

RCT
Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

- A. Citation: Powers SW, Coffey CS, Chamberlin LA, Ecklund DJ, Klingner EA, Yankey JW, Korbee LL, Porter LL, Hershey AD; CHAMP Investigators.. Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine. N Engl J Med. 2017 Jan 12;376(2):115-124. doi: 10.1056/NEJMoa1610384. Epub 2016 Oct 27. PubMed PMID: 27788026
- B. Link to PDF of full article: <https://www.ncbi.nlm.nih.gov/pubmed/?term=27788026>
- C. First date published study available to readers: 10/27/2016
- D. PubMed ID: 27788026
- E. Nominated By: Kate Rowland
- F. Institutional Affiliation of Nominator: Rush-Copley FMR
- G. Date Nominated: 11/3/2016
- H. Identified Through: NEJM
- I. PURLs Editor Reviewing Nominated Potential PURL: Corey Lyon
- J. Nomination Decision Date: 11/9/2016
- K. Potential PURL Review Form (PPRF) Type: RCT
- L. Assigned Potential PURL Reviewer: David Moss
- M. Reviewer Affiliation: Nellis Air Force Base
- A. Abstract: BACKGROUND:

Which medication, if any, to use to prevent the headache of pediatric migraine has not been established.

METHODS:

We conducted a randomized, double-blind, placebo-controlled trial of amitriptyline (1 mg per kilogram of body weight per day), topiramate (2 mg per kilogram per day), and placebo in children and adolescents 8 to 17 years of age with migraine. Patients were randomly assigned in a 2:2:1 ratio to receive one of the medications or placebo. The primary outcome was a relative reduction of 50% or more in the number of headache days in the comparison of the 28-day baseline period with the last 28 days of a 24-week trial. Secondary outcomes were headache-related disability, headache days, number of trial completers, and serious adverse events that emerged during treatment.

RESULTS:

A total of 361 patients underwent randomization, and 328 were included in the primary efficacy analysis (132 in the amitriptyline group, 130 in the topiramate group, and 66 in the placebo group). The trial was concluded early for futility after a planned interim analysis. There were no significant between-group differences in the primary outcome, which occurred in 52% of the patients in the amitriptyline group, 55% of those in the topiramate group, and 61% of those in the placebo group (amitriptyline vs. placebo, $P=0.26$; topiramate vs. placebo, $P=0.48$; amitriptyline vs. topiramate, $P=0.49$). There were also no significant between-group differences in headache-related disability, headache days, or the percentage of patients who completed the 24-week treatment period. Patients who received amitriptyline or topiramate had higher rates of

several adverse events than those receiving placebo, including fatigue (30% vs. 14%) and dry mouth (25% vs. 12%) in the amitriptyline group and paresthesia (31% vs. 8%) and weight loss (8% vs. 0%) in the topiramate group. Three patients in the amitriptyline group had serious adverse events of altered mood, and one patient in the topiramate group had a suicide attempt.

CONCLUSIONS:

There were no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline, topiramate, or placebo over a period of 24 weeks. The active drugs were associated with higher rates of adverse events.

(Funded by the National Institutes of Health; CHAMP ClinicalTrials.gov number, NCT01581281).

B. Pending PURL Review Date: 7/13/2017

SECTION 2: Critical Appraisal of Validity **[to be completed by the Potential PURL Reviewer]**

- A. Number of patients starting each arm of the study? Distributed in a 2:2:1 ratio.
1. 132 in amitriptyline
 2. 130 topiramate
 3. 66 placebo
- B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
Multi-center study. 8-17 year old children with a score of 11-139 on the PedMIDAS and a headache frequency of 4 or more days over a 28 day prospective diary.
- C. Intervention(s) being investigated?
Primary Outcome: Relative reduction of 50% or more in number of headache days compared to the baseline 28-day period.

Secondary Outcome: Headache disability according to PedMIDAS score and the absolute reduction in headache days.
- D. Comparison treatment(s), placebo, or nothing?
Amitriptyline vs topiramate vs placebo
- E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)
24 week treatment – Study stopped early due to no sig dif in treatment outcomes.
- F. What outcome measures are used? List all that assess effectiveness.
See C
- G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.
No statistical benefit.
- H. What are the adverse effects of intervention compared with no intervention?
No serious adverse event trends noted.
Amitriptyline vs placebo showed increased fatigue and dry mouth.

Topiramate vs placebo showed increase paresthesia and decreased weight.

- I. The study addresses an appropriate and clearly focused question.
(select one) Well covered
Comments:
- J. Random allocation to comparison groups:
(select one) Adequately addressed
Comments:
- K. Concealed allocation to comparison groups:
(select one) Not applicable
Comments:
- L. Subjects and investigators kept "blind" to comparison group allocation:
(select one) Adequately addressed
Comments:
- M. Comparison groups are similar at the start of the trial:
(select one) Adequately addressed
Comments:
- N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias. (select one) Adequately addressed
Comments: Patient were largely white females
- O. Were all relevant outcomes measured in a standardized, valid, and reliable way?
(select one) Adequately addressed
Comments: Used on intention to treat analysis.
- P. Are patient oriented outcomes included? If yes, what are they? Yes. Relative and absolute reduction in number of headache days as well as change in disability score.
- Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
33, unlikely to have played a role in bias.
- R. Was there an intention-to-treat analysis? If not, could this bias the results? How? Yes.
- S. If a multi-site study, are results comparable for all sites? Yes and unclear per study design and reporting. Site specific information was not provided.
- T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity? Unlikely.

U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized. Patient's 8-17 years of age with headaches at least 4 days a week.

V. In what care settings might the finding apply, or not apply? Clinical

W. To which clinicians or policy makers might the finding be relevant? All pediatric providers.

SECTION 3: Review of Secondary Literature

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions:

Mack, Kenneth J. Preventive treatment of migraine in children. Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at <http://www.uptodate.com>. Last updated: November 14, 2016. Accessed August 21, 2017.

UpToDate excerpts: "Data are limited on the effectiveness of preventive agents in children."

SECTION 4: Conclusions

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

- A. **Validity:** How well does the study minimize sources of internal bias and maximize internal validity? 2
- B. If **A** was coded 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?
- C. **Relevance:** Are the results of study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians? 2
- D. If **C** was coded 4, 5, 6, or 7, please provide an explanation.
- E. **Practice changing potential:** If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? 2

F. If **E** was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

- While not extremely common these medications are used for preventive therapy in the pediatric population with no benefit proven and a potential for harm with increased rates of adverse events noted with both therapies. Additionally, this study confirms the previously documented placebo effect rate of 50-60%. Clinicians should give serious thought to using placebo therapy for pediatric migraine therapy.

G. **Applicability to a Family Medical Care Setting:**

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? 1 (definitely could be done in a medical care setting)

H. If **G** was coded as a 4, 5, 6, or 7, please explain.

I. **Immediacy of Implementation:**

Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? 1 (definitely could be immediately applied)

J. If **I** was coded 4, 5, 6, or 7, please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes:**

Are the outcomes measured in the study clinically meaningful or patient oriented?
2

L. If **K** was coded 4, 5, 6, or 7 please explain why.

M. In your opinion, is this a pending PURL? 1 (definitely a pending PURL)

1. Valid: Strong internal scientific validity; the findings appear to be true.
2. Relevant: Relevant to the practice of family medicine.
3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
4. Applicability in medical setting.
5. Immediacy of implementation

N. Comments on your response for question M.

As a group we agree that this is a PURL that is clearly valid, relevant, practice changing and applicable to family medicine and can be implemented immediately.