Translating Best Evidence into Best Care

EDITOR'S NOTE: Studies for this column are identified using the Clinical Queries feature of PubMed, "hand" searching *JAMA*, *JAMA Pediatrics*, *Pediatrics*, *The Journal of Pediatrics*, and *The New England Journal of Medicine*, and from customized EvidenceUpdates alerts.

EBM PEARL: CONFIDENCE INTERVAL (CI) VERSUS CREDIBLE INTERVAL (CrI): Let's say your experiment demonstrates a number needed to treat (NNT) of 10 with a 95% CI (4-12). You may be tempted (or were taught) to state: "One can be 95% confident that the 'true' NNT is within the [4-12] 95% CI." In fact, that statement is not technically correct. A correct statement of the CI in the example is: "If the experiment were repeated 100 times, 95 of the CIs generated would contain the 'true' NNT" (and the 95% CI, [4-12] is only one of those 100 CIs). This technically-correct definition does not really help us understand the precision of the NNT we calculated. CrI calculations employ a priori information that some NNTs are more likely than others. The CrI (relating to the specific effect estimate [in this case, the NNT] calculated from your experiment) is more intuitive, and you *would* be able to state: "One can be 95% confident that the 'true' NNT is within the [4-12] 95% CrI." When a priori information is lacking, CrIs and CIs are numerically similar. See the abstract to the commentary by Dr Marcus (below) for an example of the CrI in the literature. (I am grateful to Alan Schwartz, PhD, University of Illinois at Chicago, for his help with this Pearl.)

LITERATURE SEARCH PEARL: MEDICAL SUBJECT HEADINGS (MeSH): MeSH is a vocabulary-based system used by the National Library of Medicine to index medically related articles. Experts assign specific conceptual terms to each article. These MeSH terms are linked to the articles. Searching with MeSH terms employs concept searching. Searching with key words is searching with the words themselves. A MeSH search tends to focus the search to the most relevant articles. MeSH is accessed from the PubMed home page https://www.ncbi.nlm.nih.gov/pubmed—the top choice of the third column (MeSH database). Enter the concept you wish to search and it will generate hierarchical choices from the database. Choose the one that is most conceptually relevant and click on the "add to search builder" button. You may then choose from a list of MeSH subheadings, for example, therapy, and add it to the search. You may add other MeSH terms as appropriate. When you click on the search button, PubMed will deliver the subset of articles that were conceptually indexed with your MeSH terms.

—Jordan Hupert, MD

Tonsillectomy for short-term benefit in obstructive sleep-disordered breathing

Chinnadurai S, Jordan AK, Sathe NA, Fonnesbeck C, McPheeters ML, Francis DO. Tonsillectomy for Obstructive Sleep-Disordered Breathing: A Meta-Analysis. *Pediatrics* 2017;139:pii: e20163491.

Question Among children with obstructive sleep-disordered breathing, what is the clinical efficacy of adenotonsilectomy, compared with watchful waiting, in sleep improvement?

Design Meta-analysis of randomized controlled and cohort trials.

Setting Not reported.

Participants Children, 1-18 years old, with obstructive, sleep-disordered breathing.

Intervention Adenotonsillectomy or watchful waiting. Follow-up generally <12 months.

Outcomes Apnea hypopnea index (AHI) score.

Main Results 11 studies were included. Meta-analysis could be performed on 3 studies and demonstrated a 4.8 improvement in AHI score (95% credible interval, 3.1-6.5) among those children who received adenotonsillectomy compared with watchful waiting. Sleep-related quality of life was also significantly improved for those children who received adenotonsillectomy compared with watchful waiting.

Conclusions Short-term benefit of adenotonsillectomy was demonstrated among children with obstructive, sleep-disordered breathing.

Commentary This meta-analysis on the effectiveness of adenotonsillectomy for obstructive sleep apnea syndrome is part of a larger review by the Agency for Healthcare Research and Quality (AHRQ).[1] The analysis concluded that adenotonsillectomy resulted in improvement in polysomnographically-measured sleep, quality of life and behavior, but not executive function. This analysis included only 11 studies meeting inclusion criteria, but confirmed hundreds of smaller or less well-designed studies showing improvements in polysomnography, symptoms, and quality of life after adenotonsillectomy. In contrast, the report of no significant change in executive function is debatable, and is affected by the selection of articles for this analysis, and

interpretation by the authors. This AHRQ meta-analysis points out a major deficiency in the field of pediatric sleep medicine and, in fact, most of pediatrics, in that only 11 of 9396 studies were considered worthy of inclusion and only 3 of these were randomized controlled trials.

This reviewer was a key informant for the AHRQ, providing input on priority areas for research but not involved in analysis or writing.

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Reference

1. Francis DO, Chinnadurai S, Sathe NA, Morad A, Jordan AK, Krishnaswami S, et al. Tonsillectomy for obstructive sleep-disordered breathing or recurrent throat infection in children. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 https://www.effectivehealthcare.ahrq.gov/ehc/products/620/2424/tonsillectomy-report-170124.pdf. Accessed April 25, 2017.

Amitriptyline and topiramate do not demonstrate benefit in pediatric migraine

Powers SW, Coffey CS, Chamberlin LA, Ecklund DJ, Klingner EA, Yankey JW, et al. Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine. *N Engl J Med* 2017;376:115-24.

Question Among children diagnosed with migraine headaches, what is the clinical efficacy of amitriptyline or topiramate, compared with placebo, in resolving the migraine headaches?

Design Randomized controlled trial.

Setting 31 sites across the US.

Participants Children, 8-17 years old with migraine headaches.

Intervention Amitriptyline, topiramate, or placebo.

Outcomes Reduction of >50% of headache days in a 28 day period at the end of a 24 week trial, compared with the first 28 days.

Main Results The trial concluded early due to futility. There were no statistically significant differences among the 3 arms of the study.

Conclusions Other than side effects, neither amitriptyline nor topiramate, compared with placebo, conferred a benefit to patients.

Commentary Migraine headaches in pediatrics is a common childhood condition and its effects on quality of life, particularly with school and emotional functioning, rival those of other, often more medically "serious" chronic illnesses such as childhood cancer or cardiac disease.[1] The Childhood and Adolescent Migraine Prevention study was designed to determine the most effective prophylactic treatment for migraine in children. It was discontinued early due to futility and adverse events observed in the treatment arms of the trial. The results of the study indicated that neither topiramate nor amitriptyline was more effective than placebo in reducing the headache frequency in children and adolescents with migraine headaches. Notably, there is a well-described high rate of placebo effect seen in prior headache and pain trials in children and adolescents.[2,3] It is conceivable, had the trial enrolled the full sample, a more subtle difference in treatment effect may have become more apparent. However, adverse events in the treatment arms indicate that the risk-benefit profile for medical prophylaxis of migraine is not favorable. Also, per the published protocol, at visit one of the study where families were instructed in the completion of the 28-day diary prior to randomization, all patients were counseled in making lifestyle changes (hydration, sleep hygiene, exercise, and healthy eating habits). This indicates that even the placebo arm was not intervention-free. The question remains whether sustained implementation of lifestyle interventions can generate a significant impact over time on headache frequency. As lifestyle-change counseling was the same across all groups, it may have dampened a mild topiramate or amitriptyline benefit.

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References

1. Powers S, Patton S, Hommel K, Hershey A. Quality of life in childhood migraines: clinical impact and comparison to other chronic illnesses. Pediatrics 2003;112:e1.
2. Faria V, Linnman C, Lebel A, Borsook D. Harnessing the placebo effect in pediatric migraine clinic. J Pediatr 2014;165:659-65.
3. Evers S, Marziniak M, Frese A, Gralow I. Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies. Cephalalgia 2009;29:436-44.

Vitamin D reduces respiratory tract infections frequency

Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systematic Review and Meta-Analysis of Individual Participant Data. *BMJ* 2017;356:i6583. doi: 10.1136/bmj.i6583.

Question What is the therapeutic efficacy of vitamin D supplementation, compared with placebo or no supplementation, in reducing respiratory tract infections (RTI)?

Design Meta-analysis of randomized controlled trials.

Setting 14 countries on 4 continents.

Participants Children and adults, ages birth to 95 years of age.

Intervention Vitamin D supplementation or placebo.

Outcomes Frequency of participants experiencing at least one RTI.

Main Results Vitamin D supplementation reduced the frequency of at least 1 RTI, number needed to treat 33 (95% CI, 20-101). Age did not independently modify the vitamin D effect.

Conclusions Vitamin D supplementation reduced overall RTI frequency.