n=35) or placebo (n=35) over 12 weeks. After a 4-week washout period, the groups crossed over for an additional 12 weeks, and 63 completed the study.[29] The frequency of attacks decreased significantly

(P<0.001) in group A (flunarizine first) compared with baseline from the 3rd month of observation and remained constant throughout the study, including after the crossover to placebo. In group B (placebo first), the frequency of headache attacks was significantly reduced (P<0.001) compared with baseline values from the 6th month of the trial, which corresponds to the 1st month with flunarizine treatment. The reduction was maintained throughout the period. No further data was provided to calculate effect sizes. The main adverse effect experienced by participants receiving flunarizine was daytime sedation (10%) and weight gain (22%).

Conclusion

There is insufficient evidence to support or refute the efficacy of flunarizine, compared with placebo, for migraine prevention in children to reduce headache frequency or severity (very low confidence in evidence, 1 Class III study[29]).

Cinnarizine

Cinnarizine is an antihistamine and an L-type calcium channel blocker not available in the United States or Canada. One Class II study was identified (3 primary outcomes, lack allocation concealment).[30] In a double-blind placebo-controlled parallel group study, children aged 5 to 17 years with a history of 4 or more migraine attacks per month for at least 6 months were randomized to receive cinnarizine (a dose of 1.5 mg/kg/d in children who weighed less than 30 kg and 50 mg/d in children who weighed more than 30 kg [n=30]) or placebo (n=32). After 3 months of treatment, the monthly headache frequency for children receiving placebo during the

last month of treatment was 7.4 (SD 4.9) compared with 4.0 (SD 3.0) in the group treated with cinnarizine (SMD 0.83 [95% CI, 0.31 to 1.35]). After 3 months of treatment, the mean severity using a pain rating scale in placebo group was 6.3 (SD 1.9) compared with 4.2 (SD 2.4) the group treated with cinnarizine (SMD 0.97 [95% CI, 0.45 to 1.50]). A reduction of more than 50% in the monthly frequency of headaches was observed in 60% of the group treated with cinnarizine and 31% of children who received placebo (*P*=0.023), RR 1.92 (95% CI, 1.09 to 3.48). Cinnarizine was well tolerated. Three subjects developed early drowsiness and 1 experienced weight gain greater than 2.5 kg. None reported extrapyramidal signs.

Conclusion

Children with migraine receiving cinnarizine are probably more likely than those receiving placebo to have a reduction in headache frequency (moderate confidence in the evidence; 1 Class II study; SMD 0.83 [95% CI 0.31 to 1.35]; confidence in the evidence upgraded due to magnitude of effect). Children with migraine receiving cinnarizine are probably more likely than those receiving placebo to have a reduction in headache severity (moderate confidence in the evidence; 1 Class II study; SMD 0.97 [95% CI, 0.45 to 1.50]; confidence in the evidence upgraded due to magnitude of effect). Children with migraine receiving cinnarizine are possibly more likely than those receiving placebo to have a greater than 50% reduction in headache frequency (low confidence in the evidence; 1 Class II study[30]; RR 1.92 [95% CI, 1.09 to 3.48]).

Nimodipine

Nimodipine is a selective calcium entry blocker for the slow calcium channels. One Class III study was identified. In this double-blind placebo-controlled crossover design study (no period effect, unspecified allocation concealment, no primary outcome), children (mean age 12.2 years +/- SD 3.3) with migraine, with or without aura, were randomized to receive placebo (n=19) or nimodipine 10 to 20 mg, three times per day (n=18) for 12 weeks.[31] Thirty subjects completed the study. After a 4-week washout period, the groups crossed over for an additional 12 weeks. During the first treatment phase, no significant difference between the 2 groups was found in mean number of migraine attacks per month during the last month of treatment (nimodipine 2.8 [SD 0.9] vs placebo 2.5 [SD 0.9]; SMD -0.33 [95% CI, -0.98 to 0.32]). At the end of the second treatment phase, children in the nimodipine group had a lower mean number of migraine attacks per month during the last month of treatment compared with the placebo group (nimodipine group 1.9 [SD 0.7]; placebo group 2.8 [SD 0.6]; SMD 1.38 [95% CI, 0.66 to 2.10]). Mild abdominal discomfort was reported by those who received nimodipine treatment (3 of 30 [1%]).

Conclusion

There is insufficient evidence to support or refute the efficacy of nimodipine treatment, compared with placebo, for migraine prevention in children and adolescents to reduce headache frequency (very low confidence in the evidence, 1 Class III study[31]).

Neurotoxins

OnabotulinumtoxinA

A single Class II study was identified as completed with posted results on clinicaltrials.gov, pending publication of the manuscript (NCT01662492).[32] In this double-blind placebo-controlled study, adolescents aged 12 to 18 years with chronic migraine (migraines for longer than 6 months, with more than 15 headache days in a 4-week period) were randomized to receive IM injection of 155 units of onabotulinumtoxinA (n=45), 74 units of onabotulinumtoxinA (n=43), or placebo (normal saline) (n=37) over a 12-week trial. The mean change in frequency of headache days per 28-day period from baseline was similar across all groups (placebo -6.8 [SD 8.2]; 74 units of onabotulinumtoxinA -6.4 [SD 7.8], with an SMD compared with placebo of 0.05 [95% CI, -0.389 to 0.490]; 155 units of onabotulinumtoxinA -6.3 [SD 7.0], with an SMD compared with placebo of 0.07 [95% CI, -0.37 to 0.51]). There was no significant difference in percentage of patients with a 50% reduction or greater in frequency of headache days across groups (placebo 30%; 74 units of onabotulinumtoxinA 33%, with an RR compared with placebo of 1.10 [95% CI, 0.58 to 2.09]; 155 units of onabotulinumtoxinA 29%, with an RR compared with placebo of 0.97 [95% CI, 0.51 to 1.89]). No serious adverse events were seen in the placebo group. Serious adverse events were seen in 5% of those treated with 74 units of onabotulinumtoxinA (1 appendicitis, 1 migraine) and in 2% of those treated with 155 units of onabotulinumtoxinA (1 cellulitis). Other adverse events were reported in 22% of those treated with placebo, 32% of those treated with 74 units of onabotulinumtoxinA, and 19% of those treated with 155 units of onabotulinumtoxinA. The most common side effects seen more in treated groups were neck pain (9% of those receiving onabotulinumtoxinA vs 0% of those receiving placebo; RR 6.88 [95% CI, 0.69 to 68.58]) and musculoskeletal pain (5% of those receiving onabotulinumtoxinA vs 0% of those receiving placebo; RR 3.44 [95% CI, 0.30 to 36.51, with continuity correction]).

Conclusion

There is insufficient evidence to determine whether adolescents with chronic migraine receiving OnabotulinumtoxinA 74 units IM are more or less likely than those receiving placebo to have a reduction in headache frequency (SMD 0.05 [95% CI, -0.39 to 0.49]) or to have at least a 50% reduction in frequency of headache days (RR 1.10 [95% CI, 0.58 to 2.09]) (very low confidence in the evidence, 1 class II study [32] downgraded for imprecision). There is insufficient evidence to determine whether adolescents with chronic migraine receiving OnabotulinumtoxinA 155 units IM are more or less likely than those receiving placebo to have a reduction in headache frequency (SMD 0.75 [95% CI, -0.37 to 0.51]) or to have at least a 50% reduction in frequency of headache days (RR 0.97 [95% CI, 0.51 to 1.89]) (very low confidence in the evidence, 1 class II study[32] downgraded for imprecision.

In children and adolescents with migraine, do pharmacologic treatments combined with CBT, compared with the same pharmacologic treatments combined with a control intervention, reduce headache frequency?

A single Class I study was identified.[33] In this double-blind placebo-controlled parallel group study, children and adolescents aged 10 to 17 years with a history of migraines occurring at least 15 times per month without medication overuse were given 1 mg/kg/d of amitriptyline and randomized to 8 sessions of CBT (n=64) or headache education (n=71). After 20 weeks of treatment, children and adolescents in the group that received amitriptyline and CBT had a lower mean number of headaches per 28 days compared with those who received amitriptyline and

headache education (SMD 0.48 [95% CI, 0.14 to 0.82]). The migraine-associated disability (as measured by PedMIDAS) at the end of 20 weeks of treatment was lower in the group that received amitriptyline and CBT (15.5 [SD 17.4]) compared with those who received amitriptyline and headache education (29.6 [SD 42.2]), SMD 0.43 (95% CI, 0.09 to 0.77). At the end of 20 weeks of treatment, a 50% reduction in headache days was seen in 66% of the group that received amitriptyline and CBT and 36% of the group that received amitriptyline and headache education (RR 1.79 [95% CI, 1.27 to 2.56]). At a 12-month follow-up, this effect was sustained; the group that received amitriptyline and CBT was more likely to achieve a 50% reduction in days with headache (49 of 57 [86%]) than the group that received amitriptyline and headache education (46 of 67 [69%]) (RR 1.25 [95% CI, 1.03 to 1.52]). The group that received amitriptyline and headache education, compared with the group that received amitriptyline and CBT, had a higher number of central nervous system adverse events (the majority were worsened migraine) (39% vs 20%; RR 8.41 [95% CI, 2.69 to 26.35]) and respiratory adverse events (11% vs 2%; RR 7.21 [95% CI, 0.93 to 56.09]).

Conclusion

Children and adolescents aged 10 to 17 years with chronic migraine who receive amitriptyline and CBT are more likely than those who receive amitriptyline and headache education to have a reduction in headache frequency (SMD 0.48 [95% CI, 0.14 to 0.82]; high confidence in the evidence; 1 Class I study,[33] confidence in the evidence upgraded due to magnitude of effect) and to have at least a 50% reduction in headache frequency (RR 1.79 [95% CI, 1.27 to 2.56]; high confidence in the evidence, 1 Class I study,[33] confidence in evidence upgraded due to magnitude of effect). Children and adolescents aged 10 to 17 years with migraine who receive amitriptyline

and CBT are probably more likely than those who receive amitriptyline and headache education to have a reduction in headache-related disability (PedMIDAS SMD 0.43 [95% CI, 0.09 to 0.77]; moderate confidence in the evidence, 1 Class I study[33]).

PRACTICE RECOMMENDATIONS

Counseling and education for children and adolescents with migraine and their families

Recommendation 1 rationale

Individuals with a family history of migraine are at higher risk of developing migraine, and female sex is a risk factor of migraine that persists into adulthood.[34] Disease prevention is the cornerstone of medical care. Migraine has multiple behavioral factors that influence headache frequency. Recurrent headache in adolescents is associated with being overweight, caffeine and alcohol use, lack of physical activity, poor sleep habits and tobacco exposure.[35] Depression is associated with higher headache disability in adolescents.[36] Weight loss can contribute to headache reduction in children who are overweight.[37] Identification and avoidance of factors that contribute to headache risk can reduce migraine frequency (INFER).

Statement 1a

Clinicians should counsel patients and families that lifestyle and behavioral factors may influence headache frequency (Level B).

Statement 1b

Clinicians should educate patients and families to identify and modify migraine contributors that are potentially modifiable (Level B).

Recommendation 2 rationale

In adults with migraine, headache on more than 6 days in a month is a risk factor for progression to chronic migraine, with medication overuse contributing to this progression.[38] Taking triptans, ergotamines, opioids*, and combination analgesics on more than 9 days in a month or taking over-the-counter simple analgesics on more than 14 days in a month can lead to medication overuse headache (There is no evidence to support the use of opioids in children with migraine. Opioids are included in this rationale to be consistent with the *International Classification of Headache Disorders*[39] regarding medication overuse). It has been suggested that clinicians consider preventive treatments in these populations.[40] Although there are no data on this topic in pediatric populations, it is hypothesized that similar relationships between frequent headache, medication overuse, and progression to chronic migraine may occur in children. In clinical trials of pediatric migraine prevention, inclusion criteria for headache frequency were variable and included a minimum of 4 headache days per month with no maximum and 3 to 4 migraine attacks per month for at least 3 months. In teenagers with migraine, those with a PedMIDAS score over 30, indicating a moderate to severe migraine related disability, had a higher risk of mood and anxiety disorders and increased severity and frequency of headache. [41]

Statement 2a

Clinicians should discuss the potential role of preventive treatments in children and adolescents with frequent headache or migraine-related disability or both (Level B).

Statement 2b

Clinicians should discuss the potential role of preventive treatments in children and adolescents with medication overuse (Level B).

Starting preventive treatment

Recommendation 3 rationale

The majority of randomized controlled trials that studied the efficacy of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. Pediatric migraine trial results demonstrated a high response to placebo, with 30% to 61% of children who received placebo having had a 50% or greater reduction in headache frequency. Children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a decrease in headache days and migraine attacks; however, there is insufficient evidence to determine whether children with migraine who are receiving topiramate are more or less likely than those receiving placebo to have at least a 50% reduction in migraine frequency or headache days, and this is also the case for reduction in migraine-related disability.[20-23] Children who receive propranolol are possibly more likely than those who receive placebo to have more than a 50% reduction in headache frequency.[25, 27] Patients receiving amitriptyline combined with CBT

as compared with those treated with amitriptyline who receive headache education are more likely to experience a decreased headache frequency and have more than a 50% reduction in headache frequency and are probably more likely to have decreased migraine-associated disability.[33] There is insufficient evidence to judge the independent effectiveness of amitriptyline on migraine prevention in children and adolescents.[21] A Food and Drug Administration (FDA) black box warning regarding risk of suicidal thoughts and behavior with amitriptyline use especially in children, adolescents, and young adults is in effect at the time of this guideline. It is possible that CBT alone is effective in migraine prevention,[11] and individual barriers to access may exist.[13] There is insufficient evidence to evaluate the effects of flunarizine,[29] nimodipine,[31] valproate,[24] and onabotulinumtoxinA[32] for use in migraine prevention in children and adolescents. Although there is evidence that cinnarizine[30] is probably more effective than placebo for migraine prevention, this medication is not available in the United States or Canada.

Statement 3a

Clinicians should inform patients and caregivers that in clinical trials of treatments for pediatric migraine many children and adolescents who received placebo improved and the majority of preventive medications were not superior to placebo (Level B).

Statement 3b

Acknowledging the limitations of currently available evidence, clinicians should engage in shared decision making regarding the use of short-term treatment trials (a minimum of 2 months) for those who could benefit from preventive treatment (Level B).

Statement 3c

Clinicians should discuss the evidence for amitriptyline combined with CBT for migraine prevention, inform them of the potential side effects of amitriptyline including risk of suicide, and work with families to identify providers who can offer this type of treatment[13] (Level B).

Statement 3d

Clinicians should discuss the evidence for topiramate for migraine prevention in children and adolescents and its side effects in this population (Level B).

Statement 3e

Clinicians should discuss the evidence for propranolol for migraine prevention and its side effects in children and adolescents (Level B).

Counseling for patients of child bearing potential

Recommendation 4 rationale

Balancing benefit and risk is important when deciding among available medical treatments. Topiramate and valproate have well-demonstrated teratogenic effects, especially when used in polytherapy.[42-45] Valproate use during pregnancy is also associated with developmental disorders

in offspring.[46, 47] An FDA black box warning regarding fetal risk from valproate use exists as of the time of this guideline. Topiramate at a daily dose of 200 mg or less does not interact with oral combined hormonal contraceptives; however, at higher doses it can have drug interactions that decrease their effectiveness.[48] The risk of major congenital malformation in offspring of women with epilepsy taking anticonvulsants is possibly decreased by folic acid supplementation.[49]

Statement 4a

Clinicians must consider the teratogenic effect of topiramate and valproate in their choice of migraine prevention therapy recommendations to patients of childbearing potential (Level A).

Statement 4b

Clinicians who offer topiramate or valproate for migraine prevention to patients of childbearing potential must counsel these patients about potential effects on fetal-childhood development (Level A).

Statement 4c

Clinicians who prescribe topiramate for migraine prevention to patients of childbearing potential must counsel these patients about the potential of this medication to decrease the efficacy of oral combined hormonal contraceptives, particularly at doses over 200 mg daily (Level A).

Statement 4d

Clinicians who prescribe topiramate or valproate for migraine prevention to patients of childbearing potential should counsel patients to discuss optimal contraception methods with their health care provider (Level B).

Statement 4e

Clinicians must recommend daily folic acid supplementation to patients of childbearing potential who take topiramate or valproate (Level A).

Monitoring and stopping medication

Recommendation 5 rationale

Migraine is a chronic disorder with spontaneous remissions and relapses. Clinical trials follow patients for limited periods of time. Patients and families often inquire about the duration of treatment. There is little information about when preventive treatment should be stopped, and the risk of relapse after discontinuation varies.

Statement 5a

Clinicians must periodically monitor medication effectiveness and adverse events when prescribing migraine preventive treatments (Level A).

Statement 5b

Clinicians should counsel patient and families about risks and benefits of stopping preventive medication once good migraine control is established (Level B).

Mental illness in children and adolescents with migraine

Recommendation 6 rationale

Several studies have been performed, with inconsistent results, that evaluated the relationship between mental illness and migraine in children. A recent systematic review of prospective or retrospective longitudinal cohort studies in children examined factors associated with the onset and course of recurrent headache in children and adolescents, with recurrent headache defined as headaches occurring at least once per month. This review found high-quality evidence suggesting that children with negative emotional states, manifesting through anxiety, depression, or mental distress, are not at greater risk of developing recurrent headache; however, it found moderate-quality evidence that suggested the presence of comorbid negative emotional states in children with headache is associated with an increased risk of headache persistence in those who already experience recurrent headaches.[34]

Statement 6a

Children and adolescents with migraine should be screened for mood and anxiety disorders because of the increased risk of headache persistence (Level B).

Statement 6b

In children and adolescents with migraine who have comorbid mood and anxiety disorders, clinicians should discuss management options for these disorders (Level B).

PUTTING THE EVIDENCE INTO A CLINICAL CONTEXT

The goal of preventive treatment is to reduce headache frequency and headache-related disability. Achieving clinically meaningful improvements should be the standard for assessing the impact of a given treatment. Involving patients and parents helps ensure that providers understand what clinically meaningful outcomes are as well as assists with treatment adherence and respects patient preferences. The choice of treatment can be guided by the presence of comorbidities (e.g., topiramate use in patients with epilepsy or the use of drugs that either decrease or increase appetite in patients with weight-related morbidity). Although topiramate is the only FDA-approved medication for migraine prevention (in children and adolescents aged 12 to 17 years), the current evidence base raises some doubts about whether this treatment achieves clinically meaningful outcomes beyond those obtained by placebo. There is insufficient evidence to confidently recommend this as a known efficacious preventive intervention. Some treatments with proven efficacy in adults, such as valproate for episodic migraine prevention and onabotulinumtoxinA for chronic migraine, have not shown the same efficacy in children and adolescents, and a higher pediatric placebo-response rate is observed.[50, 51] Analysis of placebo-response rates across pediatric migraine trials show that trial designs associated with a lower placebo-response rate included crossover design trials, single-center studies, and small sample size, with age and sex not predictive of placebo-response rates.[52] The more rigorous trials have

demonstrated a robust placebo response, and this response likely has a biological basis that can be potentially explored in clinical practice.[53]

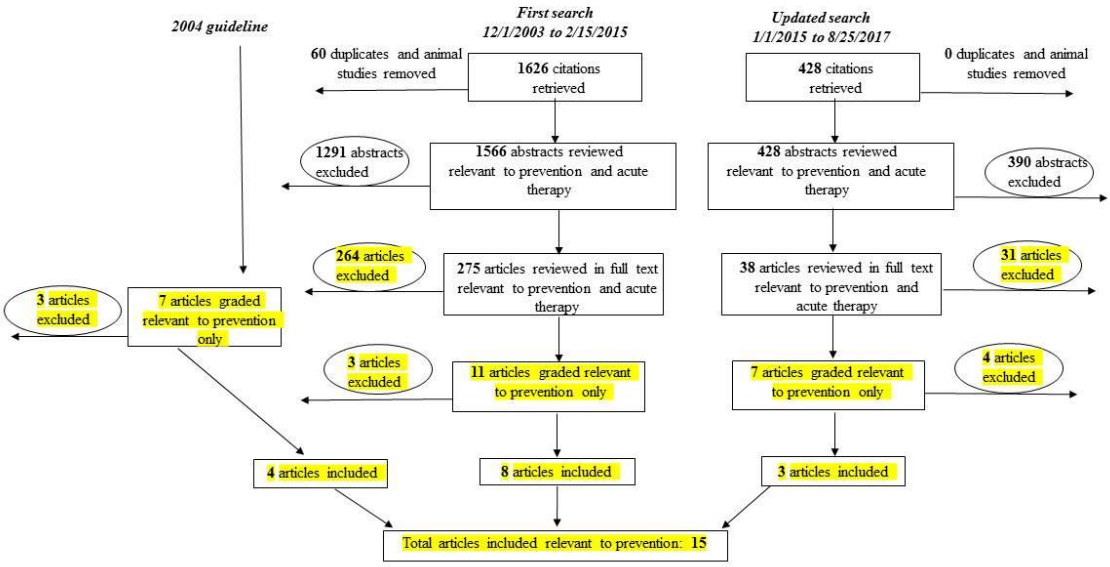
SUGGESTIONS FOR FUTURE RESEARCH

Improved classification of pediatric migraine and reliable measures of outcome and disability have improved our recognition and understanding of childhood migraine and enabled more robust clinical studies. However, variation in endpoints used in trials complicates assessment and comparison of potential benefit. The presence of high placebo-response rates in pediatric migraine demonstrates that children respond to treatment of their headache but makes identifying a therapeutic response from pharmaceutical treatments more challenging. To account for this effect, unique study designs should be taken into consideration when planning trials. New therapeutics (drugs, devices, behavioral treatments) and further well-designed studies are needed. Specifically, the efficacy of and access to the use of CBT alone needs to be informed by future well-designed randomized controlled trials. Mechanistic studies that examine mediators of improvement when a migraine patient receives a preventive intervention or placebo could be critical in understanding how and why children with headaches get better. This type of science might also suggest innovations related to new approaches to preventive therapies.

More evidence about the benefits of behavioral changes on reducing migraine burden, in particular compared with pharmacologic prevention would help guide treatment recommendation. A better understanding of factors that contribute to headache occurrence and persistence such as biologic and psychologic factors, including mood disorders, need to be investigated to identify pathophysiological pathways and biomarkers. This identification can

then be used to guide the development of new treatments and inform patients and families of their impact on outcome.

Figure 1.


2004 guideline
First search
12/1/2003 to 2/15/2015
Updated search
1/1/2015 to 8/25/2017
60 duplicates and animal studies removed
1626 citations retrieved
428 citations retrieved
0 duplicates and animal studies removed
1291 abstracts excluded
1566 abstracts reviewed relevant to prevention and acute therapy
428 abstracts reviewed relevant to prevention and acute therapy
390 abstracts excluded
264 articles excluded
275 articles reviewed in full text relevant to prevention and acute therapy
38 articles reviewed in full text relevant to prevention and acute therapy
31 articles excluded
3 articles excluded
7 articles graded relevant to prevention only
3 articles excluded
11 articles graded relevant to prevention only
7 articles graded relevant to prevention only
4 articles excluded
4 articles included
8 articles included
3 articles included
Total articles included relevant to prevention: 15

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Appendix e-1. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. AAN GDDI members 2017–2019

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD (Co-Vice-Chair); Stephen Ashwal, MD; Lori L. Billinghurst, MD; Brian Callaghan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Jeffrey Fletcher, MD; Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert); Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; Mia T. Minen, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Eric J. Ashman, MD (Ex-Officio); Jacqueline French, MD (Ex-Officio, Guideline Process Historian)

Appendix e-3: Search strategy

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) NSAIDs, (i.e. ibuprofen, naprosyn)
3) acetominophen (US)/paracetamol (international)
4) triptans: sumatriptan, rizatriptan, zolmitriptan, naratriptan, almotriptan, frovatriptan, eletriptan
5) DHE (dihydroergotamine)
6) ketorolac
7) diclofenac
8) antihistamines: diphenhydramine, hydroxyzine, pizotifen
9) caffeine
10) dopamine antagonists: chlorpromazine/metoclopramide
11) cyproheptadine
12) beta blockers
13) calcium channel blockers
14) alpha agonists (clonidine)

15) TCA (tricyclic antidepressant)

16) SNRI (serotonin-norepinephrine reuptake inhibitor)

17) SSRIs

18) Triazolopyridine derivative (trazodone)

19) anticonvulsants (divalproex sodium, topiramate, levetiracetam, zonisamide, gabapentin)

20) Botulinum toxin

21) Prednisone

22) Prochlorperazine

23) Promethazine

24) Nerve blocks

25) Cognitive behavioral therapy

Dates searched: First search: 12/1/2003 to 2/15/2015; Update search: 1/1/2015 to 8/25/2017

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1946 to Present

#	Searches	Results	Search Type

1	exp *headache disorders/dh, dt, pc, th or exp *migraine disorders/dh, dt, pc, th	8610	Advanced
2	(headache* or migraine*).ti.	31395	Advanced
3	(ibuprofen or acetaminophen or naproxen).mp.	14976	Advanced
4	(nsaids or "non steroidal antiflammatory*").mp. or exp anti-inflammatory agents, non-steroidal/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	163030	Advanced
5	(triptans or sumatriptan* or rizatriptan or zolmitriptan or naratriptan or almotriptan or frovatriptan or elitritan).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	4189	Advanced
6	exp Serotonin Receptor Agonists/	80602	Advanced
7	(chlorpromazine or dihydroergotamine or ketoralac or diclofenac).mp.	30076	Advanced
8	(acute or prevent* or abort* or prophyla* or nonpharmacolog* or "non-pharmacologic*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol	2080317	Advanced

	supplementary concept word, rare disease supplementary concept word, unique identifier]		
9	cyproheptadine.mp. or exp adrenergic beta antagonists/ or "beta block*".mp. or propranolol.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	100243	Advanced
10	exp calcium channel blockers/ or "calcium channel block*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	76878	Advanced
11	flunarizine.mp. or Flunarizine/	1676	Advanced
12	exp adrenergic alpha agonists/ or clonidine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	150524	Advanced
13	exp antidepressive agents, tricyclic/ or antidepressant*.mp. or amitriptyline.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol	66701	Advanced

	supplementary concept word, rare disease supplementary concept word, unique identifier]		
14	exp serotonin uptake inhibitors/ or venlafaxine.mp. or antihistamine*.mp. or exp histamine h1 antagonists/ or trazodone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	69292	Advanced
15	exp anticonvulsants/ or anticonvulsant*.mp. or divalproex.mp. or topiramate.mp. or levetiracetam.mp. or zonisamide.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	126907	Advanced
16	(botox or botulinum toxin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	14744	Advanced
17	exp complementary therapies/ or exp vitamins/ or exp dietary supplements/ or petasites.mp. or butterbur.mp. or riboflavin.mp. or ergocalciferol.mp. or magnesium.mp. or exp minerals/ [mp=title, abstract, original title, name of substance word, subject heading word,	673406	Advanced

	keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]		
18	melatonin.mp. or Melatonin/	19716	Advanced
19	biofeedback.mp. or biofeedback, psychology/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	8249	Advanced
20	electric stimulation therapy/ or transcranial magnetic stimulation/ or transcutaneous electric nerve stimulation/ or behavior therapy/ or cognitive therapy/ or mindfulness.mp. or internet.mp. or acupuncture therapy/ or acupuncture analgesia/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	145796	Advanced
21	music therapy.mp. or Music Therapy/	2768	Advanced
22	("cognitive behavior therapy" or cefaly).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1378	Advanced

23	(pizotifen or pizotyline).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	394	Advanced
24	(flunarazine or petadolex or phytotherap* or paracetamol or acetominophen).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	39566	Advanced
25	or/3-7	266591	Advanced
26	or/9-18	1205038	Advanced
27	or/19-24	195195	Advanced
28	(1 or 2) and 8	6834	Advanced
29	(1 or 2) and 25	5077	Advanced
30	(1 or 2) and 26	5330	Advanced
31	(1 or 2) and 27	1776	Advanced
32	28 or 29 or 30 or 31	12496	Advanced
33	limit 32 to (english language and yr="2003 - 2015")	5776	Advanced

34	limit 33 to "all child (0 to 18 years)"	1172	Advanced
35	33 and (preschool* or child* or pediatr* or paediatr* or preteen* or school* or teen* or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1312	Advanced
36	34 or 35	1320	Advanced
37	limit 36 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or "review" or systematic reviews)	732	Advanced
38	36 and (cohort* or prospective* or retrospective* or "comparative effectiveness" or outcome* or "odds ratio" or reproducib* or "confidence interval" or "cross-over" or "sensitivity and specificity" or placebo).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	807	Advanced

39	("case control*" or "meta analysis" or trial*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1479765	Advanced
40	36 and 39	590	Advanced
41	37 or 38 or 40	1036	Advanced
42	41 not (letter or comment or editorial).pt.	1025	Advanced
43	remove duplicates from 42	1021	

Same strategy EBM Reviews – 70

Embase 1988 to 2015 Week 08

#	Searches	Results	Search Type
1	exp "headache and facial pain"/dm, dt, pc, rt, th [Disease Management, Drug Therapy, Prevention, Radiotherapy, Therapy]	29641	Advanced
2	exp migraine/dm, dt, pc, rt, th [Disease Management, Drug Therapy, Prevention, Radiotherapy, Therapy]	14965	Advanced

3	(headache* or migraine*).ti.	34872	Advanced
4	(ibuprofen or acetominophen or naproxen).mp.	44927	Advanced
5	(nsaids or "non steroidal antiflammatory*").mp. or exp anti-inflammatory agents, non-steroidal/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	381700	Advanced
6	(triptans or sumatriptan* or rizatriptan or zolmitriptan or naratriptan or almotriptan or frovatriptan or elitritan).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	10273	Advanced
7	exp Serotonin Receptor Agonists/	97903	Advanced
8	(chlorpromazine or dihydroergotamine or ketoralac or diclofenac).mp.	52627	Advanced
9	(acute or prevent* or abort* or prophyla* or nonpharmacolog* or "non-pharmacologic*").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2322312	Advanced
10	cyproheptadine.mp. or exp adrenergic beta antagonists/ or "beta block*".mp. or propranolol.mp. [mp=title, abstract, subject headings,	188224	Advanced

	heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]		
11	exp calcium channel blockers/ or "calcium channel block*".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	162515	Advanced
12	flunarizine.mp. or Flunarizine/	3792	Advanced
13	exp adrenergic alpha agonists/ or clonidine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	130515	Advanced
14	exp antidepressive agents, tricyclic/ or antidepressant*.mp. or amitriptyline.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	138777	Advanced
15	exp serotonin uptake inhibitors/ or venlafaxine.mp. or antihistamine*.mp. or exp histamine h1 antagonists/ or trazodone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	202241	Advanced

16	exp anticonvulsants/ or anticonvulsant*.mp. or divalproex.mp. or topiramate.mp. or levetiracetam.mp. or zonisamide.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	228414	Advanced
17	(botox or botulinum toxin*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	24949	Advanced
18	exp complementary therapies/ or exp vitamins/ or exp dietary supplements/ or petasites.mp. or butterbur.mp. or riboflavin.mp. or ergocalciferol.mp. or magnesium.mp. or exp minerals/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	562444	Advanced
19	melatonin.mp. or Melatonin/	25034	Advanced
20	biofeedback.mp. or biofeedback, psychology/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	18037	Advanced
21	electric stimulation therapy/ or transcranial magnetic stimulation/ or transcutaneous electric nerve stimulation/ or behavior therapy/ or	195255	Advanced

	cognitive therapy/ or mindfulness.mp. or internet.mp. or acupuncture therapy/ or acupuncture analgesia/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]		
22	music therapy.mp. or Music Therapy/	4180	Advanced
23	("cognitive behavior therapy" or cefaly).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2280	Advanced
24	(pizotifen or pizotyline).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1111	Advanced
25	(flunarazine or petadolex or phytotherap* or paracetamol or acetominophen).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	75153	Advanced
26	or/4-8	490431	Advanced
27	or/10-19	1346073	Advanced
28	or/20-25	288744	Advanced

29	("case control*" or "meta analysis" or trial*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1625863	Advanced
30	exp *"headache and facial pain"/dm, dt, pc, rt, th or exp *migraine/dm, dt, pc, rt, th or (headache* or migraine*).ti.	40481	Advanced
31	30 and 26	11268	Advanced
32	30 and 27	10386	Advanced
33	30 and 28	5428	Advanced
34	or/31-33	18260	Advanced
35	limit 34 to (human and english language and yr="2003 - 2015")	9400	Advanced
36	limit 35 to (infant or child or preschool child or school child or adolescent)	964	Advanced
37	exp case control study/ or exp case study/ or exp clinical article/ or exp clinical trial/ or exp intervention study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/	3883982	Advanced
38	meta-analysis/ or systematic review/ or review.pt.	1928924	Advanced
39	comparative study/ or comparative effectiveness/ or intermethod comparison/	725779	Advanced

40	(cohort* or prospective* or retrospective* or series).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1973447	Advanced
41	or/37-40	6695419	Advanced
42	36 and 41	667	Advanced
43	30 and 9	10064	Advanced
44	limit 43 to (human and english language and yr="2003 - 2015")	5551	Advanced
45	limit 44 to (infant or child or preschool child or school child or adolescent)	662	Advanced
46	41 and 45	500	Advanced
47	42 or 46	831	Advanced
48	47 not case report/	807	Advanced
49	48 not (letter or note or short survey or editorial).pt.	790	Advanced
50	remove duplicates from 49	778	

1

2

1 **#QueryLimiters/ExpandersLast Run ViaResultsS41S40 AND NOT S6Search modes -**

2 **Boolean/PhraseInterface - EBSCOhost Research Databases**

S42	S6 OR S40	Limiters - Published Date: 20030101-20151231; English Language Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	525
S41	S40 AND NOT S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	168
S40	S8 OR S13 OR S26 OR S39	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	374

S39	S4 AND S38	Search modes - Boolean/Phrase	Database - CINAHL with Full Text Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	67

	S38	S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37	Search modes - Boolean/Phrase	View Results (26,353) View Details
	S37	"paracetamol"	Search modes - Boolean/Phrase	View Results (801) View Details Edit
	S36	"petadolex"	Search modes - Boolean/Phrase	View Results (6) View Details Edit

	S35	"flunarazine"	Search modes - Boolean/Phrase	View Results (0) View Details Edit
	S34	"pizotifen"	Search modes - Boolean/Phrase	View Results (16) View Details Edit
	S33	(MH "Feverfew")	Search modes - Boolean/Phrase	View Results (80) View Details Edit
	S32	(MH "Transcutaneous Electric Nerve Stimulation")	Search modes - Boolean/Phrase	View Results (1,041) View Details Edit
	S31	"cefaly"	Search modes - Boolean/Phrase	View Results (4) View Details Edit
	S30	(MH "Acupuncture+") OR (MH "Acupuncture Points") OR (MH	Search modes - Boolean/Phrase	View Results (8,131) View Details

		"Acupuncture Anesthesia") OR (MH "Acupuncture Analgesia")		Edit
	S29	(MH "Music Therapy") OR (MH "Music Therapy (Iowa NIC)")	Search modes - Boolean/Phrase	View Results (2,429) View Details Edit
	S28	(MH "Cognitive Therapy+") OR (MH "Behavior Therapy+") OR (MH "Cognitive Therapy (Iowa NIC) (Non-Cinahl)+") OR (MH "Behavior Therapy (Iowa NIC) (Non-Cinahl)+")	Search modes - Boolean/Phrase	View Results (12,492) View Details Edit
	S27	(MH "Biofeedback") OR (MH "Biofeedback (Iowa NIC)")	Search modes - Boolean/Phrase	View Results (2,102) View Details Edit
	S26	S4 AND S25	Search modes - Boolean/Phrase	View Results (254) View Details Edit

	S25	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24	Search modes - Boolean/Phrase	View Results (52,183) View Details Edit
	S24	(MH "Melatonin")	Search modes - Boolean/Phrase	View Results (1,011) View Details Edit
	S23	(MH "Magnesium")	Search modes - Boolean/Phrase	View Results (1,654) View Details Edit
	S22	(MH "Anticonvulsants+")	Search modes - Boolean/Phrase	View Results (8,626) View Details Edit
	S21	(MH "Histamine H1 Antagonists+")	Search modes - Boolean/Phrase	View Results (2,006) View Details Edit
	S20	(MH "Serotonin Uptake Inhibitors+")	Search modes - Boolean/Phrase	View Results (5,802) View Details

				Edit
	S19	(MH "Antidepressive Agents, Tricyclic+") OR (MH "Antidepressive Agents, Second Generation+")	Search modes - Boolean/Phrase	View Results (4,452) View Details Edit
	S18	(MH "Adrenergic Beta-Antagonists+") OR (MH "Adrenergic Beta-Agonists+") OR (MH "Calcium Channel Blockers+") OR (MH "Adrenergic Alpha-Antagonists+")	Search modes - Boolean/Phrase	View Results (16,729) View Details Edit
	S17	(MH "Dihydroergotamine")	Search modes - Boolean/Phrase	View Results (111) View Details Edit
	S16	(MH "Chlorpromazine")	Search modes - Boolean/Phrase	View Results (145) View Details Edit
	S15	(MH "Serotonin Agonists+")	Search modes - Boolean/Phrase	View Results (1,446) View Details Edit

	S14	(MH "Antiinflammatory Agents, Non-Steroidal+")	Search modes - Boolean/Phrase	View Results (16,147) View Details Edit
	S13	S4 AND S12	Search modes - Boolean/Phrase	View Results (142) View Details Edit
	S12	S7 OR S9 OR S10 OR S11	Search modes - Boolean/Phrase	View Results (137,066) View Details Edit
	S11	(MH "Vitamins+")	Search modes - Boolean/Phrase	View Results (23,047) View Details Edit
	S10	(MH "Alternative Therapies+")	Search modes - Boolean/Phrase	View Results (102,892) View Details Edit
	S9	(MH "Manual Therapy+") OR (MH "Magnet Therapy") OR (MH "Behavior Therapy+")	Search modes - Boolean/Phrase	View Results (38,029) View Details

				Edit
	S8	S4 AND S7	Search modes - Boolean/Phrase	View Results (12) View Details Edit
	S7	(MH "Butterbur")	Search modes - Boolean/Phrase	View Results (78) View Details Edit
	S6	S4 AND S5	Search modes - Boolean/Phrase	View Results (319) View Details Edit
	S5	(MH "Clinical Trials+") OR (MH "Randomized Controlled Trials") OR (MH "Study Design+")	Limiters - Published Date: 20030101-20151231; English Language; Age Groups: Infant, Newborn: birth-1 month, Infant: 1-23 months, Child, Preschool: 2-5 years,	View Results (105,150) View Details Edit

			Child: 6-12 years, Adolescent: 13-18 years Search modes - Boolean/Phrase	
	S4	S1 OR S2	Limiters - Published Date: 20030101-20151231; English Language; Age Groups: Infant, Newborn: birth-1 month, Infant: 1-23 months, Child, Preschool: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years Search modes - Boolean/Phrase	View Results (758) View Details Edit
	S3	S1 OR S2	Search modes - Boolean/Phrase	View Results (6,739) View Details Edit
	S2	(MH "Migraine/DH/DT/PC/PF/RT/TH")	Search modes - Boolean/Phrase	View Results (4,036) View Details

				Edit
	S1	(MH "Headache+/DH/DT/PC/PF/RT/TH")	Search modes - Boolean/Phrase	View Results (6,739) View Details Edit

1

2

Appendix e-4. AAN rules for classification of evidence for risk of bias

Therapeutic scheme

Class I

A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation

b. no more than 2 primary outcomes specified

c. exclusion/inclusion criteria clearly defined

d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).

iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.

iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.

f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate

Class II

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.) All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including studies with external controls such as well-defined natural history controls). (Alternatively, a crossover trial missing both of the following 2 criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.) A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

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

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

Appendix e-5. Evidence profile tables

Prevention treatment

Table of Included Studies, Migraine Prevention in Children

Lewis 2009	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Y	Y	Y	Y	Y	Y	I
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest (JULIE: ADD FOOTNOTE: reports RR of achieving >50% reduction in migraine attack rate unless otherwise indicated)			Adverse Effects	
	Adolescents 12-17 years of age with a >6 month history of migraines (ICHD-II criteria) N=103 Titrated over 4 weeks, maintained over 12 weeks	Topiramate 50mg/day (n=35), Topiramate 100mg/day (n=35) or Placebo (n=33)	*Mean number of migraine attacks per month at baseline* Placebo 4.1 SD 1.48 Topiramate 50 mg 4.1 SD 1.74 Topiramate 100 mg 4.3 SD 1.59 *Mean number of migraine attacks per month during last 4 weeks of double-blind phase* Placebo 2.1 SD 2.03 Topiramate 50 mg 1.9 SD 1.95 SMD vs placebo 0.10 (-0.38, 0.58) Topiramate 100 mg 1.1 SD 1.53 SMD vs placebo 0.56 (0.07, 1.04) *Responder Rate (proportion of individuals with at least 50% reduction in monthly migraine attack rate)* Placebo 45% 15/33 Topiramate 50 mg 46% 16/35 RR vs placebo 1.01 (0.60, 1.68) Topiramate 100 mg 83% 29/35 RR vs placebo 1.82 (1.25, 2.81)			More than one treatment emergent adverse event was seen in 74% of topiramate group and 48% of placebo group. The most common adverse events were upper respiratory tract infection, paresthesia, and anorexia. Renal calculus leading to withdrawal was reported in one subject in the topiramate 100mg/day group. The weight change from baseline for the placebo, topiramate 50mg/day and	

				topiramate 100mg/day groups respectively were 0.8 SD 2.3 kg, -0.1 SD 1.6 kg, and -0.3 SD 3.2 kg.

1

Powers 2017	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Y	Y	Y	Y	Y	Y	I
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Children and adolescents aged 8 to 17 years with migraine (ICHD-II criteria) and a frequency of at least 4 headache days over 28 days N= 361 (33 not included in primary analysis because of early trial closure) 24 weeks	Amitriptyline 1mg/kg/day (N= 132) Topiramate 2mg/kg/day (N=130) Placebo (N=66)	*Mean number of headache days per month at baseline* Amitriptyline 11.3 SD 6.0 Topiramate 11.3 SD 5.7 Placebo 11.1 SD 6.5 *Mean number of headache days per month during last 4 weeks of double-blind phase* Amitriptyline 4.6 SD 4.6 SMD vs placebo 0.11 (-0.18, 0.41) Topiramate 4.6 SD 5.3 SMD vs placebo 0.11 (-0.19, 0.40) Placebo 5.2 SD 6.5 *Responder Rate (the percentage of children with at least 50% reduction in headache frequency)* Amitriptyline 69/132 RR vs placebo 0.86 (0.68, 1.13) Topiramate 72/130 RR vs placebo 0.91 (0.72, 1.19) Placebo 40/66 *PedMIDAS score at baseline* Amitriptyline 41.3 SD 27.9 Topiramate 41.2 SD 25.0			Adverse events that occurred significantly more often in the amitriptyline group than placebo Fatigue 30% vs 14%, p=0.01 Dry mouth 25% vs 12%, p=0.03 Serious adverse events with amitriptyline: 1 event of syncope, 3 events of altered mood. Adverse events that occurred significantly more often in the topiramate group than placebo Paraesthesia 31% vs 8%, p<0.001 Decreased weight 8% vs 0%, p=0.02 Serious adverse events with	

			Placebo 42.0 SD 27.0 *PedMIDAS score at week 24* Amitriptyline 18.8 SD 25.3 SMD vs placebo 0.03 (-0.27, 0.32) Topiramate 14.4 SD 17.3 SMD vs placebo 0.27 (-0.03, 0.57) Placebo 19.4 SD 20.8	topiramate: 1 suicide attempt.

1

Winner 2005	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Children 6 to 15 years, weight >20kg Excluded if >15 headache days in 28 days prior to study N=157 20 weeks	Topiramate (N=108) Placebo (N=49) Topiramate was initiated at 15mg/day and titrated over 8 weeks to 2-3 mg/kg/day or maximal tolerated dose (maximum allowed dose 200mg a day)	*Mean number of migraine attacks per month at baseline* Placebo 5.5 SD 2.0 Topiramate 5.4 SD 1.7 *Reduction in mean monthly migraine days during the last 28 days of treatment* Placebo 2.4 SD 2.8 Topiramate 3.1 SD 3.0 *Mean number of migraine attacks during the last 28 days of treatment* Placebo 3.1 SD 2.0 Topiramate 2.3 SD 1.7 SMD 0.45 (0.10, 0.79) *Responder Rate (the percentage of children with at least 50% reduction in headache frequency)* Placebo 23/49 Topiramate 59/108 RR vs placebo 1.16 (0.85, 1.68)			The most common adverse events in the topiramate group included upper respiratory tract infection (19.4%), anorexia (13/0%), weight decrease (10.2%), gastroenteritis (9.3%), paresthesia (8.3%), and somnolence (8.3%). Serious adverse events were infection (n=2), severe migraine (n=1) and suicidal ideation (n=1). The mean change from baseline in body weight was -0.7 SD 3.9 kg for children on topiramate and 1.4 SD 2.6kg for	

				children on placebo.

1

Lakshmi 2007	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Y	Y	Y	Y	Y	Y	I
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Children 8-14 years of age with migraine headache 2 or more per month for three months N=44 4 months	Topiramate (N=21) Topiramate was introduced at 25mg/day and titrated weekly by 25mg increments to 100mg/day in 2 divided doses or the maximum tolerated dose Placebo (N=21)	*Mean number of migraine attacks per month at baseline* Topiramate 16.14 SD 9.5 Placebo 13.38 SD 7.78 *Mean number of migraine attacks per month during last 4 weeks of double-blind phase* Topiramate 4.27 SD 1.95 Placebo 7.48 SD 5.94 SMD vs placebo 0.73 (0.10, 1.35) *Responder Rate (the percentage of children with at least 50% reduction in headache frequency)* Topiramate 20/21 Placebo 11/21 RR vs placebo 1.82 (1.25, 2.95) *PedMIDAS score at baseline* Topiramate 50.66 SD 32.1 Placebo 42.66 SD 27.5 *PedMIDAS score at end of study* Topiramate 10.42 SD 6.39 Placebo 23.7 SD 19.1 SMD vs placebo 0.93 (0.30, 1.57) There was no statistically significant difference in mean migraine severity (P=0.44), no other data provided.			Commonly reported adverse events in the topiramate group included weight loss (81%), loss of appetite (23.8%), decreased concentration in school (19%), sedation (19%), paresthesias (23.8%) and abdominal pain (14.3%). No changes were seen in liver or renal function tests. The mean body weight of topiramate treated children decreased from 30.0kg SD 8.13 at baseline to 29.7 kg SD 6.94, compared to placebo (baseline 29kg SD 6.57 to 29.5kg SD 6.71, p=0.001).	

1

Ludvigsson 1974	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	yes	Not adequate	unspecified	no	yes	yes	III
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	7 to 16 year olds with migraine, 2-5 attacks a month criteria: ad hoc committee in classification of headache 1962 N=32 (28 treated) 26-week crossover study	Propranolol (20mg t.i.d <35kg, 40mg t.i.d if >35kg) Placebo Each treatment was received for 13 weeks	Response to treatment defined as excellent if they had no headache or only negligible symptoms remaining; and good if the frequency of attacks was reduced to less than one third. Period 1 Placebo 2/15 Excellent or Good Propranolol 11/13 Excellent or Good RR 6.35 (2.06, 22.72) Period 2 Placebo 2/13 Excellent or Good Propranolol 12/15 Excellent or Good RR 5.20 (1.74, 18.59)			Two children reported difficulty falling asleep on propranolol, no other adverse events were noted.	

2

Forsythe 1984	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	yes	yes	unspecified	no	yes	no	III
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Children aged 9 to 15 with migraine (no	Propranolol (first N=22) 40 mg bid Placebo (first N=17)	There was no effect of propranolol in reducing headache frequency, duration or associated nausea or vomiting compared to placebo.			Adverse events were seen equally in both groups with the most common adverse events with treatment being	

	criteria specified) N=53, 14 omitted from final analysis 30 weeks duration, crossover trial with treatment periods of 12 weeks		No data on SD, SE or p values provided in manuscript. Unable to calculate SMD for headache frequency or RR for responder rate.	increased appetite (3), abdominal pain (2), amenorrhea (2) and weight gain (2).

1

Sorge 1988	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	yes	yes	unspecified	yes	yes	yes	III
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Children with migraine N=70 Crossover study; 4 week baseline, 12 week treatment, 4 week wash-out, 12 week treatment No period effect	Placebo Flunarizine 5 mg	Flunarizine treatment reduced both the frequency and duration of headache attacks. The frequency of attacks decreased significantly ($p<0.001$) in group A (flunarizine first) compared with baseline from the 3rd month of observation and remained constant throughout the study, including after the crossover to placebo. In group B (placebo first), the frequency of headache attacks was significantly reduced ($p<0.001$) compared with baseline values from the 6th month of the trial, which corresponds to the 1st month with flunarizine treatment. The reduction as maintained throughout the observation period.			The main adverse effect on flunarizine was daytime sedation (9.5%) and weight gain (22.2%).	

			No means or SD/SE/p values provided to calculate effect sizes.	

1

Ashrafi 2014	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	No	No (3)	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Children 5-17 years of age with a history of 4 or more migraine headaches a month for at least 6 months (2004 ICHD criteria) N=68 16 weeks	Cinnarizine (a single 1.5mg/kg/day dose in children <30kg and a single 50mg dose in children >30kg, N=30) Placebo (N=32).	*Mean number of migraine attacks per month at baseline* Cinnarizine 10.4 SD 6.9 Placebo 12.4 SD 6.6 *Mean number of migraine attacks per month during the last month of treatment* Cinnarizine 4.0 SD 3.0 Placebo 7.4 SD 4.9 SMD 0.83 (0.31, 1.35) *Headache severity (using pain rating scale) at baseline* Cinnarizine 7.8 SD 1.3 Placebo 8.4 SD 1.4 *Headache severity at the end of the third month of treatment* Cinnarizine 4.2 SD 2.4 Placebo 6.3 SD 1.9 SMD 0.97 (0.45, 1.50) *Responder Rate (the percentage of children with at least 50% reduction in headache frequency)* Cinnarizine 18/30 Placebo 10/32 RR 1.92 (1.09, 3.48)			Cinnarizine was well tolerated, with three subjects developing early drowsiness, one developed >2.5kg weight gain, and none reporting extrapyramidal signs.	

2

Apostol 2008	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	No	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	12 to 17 year olds with >1 year history of migraines (2004 ICHD criteria), N=305 12 weeks	Divalproex sodium extended release 250mg (n=81), 500mg (n=74), or 1000 mg (n=73) daily Placebo (n=71)	*Change from baseline in number of migraines per weeks during last 4 weeks of treatment* Placebo 1.9 SD 2.18 DVPX ER 250mg 1.7 SD 1.84 SMD 0.1, 95% CI -0.22, 0.42 DVPX ER 500mg 2.0 SD 1.84 SMD -0.05, 95% CI -0.38, 0.28 DVPX ER 1000mg 1.8 SD 1.76 SMD 0.05, 95% CI -0.28, 0.38 *Responder Rate (50% or greater reduction in 4 week migraine rate)* Placebo 33/71 DVPX ER 250mg 33/81 RR 0.88, 95% CI 0.61 to 1.26 DVPX ER 500mg 27/74 RR 0.79, 95% CI 0.53 to 1.15 DVPX ER 1000mg 37/73 RR 1.09, 95% CI 0.78 to 1.53			Any adverse events were observed equally between placebo and treatment groups (42/73, 58% vs 154/231, 66.7%), with the most common being upper respiratory tract infection (46/231), nausea (18/231), nasopharyngitis (13/231), weight gain (11/231), somnolence (10/231). Weight gain was observed more frequently in treatment groups (500 mg DVPX ER 1.86kg, DVPX ER 1000mg 2.22kg, compared to placebo 0.88kg, $p<0.05$). An increase in ammonia level was seen in all treatment groups (5 in placebo, 4 in DVPX ER 250mg, 2 in DVPX ER 500mg, and 8 in DVPX ER	

				1000mg), leading to study drug discontinuation in three subjects in the DVPX ER 1000mg group. All three ammonia levels normalized upon discontinuation. There was a dose related decrease in platelet count and increase in uric acid noted. The mean change from baseline in platelet count was 4.6 in placebo group, -2.6 in DVPX ER, -16.6 in DVPX ER 500mg, and -27.5 in DVPX 1000mg group, none leading to study drug discontinuation. Among postmenarchal female subjects who were not on hormonal contraceptives or steroids, there was a dose related increase in testosterone binding globulin (SHBG).

1

2

Battistella 1990	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating

				outcomes specified			
	Yes	Yes No period effect	Unspecified	No	Yes	Yes	III
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Children with migraine with or without aura N= 37 8 months; crossover study	Nimodipine 10-20 mg tid Placebo Each treatment was given for 12 weeks; 4 week washout period between treatments	*Phase 1* *Mean number of migraine attacks per month during the last month of treatment* Nimodipine 2.8 SD 0.9 N=18 Placebo 2.5 SD 0.9 N=19 SMD -0.33 (-0.98, 0.32) *Phase 2* *Mean number of migraine attacks per month during the last month of treatment* Nimodipine 1.9 SD 0.7 N=19 Placebo 2.8 SD 0.6 N=18 SMD 1.38 (0.66, 2.10)			Mild abdominal discomfort was reported with nimodipine treatment (3/30, 1%).	

1

NCT01662492 Results on clinicaltrials.gov	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	
	Children 12-18 years of age with chronic migraine N=125 12 weeks	Botulinum toxin A 155U N=45 Botulinum toxin A 74U N=43 Placebo N=37	*Change in frequency of headache days per 28 day period mean (SD) from baseline* Placebo -6.8 SD 8.2 Botox 74U -6.4 SD 7.8 SMD 0.05 (95% CI -0.389 to 0.490) Botox 155U -6.3 SD 7.0 SMD 0.07 (95% CI -0.37 to 0.51)			Serious adverse events were seen in 0/37 treated with normal saline, 2/43 treated with botox 74U (1 appendicitis, 1 migraine), and 1/43 treated with botox 155U (1 cellulitis).	

			Percentage of patients with 50% or greater reduction in frequency of headache days Placebo 11/37 Botox 74U 14/43 RR 1.10 (95% CI 0.58 to 2.09) Botox 155U 13/45 RR 0.97 (95%CI 0.51 to 1.89)	Other side effects were reported in 8/37 treated with NS, 14/43 treated with botox 74U, and 8/43 treated with botox 155U. The most common side effects seen more in the treated groups were neck pain (8/86 botox versus 0/37 placebo, RR with continuity correction 6.88 (95% CI 0.68 to 68.58), and musculoskeletal pain (4/86 botox versus 0/37 placebo), RR with continuity correction 3.44 (95% CI 0.30 to 36.51)

1

Powers 2013	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes – randomization and allocation performed by statistician (confirmed with study author)	Yes	Yes	Yes	I
	Population N Trial Length	Intervention and Comparator	Efficacy Outcomes of Interest			Adverse Effects	

	Youth 10 to 17 years with chronic migraine N=135 20 weeks	Cognitive behavioral therapy plus amitriptyline (n=64) Headache education plus amitriptyline (n=71)	*Mean number of headaches per month at baseline* CBT plus amitriptyline 21.3 SD 5.2 Headache education plus amitriptyline 21.3 SD 5.2 *Mean number of headaches per month at week 20* CBT plus amitriptyline 9.8 SD 9.8 Headache education plus amitriptyline 14.5 SD 9.8 SMD 0.48 (0.14, 0.82) *Proportion of participants with a greater than 50% reduction in days with headache at endpoint* CBT plus amitriptyline 42/64 Headache education plus amitriptyline 26/71 RR 1.79 (1.27, 2.56) *PedMIDAS score at baseline* CBT plus amitriptyline 68.2 SD 31.7 Headache education plus amitriptyline 68.2 SD 31.7 *PedMIDAS score at endpoint* CBT plus amitriptyline 15.5 SD 17.4 Headache education plus amitriptyline 29.6 SD 42.2 SMD 0.43 (0.09, 0.77)	Children receiving amitriptyline plus headache education had a higher number of central nervous system and respiratory adverse events than children receiving amitriptyline plus CBT.

1

2

Appendix e-6. Rules for determining confidence in evidence

- Modal modifiers used to indicate the final confidence in evidence in the conclusions
    - High confidence: highly likely or highly probable
    - Moderate confidence: likely or probable
    - Low confidence: possibly
    - Very low confidence: insufficient evidence
- Initial rating of confidence in the evidence for each intervention outcome pair
    - High: requires 2 or more Class I studies
    - Moderate: requires 1 Class I study or 2 or more Class II studies
    - Low: requires 1 Class II study or 2 or more Class III studies
    - Very low: requires only 1 Class III study or 1 or more Class IV studies
- Factors that could result in downgrading confidence by 1 or more levels
    - Consistency
    - Precision
    - Directness
    - Publication bias
    - Biological plausibility
- Factors that could result in downgrading confidence by 1 or more levels or upgrading confidence by 1 level
    - Magnitude of effect
    - Dose response relationship
    - Direction of bias

Appendix e-7. Evidence synthesis tables

Evidence synthesis tables can be viewed at the following link: https://drive.google.com/open?id=1vZ3bq1PWJ3rB7jiIBOGF0gTLBfljoCPS

Appendix e-8. Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

Rationale for recommendation summarized in the rationale includes 3 categories of premises

- Evidence-based conclusions for the systematic review
- Stipulated axiomatic principles of care
- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements

- The patient population that is the subject of the recommendation
- The person performing the action of the recommendation statement
- The specific action to be performed
- The expected outcome to be attained

Assigning a level of obligation

Modal modifiers used to indicate the final level of obligation (LOO)

- Level A: *Must*
- Level B: *Should*
- Level C: *May*
- Level U: No recommendation supported

LOO assigned by eliciting panel members' judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of 3 rounds of voting. Consensus is defined by:

- ≥ 80% agreement on dichotomous judgments
- ≥80% agreement, within 1 point for ordinal judgments
- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10^{th} percentile

Three steps used to assign final LOO

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within 4 domains. Initial LOO anchored to lowest LOO supported by any domain.
    - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process
        - Level A: High confidence
        - Level B: Moderate confidence
        - Level C: Low confidence
        - Level U: Very low confidence
    - Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference

        - Level A: 100%
        - Level B: ≥ 80% to < 100%
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%
    - Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles
        - Level A: 100%
        - Level B: ≥ 80% to < 100%
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%
    - Belief that evidence cited from rerated conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong
        - Level B: ≥ 80% to 100% (recommendations dependent on inferences from nonsystematically reviewed evidence cannot be anchored to a Level A LOO)
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%

2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation
    - Magnitude relative to harm rated on 4-point ordinal scale
        - Large benefit relative to harm: benefit judged large, harm judged none

- Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none
- Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none
- Benefit to harm judged too close to call: benefit and harm judged to be substantially similar

▪ Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm

- Level A: large benefit relative to harm
- Level B: moderate benefit relative to harm
- Level C: small benefit relative to harm
- Level U: too close to call

▪ LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation

3. LOO optionally downgraded on the basis of the following domains
   ▪ Importance of the outcome: critical, important, mildly important, not important
   ▪ Expected variation in patient preferences: none, minimal, moderate, large

- Financial burden relative to benefit expected: none, minimal, moderate, large
- Availability of intervention: universal, usually, sometimes, limited

The rationale profiles shown in appendix e-9 summarize the results of panel ratings for each domain described above. The profiles also indicate the corresponding assigned LOOs. The last column in each indicates whether consensus was obtained for that domain.

Appendix e-9. Rationale of factors considered in developing the practice recommendations

In this appendix, EVID refers to evidence systematically reviewed; RELA to strong evidence derived from related conditions; PRIN to axiomatic principles of care; and INFER to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based. Please see appendix e-8 for the steps and rules for formulating recommendation strength.

PRACTICE RECOMMENDATIONS

Recommendation 1

Rationale

Disease prevention is the cornerstone of medical care (PRIN.) Migraine has multiple behavioral factors that influence headache frequency. Individuals with a family history of migraine are at higher risk of developing migraine, and female sex is a risk factor of migraine that persists into adulthood.[34] Modifiable factors that can contribute to migraine and recurrent headache in adolescents include being overweight, caffeine and alcohol use, lack of physical activity, and tobacco exposure (RELA).[35] Depression is associated with higher headache disability.[36] Weight loss can contribute to headache reduction in children who are overweight.[37] Identification and avoidance of factors that contribute to headache risk can reduce migraine frequency (INFER).

Statement 1a

Clinicians should counsel patients and families that lifestyle and behavioral factors influence headache frequency (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 8	Critically important 6	Yes
Variation in preferences	Large 0	Moderate 3	Modest 7	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1b

Clinicians should educate patients and families to identify and modify migraine contributors (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 9	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 2	Modest 9	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 2

Rationale

In adults with migraine, headache on more than 6 days in a month is a risk factor for progression to chronic migraine, with medication overuse contributing to this progression (RELA).[38] Taking triptans, ergotamines, opioids, and combination analgesics on more than 9 days in a month or taking over-the-counter simple analgesics on more than 14 days in a month can lead to

medication overuse headache. It has been suggested that clinicians consider preventive treatments in these populations.[40] Although there are no data on this topic in pediatric populations, it is hypothesized that similar relationships between frequent headache, medication overuse, and progression to chronic migraine may occur in children (INFER). In clinical trials of pediatric migraine prevention, inclusion criteria for headache frequency were variable and included 4 to 15 headache days per month and three to four migraine attacks per month for at least 3 months (EVID). In teenagers with migraine, those with a PedMIDAS score over 30, indicating a moderate to severe migraine related disability, had a higher risk of mood and anxiety disorders and increased severity and frequency of headache.[41]

Statement 2a

Clinicians should discuss the use of preventive treatments in children and adolescents with frequent headache or migraine-related disability or both (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 12	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 10	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Statement 2b

Clinicians should discuss the use of preventive treatments in children and adolescents with medication overuse (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 10	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 10	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 7	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 3: Starting preventative treatment

Rationale

The majority of randomized controlled trials that studied the efficacy of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. Pediatric migraine trial results demonstrated a high response to placebo, with 30% to 61% of children who received placebo having had a 50% or greater reduction in headache frequency. Children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a

decrease in headache days and migraine attacks; however, there is insufficient evidence to determine whether children with migraine who are receiving topiramate are more or less likely than those receiving placebo to have at least a 50% reduction in migraine frequency or headache days, and this is also the case for reduction in migraine-related disability (EVID).[20-23] Children who receive propranolol are possibly more likely than those who receive placebo to have more than a 50% reduction in headache frequency (EVID).[25, 27] Patients receiving amitriptyline combined with CBT as compared with those treated with amitriptyline who receive headache education are more likely to experience a decreased headache frequency and have more than a 50% reduction in headache frequency and are probably more likely to have decreased migraine-associated disability (EVID).[33] There is insufficient evidence to judge the independent effectiveness of amitriptyline on migraine prevention in children and adolescents (EVID).[21] It is possible that CBT alone is effective in migraine prevention (RELA),[11] and individual barriers to access may exist.[13] There is insufficient evidence to evaluate the effects of flunarizine,[29] nimodipine,[31] valproate,[24] and onabotulinumtoxinA[32] for use in migraine prevention in children and adolescents (EVID). Although there is evidence that cinnarize[30] is probably more effective than placebo for migraine prevention (EVID), this medication is not available in the United States.

Statement 3a

Clinicians should inform patients and caregivers that the majority of preventive medications assessed in clinical trials for the treatment of pediatric migraine are not superior to placebo, although placebo itself was effective (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 5	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 3	Modest 6	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 3b

Acknowledging the limitations of currently available evidence, clinicians should engage in shared decision making regarding the use of short-term treatment trials (a minimum of 2 months) for those who could benefit from preventive treatment (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 5	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 3	Modest 6	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 3c

Clinicians should discuss the evidence for amitriptyline combined with CBT for migraine prevention and work with families to identify providers who can offer this type of treatment[13] (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 10	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 12	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 6	Usually 8	Always 1	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 13	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Statement 3d

Clinicians should discuss the evidence for topiramate for migraine prevention in children and adolescents and its side effects in this population (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 7	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 12	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 3	Modest 8	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Statement 3e

Clinicians should discuss the evidence for propranolol for migraine prevention and its side effects in children and adolescents (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 7	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 9	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 2	Modest 10	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 4: Counseling for patients with child bearing potential

Rationale

Balancing benefit and risk is important when deciding among available medical treatments (PRIN). Topiramate and valproate have well-demonstrated teratogenic effects.[42, 43] Valproate use during pregnancy is also associated with developmental disorders in offspring (RELA).[46, 47] An

FDA black box warning regarding fetal risk from valproate use exists as of the time of this guideline. Topiramate has drug interactions that decrease the effectiveness of oral estrogen-based contraceptives (PRIN). The risk of major congenital malformation in offspring of women with epilepsy taking anticonvulsants is possibly decreased by folic acid supplementation.[49]

Statement 4a

Clinicians must consider the teratogenic effect of topiramate and valproate and medical necessity in their choice of migraine prevention therapy recommendations to patients of childbearing potential (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 13	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Statement 4b

Clinicians who offer topiramate or valproate for migraine prevention to patients of childbearing potential must counsel these patients about potential effects on fetal-childhood development (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 12	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 13	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

Statement 4c

Clinicians who prescribe topiramate for migraine prevention to patients with the potential for pregnancy must counsel these patients about the potential of these medications to decrease the efficacy of estrogen-based hormonal contraceptives (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 0	Modest 5	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 13	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

Statement 4d

Clinicians who prescribe topiramate or valproate for migraine prevention to patients of childbearing potential should counsel patients about the need to use additional contraception during treatment (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 1	Critically important 14	Yes
Variation in preferences	Large 0	Moderate 2	Modest 3	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 13	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Statement 4e

Clinicians must recommend daily folic acid supplementation to patients of childbearing potential who take topiramate or valproate (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 1	Critically important 14	Yes
Variation in preferences	Large 1	Moderate 1	Modest 4	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 14	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 12	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Recommendation 5: Monitoring and Stopping Medication

Rationale

Migraine is a chronic disorder with spontaneous remissions and relapses (PRIN). Clinical trials follow patients for limited periods of time (EVID). Patients and families often inquire about the

duration of treatment. There is little information about when preventive treatment should be stopped, and the risk of relapse after discontinuation varies.

Statement 5a

Clinicians must periodically monitor medication effectiveness and adverse effects when prescribing migraine preventive treatments (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 10	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 13	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 5b

Clinicians should counsel patient and families about risks and benefits of stopping preventive medication once good migraine control is established (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 8	Critically important 6	Yes
Variation in preferences	Large 1	Moderate 2	Modest 6	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 13	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 6: Mental health in children and adolescents with migraine

Rationale

Several studies have been performed, with inconsistent results, that evaluated the relationship between mental health and migraine in children. A recent systematic review of prospective or retrospective longitudinal cohort studies in children examined factors associated with the onset

and course of recurrent headache in children and adolescents, with recurrent headache defined as headaches occurring at least once per month. This review found high-quality evidence suggesting that children with negative emotional states, manifesting through anxiety, depression, or mental distress, are not at greater risk of developing recurrent headache; however, it found moderate-quality evidence that suggested the presence of comorbid negative emotional states in children with headache is associated with an increased risk of headache persistence (RELA).[34]

Statement 6a

Children and adolescents with migraine should be screened for mood and anxiety disorders because of the increased risk of headache persistence (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 2	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 5	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 1	Usually 6	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 8	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Statement 6b

In children and adolescents with migraine who have comorbid mood and anxiety disorders, clinicians should discuss management options for these disorders (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 0	Modest 9	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 2	Usually 9	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 7	Small 8	Yes
Strength of recommendation	R/U	C	B	A	