### **Primary Literature**

1) Prior MJ, Cooper KM, May LG, Bowen DL. Efficacy and safety of acetaminophen and naproxen in the treatment of tension-type headache. A randomized, double-blind, placebo-controlled trial. Cephalalgia. 2002 Nov;22(9):740-8.

<u>Study objectives</u>: The aim of this study was to evaluate and compare the efficacy and safety of single doses of acetaminophen 1000mg and naproxen 375mg versus placebo to treat tension-type headache over a six-hour period.

### Methods:

**Design:** Randomized, single-dose, placebo-controlled study

Allocation: Concealed allocation

Blinding: Double-blinded

Follow-up period: 48 hours after using the medication

Setting: Multicentre; outpatients of 19 investigators and new recruits within the United States

**Participants:** (n=963) Men and women aged 18 or older with history of acute tension-type headache of at least moderate intensity on a scale of none to severe that met at least two of the characteristics from the International Headache Society (IHS) diagnostic criteria and did not have symptoms of migraines (nausea, vomiting, photophobia, phonophobia, or auras). Among other specific exclusion criteria, patients had to have previous responses to over-the-counter analgesics for tension-type headaches and could not participate if there were any organic disorders or other types of headaches suspected to be associated with the headaches.

**Intervention:** Subjects received two identical capsules of acetaminophen 1000mg (n=321), naproxen 375mg (n=321), or placebo (n=321). Upon experiencing an acute tension-type headache of moderate severity or worse, subjects ingested the study medication, record their symptoms for 6 hours, and timed the duration until meaningful pain relief. After one hour, subjects could self-administer study rescue medication if their pain was at an equal level as prior to treatment.

**Outcomes:** Standard analgesic summary measures were used to assess efficacy: time-interval weighted sum of pain intensity differences from baseline (SPID), maximum pain intensity difference from baseline occurring over the observation period (MAXPID), time-interval weighted sum of the pain relief scores (TOTPAR), and maximum pain relief that occurred during the maximum observation period (MAXPAR). Other outcomes included pain intensity differences from baseline and pain relief scores, time to onset of meaningful relief, time to use of rescue medication, subject's overall impression of the study medication, and the percentage of subjects that responded by two hours.

**Patient follow-up:** (n=900); 304 acetaminophen 1000mg, 295 naproxen 375mg, and 301 placebo subjects completed the trial and followed up.

**Main results:** Acetaminophen 1000mg and naproxen 374mg both were superior to placebo from 1 to 6 hours after study medication administration ( $P \le 0.009$  and  $P \le 0.021$ , respectively). Only acetaminophen 1000mg was statistically superior to placebo for the percentage of subjects with headache pain reduced to none after 2 hours (P=0.003). However, neither medication was superior when both were compared

using the standard analgesic summary endpoints ( $\geq$ 0.498). Other efficacy endpoints showed similar trends. A larger mean pain intensity difference from baseline at one hour of treatment occurred with acetaminophen 1000mg compared to naproxen 375mg (P=0.036). There were no differences in the incidence of adverse events in either group (P=0.730).

**Conclusions:** Over-the-counter acetaminophen 1000mg and prescription naproxen 375mg are statistically superior to placebo for all predefined analgesic efficacy endpoints (SPID, MAXPID, TOTPAR, and MAXPAR) and well tolerated in the treatment of moderate to severe tension-type headache.

### Comments/critical appraisal (including assessment of internal and external validity):

The internal validity was fair. Although the allocation was concealed and the study was doubleblinded, the main limitation was that patients of the investigators were invited to participate in the study. The personal connections may have influenced the accuracy of the pain rating used to measure the effectiveness of the medications. In addition, there was a statistically significant difference in gender between the drug and placebo groups with the placebo group having significantly fewer women (P=0.004). However, authors state that a previous study found no different in analgesic response between genders.

The external validity of the trial was fair. The mean age of subjects reflected the worldwide peak in incidence of tension-type headaches around the third decade (mean ages: acetaminophen = 33.2; naproxen = 34.6; and placebo = 33.8). Study inclusion criteria selected for patients with less severe headaches than stated by the IHS (see Table 1 of the study). Deviations from the IHS criteria included the choice to accept people with 4-10 headaches per month, not include patients with photophobia or phonophobia, and not specify any average duration. Whereas, to match the IHS criteria they should have included patients with headaches up to 14 times per month, with either photophobia or phonophobia, and a duration of 30 minutes to 7 days. However, a positive aspect of the study was that it accounted for the realistic situation where patients will take rescue medication and allowed administration of the rescue medication an hour after administering the study medication.

Lastly, the authors' phrased their conclusions in a biased manner within the abstract and the summary paragraph. Since the title and objectives aim to compare both acetaminophen and naproxen to placebo, the conclusions should be stated as so. The authors avoid any statements that naproxen was not effective compared to placebo in eliminating pain to none after two hours. This may cause readers who do not look deeper into the paper to assume incorrectly that both drugs are effective over placebo in eliminating pain after 2 hours.

2) Pini LA, Del Bene E, Zanchin G, Sarchielli P, Di Trapani G, Prudenzano MP, et al. Tolerability and efficacy of a combination of paracetamol and caffeine in the treatment of tension-type headache: a randomised, double-blind, double-dummy, cross-over study versus placebo and naproxen sodium. J Headache Pain. 2008 Dec;9(6):367-73.

<u>Study objectives</u>: The purpose of this study is to confirm previous studies that showed good safety and tolerability of the combination of paracetamol 1000mg in combination with caffeine 130mg (PCF) in an Italian population, by comparing with naproxen sodium 550mg and placebo. <u>Methods</u>:

Design: Randomized, double-dummy crossover, placebo controlled trial

Allocation: Concealed allocation

Blinding: Double-blinded

Follow-up period: 48 hours after taking medication for the third headache

**Setting:** Multicentre across eight headache outpatient centres throughout Italy from December 2004 to May 2007.

**Participants:** (n=111) Men and women outpatient volunteers between 18 and 65 years of age with a clinical history of tension-type headaches. Patients met ICHD-II criteria of episodic tension-type headache with the following changes: absence of nausea, vomiting, photophobia and phonophobia (to exclude subjects with migraine headaches). All patients must have a mean frequency of 4 to 14 days per month, previous response to treatment using over-the-counter pain-killers, daily consumption of at least two cups of coffee, adequate contraception in women, and no organic disorders associated with headaches upon examination. Among other exclusion criteria, patients could not have chronic headache, either recurrent or continuous, concomitant use/overuse of NSAIDs or analgesics, treatment with antiplatelet or anticoagulant drugs, migraines, or post-traumatic headache.

**Intervention**: All subjects received three identical boxes numbered 1 to 3 to indicate the required order of use. In each box, the following drugs were provided: 1) one soft gel capsule containing one tablet of placebo and one sachet containing paracetamol 1,000 mg + caffeine 130 mg; 2) one soft gel capsule containing one tablet of naproxen sodium 550 mg and one sachet of placebo; and 3) one soft gel capsule containing one tablet of placebo and one sachet of placebo. Ibuprofen 600mg was provided as a rescue medication to take 2 hours after the administration of the trial medication, if needed for pain. Patients had to use boxes in order for 3 consecutive headaches, not more than 48 hours apart, recording pain and adverse event score hourly up to the 4<sup>th</sup> hour after the drug was used.

**Outcomes**: Measuring safety and tolerability of acetaminophen 1000mg and caffeine 130mg in an Italian population was the primary outcome of the study. It was determined by comparing vital signs at screening and final visits. Adverse events recorded on a symptom checklist hourly for 4 hours after study medication ingestion, qualitative intensity and severity ratings, and global assessment of tolerability using a 5-point verbal rating scale also contributed to the tolerability and safety assessment. The secondary outcome was to study the efficacy of the intervention. Data was collected regarding pain intensity and relief, then the following parameters were calculated: Pain intensity difference (PID), sum of pain intensity differences (SPID), and total pain relief (TOTPAR). Lastly, the patients chose which box they would take at their next headache, based on both tolerability and efficacy.

**Patient follow-up:** 99 patients completed the trial and were included in study results, while only 91 patients were included in the intention-to-treat group (took all 3 medications and went to at least one post-dose evaluation).

**Main results:** The incidence of adverse events in the 4-hour follow-up period was 36.6% in the PCF group, 31.2% in the naproxen group, and 36.6% in the placebo group. There were discordant pairs of 5.4% in the PCF and naproxen and 14% comparing PCF and placebo. Naproxen was also non-inferior to placebo in safety and tolerability. Naproxen was only 1% higher than placebo or acetaminophen in drowsiness and dyspepsia, respectively. Both PCF and naproxen provided significantly more relief than

placebo (P<0.05), but were not significantly different from each other. Ten percent of patients used rescue medication after the placebo, whereas only 4.8% and 3.3% of patients used the ibuprofen after PCF and naproxen, respectively. Overall, naproxen was the most favoured treatment over PCF and placebo (44.6% versus 32.6% and 22.8%, respectively).

**Conclusions:** The authors concluded that there was no difference between naproxen and PCF in pain intensity and relief. Acetaminophen 1000mg and caffeine 130mg were did not show specific stimulatory effects from caffeine. They concluded the PCF is an appropriate candidate for first line treatment of acute episodic tension-type headache.

#### Comments/critical appraisal (including assessment of internal and external validity)

The internal validity of the trial was strong. The authors designed the trial as a double-dummy crossover and randomized every patient to the three arms of the study to eliminate random biases. Crossover trials are appropriate in this type of ailment study, where drugs work for short-term relief and there is no lengthy washout period required. They also made good attempts to adequately blind patients by using identical colour, size, shape and taste of the trial supplies. A random computer generated algorithm, revealed within the publication, prevented researchers or a healthcare providers from knowing the treatment assignment until the database was officially locked. All study methods were described in detail and no obvious weaknesses in internal validity were observed.

The study had fair external validity because the study took place in Italy. The overall population reflected a typical population in terms of the percentage of females to males (59.6% vs. 40.4%) and the average age was around 35 years old, which is very reflective of peak age of tension-type headaches. However, researchers specifically selected patients who drank at least two cups of coffee per day. Since the intervention contains caffeine, the responses in patients who do not drink coffee at all or drink more than 2 cups of coffee do not accurately fit into the study participant description and may have different efficacy or tolerability if they take acetaminophen with caffeine. Patients in North America who do not drink as much strong European blends of coffee may experience more stimulatory effects and therefore, the risks may outweigh the benefits, which the authors regard as not being a concern. Despite this concern, the study population fit the typical tension-headache patient.

Overall, this was a well-conducted trial, which proved the effectiveness of both PCF and naproxen over placebo. However, the authors should have included an arm of only acetaminophen to compare against the PCF arm. This would allow researchers to identify whether the additional caffeine had a true benefit in short-term use for tension-type headaches.

### Secondary and Tertiary Literature

3) Verhagaen AP, Damen L, Berger MY, Passchier J, Merlijn V, Koes BW. Is any one analgesic superior for episodic tension-type headache? J Fam Pract. 2008;55(12):1064-1072.

**Study objectives:** Describe and assess data from randomized controlled trials (RCTs) concerning the efficacy and tolerability of analgesics for treatment of acute episodes of tension type headaches in adults. The main outcome measures were pain relief or recovery over 2 to 6 hours.

**Scope** – Patients were aged 18 years or older and had to meet reasonable criteria to distinguish the tension-type headache from a migraine. Only interventions that included analgesics for the treatment or management of tension-type headaches, assessed between within 2 to 6 hours of medication use.

**Methods**: The systematic review retrieved studies identified through a key term search within Medline and EMBASE from inception to January 2005. Only RCTs and Cochrane Controlled Trials were included in the search strategy. Two authors independently rated the methodological quality of trials from the search results using the Delphi list (high quality studies had to include 6 of 10 Delphi criteria). Originally, there were 1878 studies screened for retrieval, but after a title and abstract review there were only 41 were included in the meta-analysis. Reasons for exclusion included but were not limited to failing to meet the described study population requirements and not meeting the definition of an RCT.

**Main results**: Overall, out of 10 high-quality qualitative studies totalling 30 comparisons of non-steroidal anti-inflammatory drugs (NSAIDs) to placebos, 86.6% (26 of 30 studies) significantly favoured NSAIDs for short-term pain relief. Six of 15 quantitative studies of high quality resulted in similar trends toward NSAIDs being more effective. There were no significant differences in adverse effects between any of the drug group and placebo groups. NSAIDs compared to acetaminophen in quantitative studies resulted in NSAIDs appearing more effective when 5 high quality and 2 low quality studies were pooled. Nine of 13 comparisons in 6 high quality studies qualitative studies found that NSAIDs were not more effective than acetaminophen for short-term pain relief of acute episodes of tension-type headache due to conflicting evidence. Only high quality naproxen trials were included in the meta-analysis. The first trial compared ketoprofen 12.5/25mg against naproxen 275mg and found a relative risk of 0.96 (95% CI: 0.7-1.2).

Overall, when comparing between different NSAIDs, naproxen and zomepirac had the highest central nervous system adverse events compared to aspirin, ibuprofen and ketoprofen. Compared to ibuprofen and ketoprofen, they also were more associated with gastrointestinal side effects.

**Conclusions:** The authors concluded that although all non-narcotic analgesics have equivalent efficacy when used for tension-type headache, ibuprofen has the most favourable side-effect profile. Over naproxen and other NSAIDs, ibuprofen is the first choice non-narcotic analgesic for episodic tension-type headaches.

### Comments/critical appraisal (including assessment of internal and external validity)

The internal validity was good because it used Cochrane standards of reviewing literature, which is of high validity. However, the internal validity in this meta-analysis also depended on the authors' ability to accurately rate the quality of methods, data extraction and data analysis, as well as any differences in effect sizes between funding sources of trials. There were challenges in some trials reporting blinding and allocation procedures, then not following through. Since there were many trials published before 1995, there were no efforts to contact study authors to clarify any questions or inconsistencies. This means that the authors of the systematic review may have not interpreted the quality of the studies correctly, which would lead to inaccurate classifications of studies as low or high quality. Nonetheless, only 35% of studies were to be of high quality and poor study design does not make it accurate to report data from the lower quality studies. Unfortunately, only 13 of the total 41 RCTs used a crossover design. Ideally, for short trials on headaches a crossover design decreases risk of chance and increases internal validity of studies.

This well-conducted systematic review used relevant patient inclusion criteria, so the external validity was good. The mean number of patients in each trial was 252.7 (range: 12 to 900), altogether totalling to approximately 10,363 patients included. A higher number of women were included over men (69.3%, range 35-97%). The participants ranged from the age of 18 to 87. The World Health

Organization estimates that in developing countries tension-type headaches affect over 80% of women and around 60% of males<sup>1</sup>. Therefore, the study reflects the general gender trends of tension-type headaches. It did not provide a mean age in this publication, although it probably exceeded the peak observed age around the third decade of life (1). The authors stated the generalizability of the findings might be limited for drugs that only had 1 to 2 studies evaluated, such as naproxen. However, not many high quality studies regarding naproxen for tension-type headaches have been published. The authors may have found more studies if they had searched International Pharmaceutical Abstracts and additional databases.

#### References:

- 1. WHO. Headache disorders. 2004 [updated 2003 Mar; cited 2012 Feb 23]. Available from: http://www.who.int/mediacentre/factsheets/fs277/en/
- 4) Haag G, Diener HC, May A, Meyer C, Morck H, Straube A, et al. Self-medication of migraine and tensiontype headache: summary of the evidence-based recommendations of the Deutsche Migräne und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesellschaft (ÖKSG) and the Schweizerische Kopfwehgesellschaft (SKG). J Headache Pain. 2011 Apr;12(2):201-17.

**Study Objective**: The purpose for this review article is to update the previous guidelines presented by the German Migraine and Headache Society (DMKG) in 2004. The authors state that the old guidelines contain recommendations based on individual experiences, limited study selection, misinterpretation, or methodologically unacceptable studies. There are also important new treatment alternatives and scientific findings that they want to incorporate into guidelines. Main topics discussed include self-treatment for migraines, tension-type headaches, and combinations of both headaches. However, it strives to conduct an accurate literature search and control the quality of information discussed within the guidelines. Authors have aimed to provide recommendations that reflect the quality delivered in evidence-based expert guidelines. Ultimately, this paper hopes to improve treatment of headaches, specifically for newer medications not previously discussed, initiated by patients without any consultation to physicians.

**Scope**: This clinical guideline did not clearly specify inclusion and exclusion criteria of patients. There were no details or descriptions regarding primary endpoints, specific inclusion criteria of interventions, outcomes, and durations of included studies.

**Methods**: A literature search of MEDLINE and the Cochrane Central Register of Controlled Trials used the search string "drug name" and "headache# or migraine) and clinical trial from 1966 to 2007 with limitations to German and English studies. Studies must have been double-blind controlled clinical studies on headache disorders with medications that received over the counter in Germany, Austria, or Switzerland at a dose not exceeding the maximum without a prescription. Without a placebo control, the drug needed to compare to a fixed-dose drug included in the recommendations and proven efficacious. Avoiding publication bias occurred by excluding all other trials not stated above.

Recommendations are based on first choice (rated A evidence; scientific efficacy, clinical impression of efficacy, and tolerability of at least ++). Recommendations are based on second choice (rated B evidence; scientific efficacy, clinical impression of efficacy, and tolerability of at least +).

Recommendations only in individual cases occur with limited evidence (rated D evidence; scientific efficacy less than +; clinical impression of efficacy and tolerability of at least +).

**Main results**: For tension-type headache, naproxen is neither first nor second line therapy. The quality of scientific evidence supporting its use is Level D. No naproxen studies were included that contributed to scientific evidence of efficacy, concluding that none of the study results concerned the respective question, as categorized in accordance with the guidelines of the US Headache Consortium using a 5-point scale from +++ to =. There was low clinical impression of effectiveness, as rated by the authors on a 5-point scale in accordance with the guidelines of the US Headache Consortium from +++ to 0. There was also a low clinical impression of tolerability, as rated by the authors on a 5-point scale in accordance with the guidelines of the US Headache Consortium from +++ to 0.

**Conclusions**: There is a lack of proof around the efficacy from 200 to 250mg of naproxen or naproxensodium. This review only recommends using naproxen for self-medication of tension-type headaches on a case-by-case basis, not as a first or second drug of choice.

### **Comments/Critical Appraisal:**

There was excellent care put towards choosing well-designed studies, but very little information disclosed about patients, interventions, durations, and primary outcomes of the studies used to draw the medication therapy conclusions. This leads to poor internal validity within the methodology by potentially grouping studies with completely different patient populations or including studies with poor endpoints.

To address the external validity is difficult because this review did not intend to be completely comprehensive, but rather to improve on a previously created guideline. As is, the authors were almost too selective with their inclusion criteria, which may have limited the generalizability. One minor problem is that the study stated that doses up to 220mg of naproxen sodium as a monoanalgesic are not effective, but did not explore higher doses. Although narrowing the patient population is usually beneficial, it may have been valuable to include studies that looked other doses to increase the number of studies included in the guidelines. Overall, authors should have provided more evidence about all of the studies included in making the recommendations, specifically for naproxen. Within the study references, no studies looked at naproxen as a primary endpoint. Therefore, the decision to include naproxen in this paper is questionable.

### References:

e-CPS. Naprelan. Compendium of pharmaceutical and specialties [Internet]. 2012 [cited 21 Feb 2012]. Accessed from: <u>https://www-e-therapeutics-</u>

<u>ca.proxy.lib.uwaterloo.ca/cps.select.preliminaryFilter.action?simplePreliminaryFilter=naproxen+sodium</u> <u>#m700955n00053</u>

5) Woods TM, Dunican KC, Desilets AR. Pharmacotherapy and lifestyle interventions for tension-type headaches. Am J Lifestyle Med. 2009;3(3):238-248. Source description: Review article; peer reviewed. Studies discussed were from Prior et al (abstract provided above) and Miller DS, Talbot CA, Simpson W, Korey A. A comparison of naproxen sodium, acetaminophen and placebo in the treatment of muscle contraction headache. Headache. 1987;27:392-396.

**Summary**: The author describes a randomized, double-blinded, placebo-controlled trial with a dose of 375mg compared acetaminophen 1000mg and placebo. Naproxen was superior to placebo (P $\leq$ 0.021), but was no more effective than acetaminophen ( $\geq$ 0.498). Another study compared naproxen 500mg, acetaminophen 650mg and placebo. In this study, the naproxen was superior to acetaminophen (P<0.01) and placebo (P<0.01) throughout the 6-hour study period. Overall, the naproxen worked more quickly and was more effective at reliving pain (P<0.01). Non-clinically significant side effects were slightly higher in naproxen users over acetaminophen and placebo groups, consisting of nausea, weakness, fatigue, upset stomach, vertigo, and sleepiness.

Overall, the authors state that no treatment is more efficacious for episodic or acute tension type headaches. However, based on the evidence above, they conclude that recent literature supports NSAIDs, including naproxen, as first-line therapies, possibly because of their overall better gastrointestinal tolerability profile.

#### **Comments/Critical Appraisal**

The internal validity of the study was poor because authors failed to define their study selection requirements and appeared to include a high volume of unrelated studies. This may have caused selection bias that highlighted only the positive or negative studies the authors wanted to represent. There was not statement to address conflicts of interest, which is always important to disclose either in any publication. This causes the reader to question the internal validity of these results.

External validity of this study is poor. The main problem with trying to apply these results to an external population is that the population in this review is not clear. Although the authors state they are studying analgesic use in episodic tension-type headaches, none of the patient population characteristics are mentioned. Another factor that compromises external validity is the potential that the authors did not thoroughly gather a representative sample of studies from their literature search. Authors only searched Medline, not other databases, and they searched from 1966 but failed to use the older terminology for tension-type headaches of 'muscle contraction headache' in their search terms. This decreases the number of older studies that they may have been able to add to the review, which is necessary in a review about tension-type headaches, where most of the primary literature is from older literature. Finally, the authors conclude to use any NSAID as first-line therapy over acetaminophen because of their overall better gastrointestinal side effect profile. This not only contradicts previous studies, but is very broadly stated and not helpful for clinicians wanting to recommend a specific drug and dose from the information found in this review article.