**Metaanalysis – Systematic Review**

**Potential PURL Review Form**

**Treating migraine: The case for aspirin *J Fam Pract*. 2014;63:94-96.**

**PURLs Surveillance System**

**Family Physicians Inquiries Network**

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| **SECTION 1: Identifying Information for Nominated Potential PURL** | | | | |
| **1.** Citation | | Aspirin with or without an antiemetic for acute migraine headaches in adults.  Kirthi V, Derry S, Moore RA.  Cochrane Database Syst Rev. 2013 April 30;(4): CD008041. doi: 10.1002/14651858.CD008041.pub3.  PMID: 23633350 | | |
| **2.** Hypertext link to PDF of full article | | http://ncbi.nlm.nih.gov/pubmed/?term=23633350 | | |
| **3.** First date published study available to readers | | 04/13/13 | | |
| **4.** PubMed ID | | 23633350 | | |
| **5.** Nominated By | | Nil Das | | |
| **6.** Institutional Affiliation of Nominator | | UPMC | | |
| **7.** Date Nominated | | 06/11/13 | | |
| **8.** Identified Through | | TOC | | |
| **9.** PURLS Editor Reviewing Nominated Potential PURL | | Kate Rowland | | |
| **10.** Nomination Decision Date | | 06/13/13 | | |
| **11.** Potential PURL Review Form (PPRF) Type | | Meta-analysis | | |
| **12.** Other comments, materials or discussion | |  | | |
| **13.** Assigned Potential PURL Reviewer | | Dionna Brown, MD | | |
| **14.** Reviewer Affiliation | | University of Chicago | | |
| **15.** Date Review Due | | 07/25/13 | | |
| **16.** Abstract | | This is an updated version of the original Cochrane review published in Issue 4, 2010 (Kirthi 2010). Migraine is a common, disabling condition and a burden for the individual, health services and society. Many sufferers choose not to, or are unable to, seek professional help and rely on over-the-counter analgesics. Co-therapy with an antiemetic should help to reduce nausea and vomiting commonly associated with migraine headaches.  OBJECTIVES:  To determine the efficacy and tolerability of aspirin , alone or in combination with an antiemetic, compared with placebo and other active interventions in the treatment of acute migraine headaches in adults.  SEARCH METHODS:  We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Oxford Pain Relief Database, ClinicalTrials.gov, and reference lists for studies through March 10, 2010 for the original review and to January 31, 2013 for the update.  SELECTION CRITERIA:  We included randomised, double-blind, placebo-controlled or active-controlled studies, or both, using aspirin to treat a migraine headache episode, with at least 10 participants per treatment arm.  DATA COLLECTION AND ANALYSIS:  Two review authors independently assessed trial quality and extracted data. Numbers of participants achieving each outcome were used to calculate relative risk and numbers needed to treat (NNT) or harm (NNH) compared to placebo or other active treatment.  MAIN RESULTS:  No new studies were found for this update. Thirteen studies (4222 participants) compared aspirin 900 mg or 1000 mg, alone or in combination with metoclopramide 10 mg, with placebo or other active comparators, mainly sumatriptan 50 mg or 100 mg. For all efficacy outcomes, all active treatments were superior to placebo, with NNTs of 8.1, 4.9 and 6.6 for 2-hour pain-free, 2-hour headache relief, and 24-hour headache relief with aspirin alone vs placebo, and 8.8, 3.3 and 6.2 with aspirin plus metoclopramide vs placebo. Sumatriptan 50 mg did not differ from aspirin alone for 2-hour pain-free and headache relief, while sumatriptan 100 mg was better than the combination of aspirin plus metoclopramide for 2-hour pain-free, but not headache relief; there were no data for 24-hour headache relief. Adverse events were mostly mild and transient, occurring slightly more often with aspirin than placebo. Additional metoclopramide significantly reduced nausea (*P*< 0.00006) and vomiting  (*P* =0.002) compared with aspirin alone.  AUTHORS' CONCLUSIONS:  We found no new studies since the last version of this review. Aspirin 1000 mg is an effective treatment for acute migraine headaches, similar to sumatriptan 50 mg or 100 mg. The addition of metoclopramide 10 mg improves relief of nausea and vomiting. Adverse events were mainly mild and transient, and were slightly more common with aspirin than placebo, but less common than with sumatriptan 100 mg.  Update of  *Cochrane Database Syst Rev.* 2010;(4):CD008041. | | |
| **17.** Pending PURL Review Date | |  | | |
| **sECTION 2: Critical Appraisal of Validity** | | | | |
| **1.** What types of studies are included in this review? | Randomized controlled trials | | | |
| **2.** What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses. | This Cochrane review used 13 studies (4222 participants) to assess efficacy of aspirin alone and in combination with metroclopramide (antiemetic) and sumatriptan for the treatment of acute migraine in adults. The primary outcomes measured were pain free after 2 hours without the use of rescue medications and reduction in headache pain at 2 hours.  Secondary outcomes included 24 hour pain outcomes, adverse events, and measure of pain intensity and pain relief using categorical scales that were self reported. Aspirin 900 mg or 1000 mg and aspirin 900 mg plus metoclopramide 10 mg were both better than placebo for patients to be pain free after 2 hours of headache (relative risk [RR], 2.1; 95% confidence interval [CI], 1.70-2.55; NNT=8.1 and RR, 2.7; 95% CI, 1.6-4.6; NNT=8.8, respectively). There was no difference in aspirin 1000 mg vs sumpitriptan 50 mg for patients to be pain free after acute migraine. There was not a greater benefit of aspirin 900 mg with metoclopramide 10 mg versus sumatriptan 100 mg for pain relief in 2 hours  (RR, 0.64; 95% CI, 0.45- 0.87). The NNT for sumatriptan compared with aspirin plus metoclopramide was 9.8.  In terms of reduction of headache pain after 2 hours, aspirin 900 mg or 1000 mg and aspirin with metoclopramide 10mg were better than placebo (RR,1.6; 95% CI, 1.5-1.8; NNT=4.9  and RR, 2.2; 95% CI, 1.8-2.6; NNT=3.3, respectively). There was no difference in aspirin 1000 mg and sumatriptan 50 mg for headache relief after 2 hours. There was also no difference found with using aspirin 900 mg with metroclopramide 10 mg compared with sumitriptan 100 mg for reduction in headache pain after 2 hours.  In terms of headache relief after 24 hours, aspirin 1000 mg was better than placeo (RR, 1.6; 95% CI, 1.4-2.0; NNT=6.6). In terms of adverse events, there was inconsistent reporting in the studies, with mainly nonspecific digestive and nervous system complaints.  The only statistically significant events were for sumatriptan 100 mg vs aspirin plus metoclopramide, with a number needed to harm (NNH) of 8.4. Although it is a concern, the authors mentioned that the studies were underpowered to determine a difference between treatments for adverse events and that single dosing of medication may underestimate potential problems associarted with long-term use of aspirin. In most studies, no serious adverse events were reported. Additionally, there were no treatment- specific adverse events reported for individual drugs. | | | |
| **3.** Study addresses an appropriate and clearly focused question - ***select one*** | Well covered  Not addressed  Adequately addressed  Not reported  Poorly addressed  Not applicable  Comments:  Focused primary outcome, but it seems as though there were many secondary outcomes, which may make it difficult to draw a conclusion regarding the best treatment for migraine. | | | |
| **4.** A description of the methodology used is included. | Well covered  Not addressed  Adequately addressed  Not reported  Poorly addressed  Not applicable  Comments: | | | |
| **5.** The literature search is sufficiently rigorous to identify all the relevant studies. | Well covered  Not addressed  Adequately addressed  Not reported  Poorly addressed  Not applicable  Used Medline Ovid searches as well as Cochrane register. | | | |
| **6.** Study quality is assessed and taken into account. | Well covered  Not addressed  Adequately addressed  Not reported  Poorly addressed  Not applicable  Comments: Used randomized double-blind placebo-controlled studies | | | |
| **7.** There are enough similarities between selected studies to make combining them reasonable. | Well covered  Not addressed  Adequately addressed  Not reported  Poorly addressed  Not applicable  Stated that reviewers used Labbe plots that assess heterogeneity. | | | |
| **8.** Are patient oriented outcomes included? If yes, what are they? | Yes, definitely, primary outcomes used were pain-free status at 2 hours and “headache relief”— reduction in headache pain. Secondary outcomes included pain-free status and reduction in pain after 24 hours, as well as adverse events. | | | |
| **9.** Are adverse effects addressed? If so, how would they affect recommendations? | Yes, but these were nonspecific;  It is stated that sumatriptan had more adverse effects than aspirin, but these were transient since a single dose was given, usually a 1000 mg dose, which was statistically significant, with an NNH of 8.4. But the authors also stated that a limitation of the review is that single-dose studies are not going to help with potential long-term side effects and that individual studies were underpowered to determine differences in treatments for adverse events. There were single case events of renal colic phlebitis, atrial fibrillation, and palpitations that were likely unrelated to study treatments. As expected, most aspirin-related side effects were mild GI complaints, such as vomiting, abdominal pain, and nausea. | | | |
| **10.** Is funding a potential source of bias? If yes, what measures (if any) were taken to insure scientific integrity? | No, the funding for the review came from the Pain Research Funds, the National Health Service’s Cochrane Collaboration Programme Grant scheme, and the the NIHR Biomedical Research Center Program. | | | |
| **11.** To which patients might the findings apply? Include patients in the meta-analysis and other patients to whom the findings may be generalized. | All adults ages 16-65 years who had been diagnosed with migraine and experience acute migraine headaches, whether or not they are taking prophylactic treatment. | | | |
| **12.** In what care settings might the findings apply, or not apply? | Outpatient care settings | | | |
| **13.** To which clinicians or policy makers might the findings be relevant? | All physicians who care for patients with migraine headache | | | |
| **SECTION 3: Review of Secondary Literature**  **[to be completed by the Potential PURL Reviewer]** | | | | |
| **Citation Instructions** | | |  | | |
| **1.** DynaMed excerpts | | | Simple analgesics or combination analgesics recommended for mild-to-moderate migraine; acetaminophen 1000 mg relieves pain in acute migraine (level 1 [likely reliable] evidence); nonsteroidal anti-inflammatory drugs (NSAIDs) are reasonable first-line treatment (AAN Grade A); effective NSAIDs include ibuprofen (level 1 [likely reliable] evidence) and naproxen (level 1 evidence); acetaminophen/aspirin /caffeine combination (Excedrin Migraine) is reasonable first-line treatment (AAN Grade A) and may be more effective than ibuprofen alone (level 2 [mid-level] evidence) or oral sumatriptan (level 2 evidence).  Acetaminophen/isometheptene/dichloral-phenazone combination (Midrin) may also be used for first-line treatment (AAN Grade B); antiemetic drugs may be effective as monotherapy for acute migraine; prochlorperazine (Compazine) IV, intramuscularly, or rectally appears effective for acute migraine (AAN Grade B, level 2 evidence) and may be more effective than IV ketorolac or subcutaneous sumatriptan (level 2 evidence). All marketed oral triptans may provide pain relief at 1 hour and eliminate pain at 2 hours for migraine (AAN Grade A, level 2 (evidence). Sumatriptan (subcutaneous or intranasal) associated with faster headache relief but more recurrent headaches than dihydroergotamine (subcutaneous or intranasal) (level 2 evidence) | | |
| **2.** DynaMed citation/access date | | | Title. Migraine Treatment of Acute Attack. In: DynaMed [database online]. Available at: [www.DynamicMedical.com](http://www.DynamicMedical.com) Last updated: 7/17/13. Accessed 7/21/13 | | |
| **3.**  Bottom line recommendation or summary of evidence from DynaMed  (1-2 sentences) | | | Aspirin 1000 mg and NSAIDs are reasonable first treatments for acute migraines and antiemetics and triptans can be used for more severe migraine symptoms. | | |
| **4.** UpToDate excerpts | | | Acetaminophen: Acetaminophen is an effective abortive agent in some patients. This was illustrated in a population-based randomized, placebo-controlled trial of patients with self-reported migraine, which found acetaminophen at a dose of 1000 mg to be highly effective for treating pain, functional disability, photophobia, and phonophobia, although the study excluded patients with severe symptoms requiring bed rest or associated with vomiting more than 20 percent of the time.  Sumatriptan: All three preparations of sumatriptan – subcutaneous, oral, and intranasal – have proven efficacy in randomized, placebo-controlled trials of acute migraine therapy. In a systematic review (search date 1997) that included 36 randomized trials and 7437 patients, subcutaneous sumatriptan (6 mg) was significantly more effective than oral sumatriptan (100 mg), but it was associated with more adverse events. Subcutaneous sumatriptan had the fastest onset of action. Intranasal sumatriptan (typically 1 insufflation of sumatriptan 20 mg, repeated at 2 hours if necessary) had a faster onset of action than oral, and fewer side effects than injectable. In one trial of subcutaneous sumatriptan in 639 patients, administration of a second dose of the drug 60 minutes after the first in those who did not respond well initially provided little additional benefit. In a second report, initial administration of 50 mg of oral sumatriptan was as effective as 100 mg, suggesting that the lower dose provided the best combination of efficacy and tolerability; either 50 or 100 mg was more effective than a 25 mg dose.  Use in adjunctive therapy: Antiemetics are commonly also used as adjunctive therapy to treat migraine. As an example, NSAIDs can be combined with metoclopramide to decrease nausea and vomiting. The efficacy of this approach was illustrated in a study that compared lysine acetylsalicylate (equivalent to 900 mg aspirin) plus 10 mg of metoclopramide with oral sumatriptan (100 mg) or placebo. Headache intensity decreased in 57, 53, and 24 percent of patients, respectively. Thus, in patients who will not use suppositories, or who are having difficulty tolerating oral analgesics, an analgesic plus metoclopramide is a reasonable, relatively low-cost alternative. | | |
| **5.** UpToDate citation/access date | | | Title. Acute Treatment of Migraine in Adults. Authors: Bajwa & Sabahat. In: UpToDate [database online]. Available at: <http://www.uptodate.com>. Last updated: 6/18/13. Accessed 7/21/13. | | |
| **6.**  Bottom line recommendation or summary of evidence from UpToDate  (1-2 sentences) | | | Aspirin at a high dose of 1000 mg is a good abortive agent for acute migraines, according to new studies. Sumatriptan at a 50 mg or 100 mg dose is best for migraine treatment since the lower dose of 25 mg is usually not strong enough and the 100 mg dose has increased side effects. Metoclopramide used in conjunction with an analgesic can help migraine symptoms. | | |
| **7.** PEPID PCP excerpts  [www.pepidonline.com](http://www.pepidonline.com)  username: fpinauthor  pw: pepidpcp | | | Triptans are considered to be “specific” therapies for acute migraine since, in contrast to analgesics, they act at the pathophysiologic mechanism of headache:  Antiemetics as adjunctive therapy for patients with severe nausea/vomiting:  The following NSAIDs reduced headache severity more than placebo 2 hours after treatment: aspirin (1000 mg; NNT=2.4), ibuprofen (1200 mg; NN=1.8), naproxen (750 mg; NNT=2.0), tolfenamic acid (not available in the US; NNT=1.2), and the combination acetaminophen/aspirin /caffeine (Excedrin Migraine, et al); NNT=1.7) A meta-analysis of RCTs of parenteral metoclopramide (Reglan) revealed significant pain reduction (odds ratio, 2.84; 95% CI, 1.05-7.68). | | |
| **8.** PEPID citation/access data | | | Author.      Title. Migraine Headaches: Therapeutics in: PEPID [database online]. Available at: <http://www.pepidonline.com>. Last updated: 10/12/12. Accessed7/21/13 | | |
| **9.** PEPID content updating | | | 1. Do you recommend that PEPID get updated on this topic?  Yes, there is important evidence or recommendations that are missing  No, this topic is current, accurate and up to date.  If yes, which PEPID Topic, Title(s):  2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon () that should be updated on the basis of the review?  Yes, there is important evidence or recommendations that are missing  No, this topic is current, accurate and up to date. | | |
| **10.** Other excerpts (USPSTF; other guidelines; etc.) | | |  | | |
| **11.** Citations for other excerpts | | |  | | |
| **12.**  Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences) | | |  | | |
| **SECTION 4: Conclusions**  **[to be completed by the Potential PURL Reviewer]**  **[to be revised by the Pending PURL Reviewer as needed]** | | | | |
| **1.** **Validity:** How well does the study minimize sources of internal bias and maximize internal validity? | | | | Give one number on a scale of 1 to 7  (1=extremely well; 4=neutral; 7=extremely poorly)  1 2 3 4 5 6 7 |
| **2.** If 4.1 was coded as 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? | | | | All studies were randomized and double blinded and all reported on withdrawals and dropouts, minimizing bias. |
| **3. Relevance:** Are the results of this study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians? | | | | Give one number on a scale of 1 to 7  (1=extremely well; 4=neutral; 7=extremely poorly)  1 2 3 4 5 6 7 |
| **4.** If 4.3 was coded as 4, 5, 6, or 7,lease provide an explanation. | | | | We all see numerous patients with acute migraine. |
| **5. 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? | | | | Give one number on a scale of 1 to 7  (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)  1 2 3 4 5 6 7 |
| **6.** If 4.5 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. | | | | Recommending a single dose of aspirin 975 mg (3 adult tablets) or 1000 mg (if available) would definitely be a practice changer. (The difference between 975 and 1000 mg would probably not be pharmacologically or clinically relevant.) |
| 1. **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, educating or counseling a patient; or creating a system for implementing an intervention? | | | | Give one number on a scale of 1 to 7  (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)  1 2 3 4 5 6 7 |
| **8.** If you coded 4.7 as a 4, 5, 6 or 7, please explain. | | | |  |
| **9. 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? | | | | Give one number on a scale of 1 to 7  (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)  1 2 3 4 5 6 7 |
| **10.** If you coded 4.9 as 4, 5, 6, or 7, please explain why. | | | | The potential harm of taking high doses of aspirin repeatedly. |
| **11. Clinical meaningful outcomes or patient oriented outcomes:**  Are the outcomes measured in the study clinically meaningful or patient oriented? | | | | Give one number on a scale of 1 to 7  (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)  1 2 3 4 5 6 7 |
| **12.** If you coded 4.11 as a 4, 5, 6, or 7, please explain why. | | | | Decreasing patient pain is important |
| **13.** In your opinion, is this a Pending PURL?  Criteria for a Pending PURL:   * Valid: Strong internal scientific validity; the findings appears to be true. * Relevant: Relevant to the practice of family medicine * 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. * Applicability in medical setting: * Immediacy of implementation | | | | Give one number on a scale of 1 to 7  (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)  1 2 3 4 5 6 7 |
| **14.** Comments on your response in 4.13 | | | | I think using high-dose aspirin to relieve acute migraine pain is new to many physicians. The concern, though, is the long-term use of high-dose aspirin. In addition, it would be nice if aspirin were compared with usual treatment, such as NSAIDs and Excedrin Migraine equivalents, due to potential side effects at higher doses. |