EVMS JC: Critical Appraisal Worksheet: Systematic Review/Meta-analysis

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Reviewer: Kristin Herbert, DO

Citation: Patniyot IR, Gelfand AA. Acute Treatment Therapies for Pediatric Migraine: A Qualitative Systematic Review. *Headache*. 2016;56:49-70.

Guide	
1. Did the review explicitly address a sensible question?	Yes, the review evaluated the safety and efficacy of available treatments of pediatric patients presenting to an Emergency department with migraine or benign primary headache.
2. Was the search for relevant studies details and exhaustive?	No. Although some electronic databases were used and both bibliographies from selected articles and meeting abstracts were included the authors did not include EMBASE, DARE or Cochrane databases. Search terms were limited to 15 terms in total (excluding redundant terms) A typical Cochrane systematic review has 150 or more search terms. Furthermore, they evaluated the cited references w/in articles and evaluated the American Headache Society scientific abstracts from 2014-2015.
3. Were the primary studies of high methodological quality?	Not really. The authors did not use either GRADE criteria or the Oxford Quality or Jadad Score to either assess or set a minimum standard of quality or bias for the studies they elected to include. (see links) They used 31 of 410 records screened. Of these 31, 17 studies were randomized control trials, 9 were retrospective reviews, and 5 were prospective chart reviews.
4. Were the criteria for study inclusion pre-determined and clearly stated?	Not really., The authors had fairly broad criteria below however they did not attempt to apply any pre-determined quality standards before including a study in their "systematic review" : 1) discussed migraine or benign primary headache management, (2) it was conducted in the emergency department or outpatient setting, and (3) it enrolled pediatric patients (<18yo). The reviewed therapies included those pertaining to antiemetic use, fluids, opioids, and headache targeted therapy (NSAIDS, acetaminophen, 5HT receptor agonists, dopamine receptor antagonists, and anesthetics.)
5. Did the authors adequately assess the quality of the included studies?	No. There was no application of broadly accepted measures (GRADE or Jadad) of quality or bias included in their analysis. There was no independent assessment of articles by two or more authors regarding studies appropriate for inclusion and no kappa score regarding that agreement included.
CLINICAL IMPORTANCE	
6. What were the overall results of the review? *(Are the results of all included studies clearly displayed? Are the results similar from study to study? Is there a clinical bottom line? If the study results combined, was it appropriate to do so?)*	The authors did not attempt to report pooled data in any form other than by narrative. Effective treatments for acute migraine or benign primary headache in the analgesic category include ibuprofen, and to a lesser degree acetaminophen. Ketorolac was not compared to other NSAIDs, but was found to be less effective than prochlorperazine. Of the phenothiazines, prochlorperazine was considered most effective. Of the triptan medications, almotriptan, rizatriptan, zolmitriptan nasal spray, supatriptan nasal spray, and combination sumatriptan/naproxen are effective agents for acute treatment. Treatments considered probably effective included IVF, chlorpromazine, valproate sodium, injectable sumatriptan, and IV DHE. Treatments with oral zolmitriptan showed inconsistent results. Treatments considered ineffective included isolated oral sumatriptan and oral DHE. There was insufficient evidence to comment on propofol, magnesium, and bupivacaine efficacy.

	The results of all included studies are clearly displayed in tables grouped into treatment method. There were several therapies that were deemed to be effective based on the review of the articles, but there did not emerge a clear answer of what is the best way to approach a pediatric patient presenting to the ED with a migraine or benign primary headache. The study results were not combined. Though, for studies with a high placebo response rate, therapeutic gain was computed, defined as the difference in response rate between the treatment group and the placebo group. Comparison of the therapeutic gain between studies should be interpreted with caution given the inherent differences in study design and study population.
7. How precise are the results? *(What were the confidence intervals? p-values?)*	**Fluids:** NS 10ml/kg IV, 17.8% (95% CI 6.1-29.4%) reported minimally significant improvement in visual analog scale (VAS). **Analgesics:** 1) Randomized, double-blinded, placebo-controlled crossover study. Multicenter. Home treatment. -Ibuprofen superior to placebo: OR 2.9, (95%CI 1.0-8.1); Ibuprofen superior to acetaminophen (OR 2.2, 95% CI 1.1-4.0); and acetaminophen superior to placebo (OR 2.0, 95%CI 0.9-4.3) **Dopamine Receptor Antagonists:** 1) Retrospective review of IV prochlorperazine and IV hydration. Tertiary Peds ED -75% reached primary endpoint at 1hr, 90% at 3hrs. HA resolved in 95% in 24hrs. 2) Prospective study of IV prochlorperazine with IV diphenhydramine. Tertiary Peds ED -94% reached primary endpt. 100% pain free at d/c. Of pts w/ confirmed migraine, 68% w/ HA relapse in 1st wk. 3) Prospective randomized, double-blind study trial comparing effectiveness of IV prochlorperazine to IV ketorolac. Multicenter. Peds ED. -By 60mins 55.2% in ketorolac and 84.8% in prochlorperazine groups successfully treated (95%CI 8-52%) 4) Retrospective cohort review compared tx failure and adverse effects of chlorpromazine to prochlorperazine. Peds ED. -40% chlorpromazine and 15% of prochlorperazine group had treatment failure. Pts w/ chlorpromazine had higher rate of admission (16% vs 4.7%, p<0.0008) and received more rescue meds (29.3% vs 9.9%, p<0.0001). **Valproate Sodium:** 1) Retrospective Review of IV VPA. Outpt HA clinic. -47% pts w/ major improvement in pain (1 or 2 doses); pts w/ only 1 dose 80% had 40% reduction in pain. **Propofol:** 1) Retrospective chart review of propofol vs NSAIDs, Prochlorperazine, and diphenhydramine. -Propofol had 80.1% pain reduction v 61.1% in controls; p<0.05. **Magnesium:** 1) Retrospective chart review of IV Mg for tx of HA. 35% showed favorable response. **Bupivicaine:** 1) Retrospective chart review eval therapeutic response of muscle blocks into b/l paraspinal muscles of back. -HA relief in 46%, 38% partial relief. **Opioids:** No studies evaluating tx of peds migraine with opioids. However,

	1) Retrospective, observational study eval EMR for tx of peds HA in ED. Multicenter. Multistate. -Pt w/ dx of migraine (OR 1.63, 95%CI 1.34-1.89, p<0.001) or HA (OR 1.60, 95% CI 1.42-1.80, p<0.001) were more likely to be prescribed an opioid than those w/out a formal dx. As age increased so did likelihood of being prescribed an opioid (OR 1.14, 95% CI 1.12-1.16, p<0.001) **Triptans: Almotriptan:** **Triptans: Rizatriptan:** **Triptans: Zolmitriptan:** 1) Randomized, double-blind, placebo-controlled. Multicenter -Nasal spray zolmitriptan higher HA response rate at 1hr (58.1%) than placebo group (43.3%; OR 1.8; 95%CI 1.1-2.9; p < 0.05). 2) Randomized, double-blind, parallel-group, placebo-controlled. Multicenter. -HA freedom higher in zolmitriptan 5mg nasal spray group (29.7%) vs placebo (16.6%, p < 0.001). **Triptans: Sumatriptan:** 1) Randomized, double-blind, placebo-controlled cross-over design: outpt. -86% of intranasal sumatriptan group showed improvement vs 43% of placebo (p < 0.031). 2) Randomized, double-blind, placebo-controlled, 2 way crossover design; oupt multicenter. -64% of tx group showed improvement vs 39% of placebo (p= 0.0003) . 3) Randomized, double-blind, placebo-controlled crossover trial of oral sumatriptan. -Oral Sumatriptan not more effective than placebo. 4) Randomized, double-blind, placebo-controlled, parallel group 12wk trial of sumatriptan/naproxen; outpt multicenter. -2hr pain free rates higher with sumatriptan/naproxen 10/60mg (29%; p = 0.003), 30/180mg (27%; adjusted p=0.003), and 85/500mg (24%; adjusted p = 0.003) vs placebo (10%). **Dihydroergotamine (DHE):** 1) Retrospective chart review: inpt pediatric hospital -Excellent response 24/30 (80%); Fair response 3/30 (10%); poor response 3/30 (10%). 2) Double-blind, placebo controlled, cross-over study; multicenter inpt pediatric hospitals. -7/12 (58%) in oral DHE tx group, 2/12 (17%) after placebo 95% CI 14-70%) had HA reduction at 2hrs ≥ 2 grades on 5pt scale. Not statistically significant.
8. Were the results similar from study to study?	The results were similar within each method of management in regards to if there was improvement or not of the headache. However, the way the improvement was measured between the various groups was different.
APPLICABILITY	
9. How can I best interpret the results to apply them to the care of my patients?	This review shows that there are several ways to potentially manage a pediatric patient with a migraine vs benign primary headache. Within the different classes of medication there appeared to be a best medication, though comparison between the classes was not widely studied. Also, there appears to be no room for the use of opioids in the management of pediatric headaches at this time.
10. Were all patient important outcomes considered?	No, not every study looked at how long the pt was headache free or if they returned to the ED or clinic. Most studies did look at side effects of the treatment modalities, but a few did not.

11. Are the benefits worth the costs and potential risks?	Treating a pediatric patient's headache with the proven studied medications is worth the cost and side effects were relatively low and mostly treatable. E.g. akathisia or taste disturbance.

Limitations:
-There is a large subjective component to determining whether a treatment modality improved or not.
-Small sample sizes of some studies
-Few RCTs for pediatric migraine in the ED setting, so some studies methodologically less rigorous.
-Variability in outcome measures between studies, limiting comparison between studies.
-Some study results could be affected by the cumulative effect of other meds administered prior to ED arrival.
-Statistical analysis of study results not provided for every study.
-This review was not much more than a listing of some of the available treatment modalities for pediatric migraines and primary headaches.

Clinical Bottom Line:
There is more research to be done on the best treatments for pediatric migraines and HAs. Though, this review provided some various proven treatment modalities that should be used when treating this population.