Extended Abstracts: Acetaminophen

Primary Literature

1) Steiner TJ, Lange R, Voelker M. Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. Cephalagia, 2003; 23 (1): 59-66.

Study Objective:

The objective of this study was to compare two doses of each acetaminophen (paracetamol) and aspirin for the treatment of episodic tension-type headache (TTH) because there is no clear evidence regarding dose-related efficacy of these commonly used over-the-counter analgesics.

Methods:

Design: Placebo-controlled, single dose, randomized parallel-groups comparative trial

Allocation: Concealed

Blinding: Double-blinded, double-dummy

Follow-up period: Within 14 days of treatment of TTH

Setting: Undefined; at home or wherever the episode TTH occurs

Participants: (n= 638)

Patients were recruited through advertisements in physician offices and local newspapers. Subjects ranged from ages 16-65 years old, and had to meet the IHS diagnostic criteria for episodic TTH, but not for migraines. They also had to have no other serious physical or mental illness, treatment contraindications to acetaminophen or aspirin. Patients were excluded if they were on any anti-depressants or other drugs that interact with the medication studied. Women who were pregnant or may become pregnancy were also excluded, and during the trial women were to use contraception.

Intervention:

Patients were given aspirin 500mg (n=126) and 1000mg (n=128), acetaminophen 500mg (n=128) and 1000mg (n=128), and placebo (n=128) for a five arm study for TTH of at least moderate intensity.

Outcomes: Subjective pain relief response 2 hours after treatment.

Patient Follow-up: 542 out of 638 patients

Main Results:

Within 4 hours of treatment, most efficacy in pain relief was seen, although patients were able to take rescue medication after 2 hours of the initial treatment. Therefore, data before the rescue medication was used. Response rates were based on the percentage of patients who recorded “I feel total relief” or “I feel some worthwhile effect”. Patients with placebo at 2 hours had a response rate of 54.5%. The response rates for the treatments arms were as follows: aspirin 500mg (70.3%; p=0.011), aspirin 1000mg (75.7%; p=0.0009), acetaminophen 500mg (63.8%; p=0.104), and acetaminophen 1000mg (71.2%; p=0.007). All treatments were found to be significantly better than placebo, except for acetaminophen 500mg.

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Conclusions:

For the treatment of episodic TTH, aspirin 1000mg, as well as acetaminophen 1000mg and aspirin 500mg to a slightly lesser degree, are effective alternatives.

Comments/Clinical Appraisal:

When looking at the internal validity of this study, various limitations must be considered. Upon randomization of subjects, all participants were given a diary card with one dose of the trial medication. Participants were permitted to take a rescue medication after 2 hours if required, yet they state most efficacy was seen within the first 4 hours. The additional pain medications patients were taking was not included or mentioned in the study. Although this statement was made, the study did mostly look at the patients' outcome at the 2 hour mark prior to rescue medication. When assessing the pain intensity and functional impairment at 4 and 24 hours, the unknown potential rescue medication could have affected the results of these end-points. Another important limitation with internal validity was the use of subjective scales for pain treatment, as well as subjective judgement of a 'moderate' TTH. There would be no true standardization of the results as all patients would have a different interpretation of their TTH severity, as well as adverse events. However, for this type of study, there would not be a more appropriate way to test the treatment alternatives. No information was provided regarding funding for the trial or if any biases between the authors.

With respect to external validity of the study, the study did have an equal ratio of men and women between treatment arms (approximately 30% men and 70% women), but when looking at the results of the study, they may be less generalizable to the male population, as they only made up 30% of the study population. Additionally, the mean age of participants was about 40 years old; therefore, the data should not be extrapolated to patients much younger or older than this age. Participates were treated in an outpatient setting, and took the medication when their TTH arose. It helps reflect on the self-care population who would treat their TTH in community. The study was performed in the United Kingdom, and there was no mention of racial or culture groups, therefore the data may not necessarily be generalizable to other populations outside of the United Kingdom, unless they are patients of similar backgrounds.

Considering the impact of this study on the algorithm, its application may be limited due to some factors of internal and external validity. The results for effectiveness of the analgesics are more applicable to the female population close to the age of 40.

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2) Schachtel BP, Furey SA, Thoden WR. Nonprescription ibuprofen and acetaminophen in the treatment of tension-type headache. J Clin Pharmacol, 1996; 36: 1120-25.

Study Objective:

The objective of this study was to compare a single 400mg dose of ibuprofen and 1000mg of acetaminophen versus placebo for the effectiveness in treatment of TTH.

Methods:

Design: Placebo-controlled, single dose, randomized controlled trial

Allocation: Concealed

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Blinding: Double-blinded

Follow-up period: 4 hours

Setting: Undefined; in a room setting, patients remained in a room for 4 hours

Participants: (n= 455)

Patients were recruited who were 18 years of age or older, with a history of muscle contraction headache (also known as tension-type headache). Some descriptive factors of their headaches were to include: tight or pressing; contraction of the scalp, head, neck, shoulder muscles. Participants had to have usual moderate to severe intensity TTH, with at least two per month for the last 12 months. The participants also had to have response to over-the-counter analgesics. If symptoms of migraine headaches were present or participants had a history of them, they were excluded. Also, if these participants had taken tranquilizers, mood-altering drugs or other analgesics within 4 hours of the evaluation, they were excluded from the trial.

Intervention:

Patients were given a single dose of ibuprofen 400mg (n=153), acetaminophen 1000mg (n=151) or placebo (n=151).

Outcomes: Relief of headache pain intensity at 30 minutes, and 1, 2, 3, and 4 hours.

Patient Follow-up: 455 participants

Main Results:

Compared to placebo, both ibuprofen and acetaminophen worked significantly in decreasing pain intensity and achieving TTH pain relief (63% receiving ibuprofen, 34% receiving acetaminophen and 7% receiving placebo; $p<0.01$). Between acetaminophen and ibuprofen, ibuprofen was found to be significantly better at decreasing TTH pain ($p <0.01$). Faster relief was seen with 400mg of ibuprofen than with 1000mg of acetaminophen ($p<0.001$).

Conclusion:

Ibuprofen 400mg and acetaminophen 1000mg were both effective in the treatment of TTH pain, but ibuprofen was significantly better in achieving pain relief.

Comments/Critical Appraisal:

There are strengths and limitations of this study that must be considered when looking at internal validity. Firstly, the study fully blinded the patients receiving treatment by using opaque capsules which helped enhance interval validity, as it is a double-blinded, randomized control study. The studies population was only 455 which is a smaller sample size, therefore can affect the validity of the study and its generalizability. Subjective Headache Pain Intensity Scale, and Headache Pain Relief Scales were used to rate each patients headache, it is important to take into account variations between the ratings of patients. Experimenter bias in this study can also affect its validity because it was funded by Whitehall-Robins Healthcare and two of the authors are employees of the company.

When discussing external validity, a limitation of the study is that patients were recruited with moderate intensity TTH, but upon taking the medication they were to sit in a room (setting undefined) for 4 hours until the experiment was complete. Participants were only allowed to engage in quite tasks

during these 4 hours, and could not consume any caffeinated beverages. The setting of the study is a limitation because it affects the generalizability to the self-care population. These patients with TTH that will take ibuprofen or acetaminophen analgesics will continue on their regular routine for the most part, and not be sitting quietly in a room for 4 hours. The results of this study also cannot be extrapolated to the pediatric population as they were not studied, or the geriatric population as the mean age of participants was 22 years. In each treatment arm, approximately 60% of the participants were of the female gender; therefore this may affect the validity of the study in the male population.

With respect to the patient self-care algorithm, the study helps analyze two population simple analgesics for TTH relief. The study showed good results between the effectiveness of ibuprofen and acetaminophen, but it is important to know that the setting is not generalizable to the community outpatient setting for TTH treatment.

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3) Prior MJ, Cooper KM, May LG, Bowen DL. Efficacy and safety of acetaminophen and naproxen in the treatment of tension0type headache. A randomized, double-blind, placebo-controlled trial. Cephalalgia, 2002; 22 (9): 740-48.

Study Objective:

The objective of the authors of this study was to compare the efficacy and safety of acetaminophen 1000mg and naproxen 375mg versus placebo for the treatment of TTH over a 6 hour period.

Methods:

Design: Placebo-controlled, single-dose, randomized, multicentre

Allocation: Concealed

Blinding: Double blinded

Follow-up period: 48 hours after the use of the study medication

Setting: Undefined

Participants: (n=963)

Patients were over the age of 18, and had a history of moderate type TTH with at least two of the following: tightening, pressing, but non pulsating traits; bilateral or various locations; physical activity did not cause aggravation. Patients were not to have any nausea, vomiting, photophobia, phonophobia or auras accompanying their TTH. They also had to have a history of responsive headaches to OTC treatments, and they did not have any disorders associated with headaches. These patients also have between 4-10 TTH per month.

Intervention: Patients were given acetaminophen 1000mg, naproxen 375mg or placebo.

Outcomes: Pain relief scores (using a scale of 0-4) were used to determine the efficacy of treatment

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Patient Follow-up: 900 of 915 patients who took the medication finished the study

Main Results:

Compared to placebo, both acetaminophen 1000mg and naproxen 375mg provided significantly more TTH pain relief ($p \leq 0.009$ and $p \leq 0.021$, respectively). Based on the results, the difference between acetaminophen and naproxen for pain relief was not significantly different. At the 1 hour mark post onset of TTH, acetaminophen has found to have more effect on pain ($p=0.036$). Compared to placebo, acetaminophen significantly reduced the pain from hours 1-6 ($p \leq 0.015$), and the effect of naproxen was seen to be significantly better than placebo from hours 2-6 ($p \leq 0.001$). Between the 2 treatments, no significant different in adverse events were reported ($p=0.730$).

Conclusions:

For the treatment of TTH pain, acetaminophen 1000mg was found to be significantly better than naproxen 375mg at the 1 hour mark from baseline, but both naproxen and acetaminophen were effective.

Comments/Critical Appraisal:

In examining the internal validity, the study was appropriately double-blinded, placebo-controlled, where all patients received identical, blistered study medication which was the same colour, size and shape. Patients were able to take rescue medication after 1 hour if required, but this time was documented, and the remaining pain scores after the rescue medication were set to the last pain score prior to the additional medication. This consideration helps evaluate the results of the study and more accurately look at the effect of each treatment arm's single-dose on TTH. Of each treatment group, there were large differences in gender which was significant, and the placebo group incorporated fewer women, which can threaten the internal validity of the study. Another potential threat to the internal validity of the study was that it was conducted, analyzed and supported by McNeil Consumer & Specialty Pharmaceuticals, which could account to experimenter bias as the lead author is an employee of the company. Subjective scales were used to judge the improvement of the participants' pain scale, which is not a standardized process due to inter-patient variability, but is the best method to assess treatment of TTH.

When considering the external validity of the study, there are some limitations. The mean age of participants was close to 33, with only 8.6% of participates older than 50, and 2.1% of participants over 60; additionally, 3 participants were over the age of 70. The results of the study, therefore, should not be extrapolated to younger or older adults. This study did take place within the United States, and it was discussed that greater than 90.6% of the study population were Caucasian, thus the results are not generalizable to many other ethnic groups. The vast majority of participants, approximately 70%, where female, so the results are not representative of the effect of these analgesics on TTH pain relief in men.

This study does hold some value towards the suggested algorithm for the use of acetaminophen 1000mg for the treatment of TTH as it was shown to be superior to placebo. In this case, naproxen was also shown to be superior to placebo, but it was of a prescription dosage, and is not suitable for the self-care population. Naproxen 220mg strength is available for self-selection in pharmacies.

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Secondary and Tertiary Literature

4) Bendtsen L, Evers S, Linde M, et al. EFNS guideline on the treatment of tension-type headaches – Report of an EFNS task force. Eur J Neurol. 2010; 17 (11): 1318-25.

Study Objective:

To provide expert and/or evidence-based recommendations for the treatment of TTH based on a literature search and expert panel consensus.

Scope:

Trials were included that looked at participants who were over the age of 18, and the studies had to include reasonable criteria to differentiate between TTH and migraines in participants. For pharmacological treatments of TTH, randomized-control trials, as well as comparative treatment trials were included and controlled trials for non-drug treatments. Recommendations based on this screening and expert opinion were rated as level A, B, or C, and included practice tips.

Methods:

Medical reference systems (MedLine, Science Citation Index, and Cochrane Library) were searched for various clinical studies on TTH, as well as the recommendations of treatment from the British Association for the Study of Headache, and the review book entitled *The Headache*, 3rd edition.

Design: Review, Expert Opinion/Guidelines

Main Results:

Simple analgesics and NSAIDs

Through their literature search, it was found that acetaminophen 1000mg was significantly more effective than placebo in the majority of studies, but not all trials. In three of the trials examined, doses of 500mg to 650mg of acetaminophen were not significantly better for treatment than placebo. When looking at comparisons between simple analgesics, five studies reported that NSAIDs were significantly better in the treatment of TTH then acetaminophen, yet three other studies found no difference between the agents.

With respect to adverse events with simple analgesics, between NSAID, acetaminophen, and placebo, the review did not distinguish any differences in adverse events. Nevertheless, gastrointestinal side effects are more common with NSAIDs, but liver toxicity can occur with acetaminophen at high doses.

Conclusion:

Acetaminophen 1000mg may be less effective in the treatment of TTH than NSAIDs, but it has a better side effect profile with respect to gastric toxicities.

Comments/Critical Appraisal:

In regards to internal validity, the author's provided a good description of their research strategies with the list of databases and key terms searched. For the review of pharmacotherapy for TTH, only randomized-control trials and trials comparing treatments were analyzed. Individual literature searches were performed by each author, and for each recommendation made in the guidelines they had to be agreed upon unanimously. All of these mentioned factors help strengthen the internal validity

of these guidelines, the expert opinions and recommendations. With the incorporation of mostly randomized-control trials and comparative trials, the review demonstrates the incorporation of higher quality studies. There are no noted authors' biases as the review/guidelines were created without additional external support.

There are few limitations of these guidelines/recommendations concerning external validity. The review of literature only incorporation trials that included participants over the age of 18; thus, these recommendations cannot be extrapolated to the pediatric population. The guidelines do discuss and include recommendations for non-pharmacological and prescription medications for TTH, but the prescription options fall outside of the scope for the self-care population.

These guidelines and recommendations help provide a general overview for the treatment of TTH in adults, which include both non-pharmacological and pharmacological alternatives. This level evidence is provided through these expert opinions and evidence that can help guide treatment, while also taking into consideration patient specific factors.

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5) Lenaerts ME. Pharmacotherapy of tension-type headache (TTH). Expert Opin Pharmacother. 2009; 10(8): 1261-71.

Study Objective:

The author's aim of this paper was to review abortive and prophylactic medications for TTH, and make practical recommendations based on efficacy from the literature.

Scope:

No information was provided with regards to the scope of studies included (patients, interventions, outcomes, or durations).

Methods:

No systematic search strategy was discussed in the review paper, when looking at the papers used for analgesics and NSAIDs, mostly randomized-controlled trials were included and listed in table format.

Design: Review, Expert Opinion/Guidelines

Main Results:

Upon the author's review of the literature, various studies incorporating acetaminophen use in TTH were discussed. It was noted that 1000mg of acetaminophen was shown to have similar efficacy as aspirin 625mg in the treatment of TTH. With a lower dose of acetaminophen (650mg) in another trial, naproxen 550mg was better in reducing TTH pain intensity. A randomized-control trial of 457 patients was discussed as ketoprofen 25mg providing TTH relief in 70% of patients, acetaminophen relieving 60% and placebo 36%, but the differences between treatments were not statistically significant. Ibuprofen 400mg in one studied better treated patients TTH then acetaminophen 1000mg with respect to fast and complete pain relief.

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Conclusion:

For treatment of TTH, the mainstay for treatment is NSAIDs of the abortive analgesics through evidence-based efficacy. Acetaminophen 1000mg, ASA 1000mg, ibuprofen 200-400mg, ketoprofen 25mg were all said to have high efficacy in treatment of TTH with grade I evidence.

Comments/Critical Appraisal:

Looking at the internal validity, the author of the expert opinion paper did not disclose the method or databases used to select the literature. The paper was also lacking how trials were included or excluded. From the review table though, the paper did only include randomized-control trials when looking at simple analgesics. There may be some subjective bias with the lack of literature search information. With respect to experimenter biases, there were no conflicts of interest with the paper.

With the external validity of this article, no main ages were given with respect to the populations studied in the reviewed randomized-control trials. Most of the randomized-control trials are done in adults, but nothing is stated to the mean age, therefore the recommendations may not be generalizable to elderly or pediatric populations. The recommendations also include other prescription medication that would not be appropriate for self-care population.

With respect to the application of this guideline and expert opinion to the self-care algorithm, the data of the paper can be useful for an overall look at analgesics for the treatment of TTH in adults. It does summarize well the evidence for simple analgesics, including placebo comparative and between analgesics, although there are issues with validity. If patients fail self-care options for TTH relief, clinicians could review this article to look into other alternatives for treatment.

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6) Verhagen AP, Damen L, Berger MY, et al. Is any one analgesic superior for episodic tension-type headache? J Fam Pract. 2006; 55(12): 1064-72.

Study Objective:

The objective of this review article was to describe and assess the efficacy and safety of analgesics for the treatment of acute TTH episodes in adults.

Scope:

Only randomized-control trials were included in the review that looked at analgesic treatment of TTH in adult patients over 18 years of age. Forty-one randomized-control trials were included in the review. For recommendations or consensus, 2 authors were used to solve disagreements, and if no consensus could be achieved, a third author was called upon to make the final decision. Overall, in the studies used, the majority of patients were women (69.3%)

Methods:

Literature searches were performed on Medline, EMBASE and The Cochrane Controlled Trials Register looking for randomized-control trials from inception to January 2005.

Design: Meta-analysis

Main Results:

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Acetaminophen was compared to placebo in 17 of the 41 randomized-control trials reviewed. For short term pain relief of TTH, acetaminophen was shown to be more effective than placebo in 5 high-quality studies, and similar results were seen in 3 lower quality studies. Only one studied with acetaminophen 500mg showed no significant pain relief compared to placebo. Conflicting evidence was seen, but many trials showed 1000mg of acetaminophen was significantly better at relieving TTH pain than placebo.

Frequently reported side effects of acetaminophen from these studies reviewed included: stomach upset, dizziness, nausea, drowsiness, but the difference between these side effects and placebo where not found to be statistically significant.

An analysis looking at NSAIDs versus acetaminophen was included, and for short-term pain relief NSAIDs were favoured. Conflicting evidence was also seen with acute episodes of TTH in other studies, which found that NSAIDs were not significantly more effect for pain relief compared to acetaminophen. No significant different in side effects were reported between NSAIDs and acetaminophen.

Conclusion:

No one NSAID was better than another in the short-term treatment of TTH, but ibuprofen is a reasonable first choice as it has a favourable side effect profile. The decision for treatment of TTH may depend more on a patient's tolerance of any of the analgesic agents. Acetaminophen, though it may be less effective than NSAIDs, may be preferred when someone has a contraindication to NSAIDs. The side effect profile between NSAIDs and acetaminophen showed no significant difference.

Comments/Critical Appraisal:

The internal validity of this review had many strong points to be mentioned. The literature research method was well outlined in the search strategy and study selection. Only randomized-control trials were incorporated in the review which helps provide some better evidence for effectiveness of these analgesics on TTH pain relief. The keywords searched were also identified, which helps enhance the internal validity. The study also identifies how many high quality and low quality studies showed how effective acetaminophen or other analgesics are. This assessment of trials could influence subjective bias, but it helps enhance interval validity by highlighting the quality of studies included.

With respect to external validity of this meta-analysis, the age of patients in the trial ranged from 18 to 87 years old, though no additional information was provided as to the distribution and age ranges. Therefore, the generalizability of the recommendations should not be extended to the pediatric population, and should be considered with caution in the geriatric population. Depending on the medications studied in the primary literature, some were only studied in 1 to 2 trials (like head to head trials of NSAIDs) which may affect the generalizability of these drugs and conclusions made.

The meta-analysis and recommendations can be very helpful to the patient self-care algorithm as it recommends useful and practical tips for the community setting. They make reference to understanding patient specific factors that arise. The level of evidence and summary was of high value, and maintained good internal and external validity.
