

Extended Abstracts: Ibuprofen

Primary Literature

- 1) 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: This trial was conducted to examine the relative analgesic effectiveness of ibuprofen compared with acetaminophen and placebo in volunteers with tension-type headaches.

Methods:

Design: single-centre, single-dose, randomized, placebo-controlled trial

Allocation: unconcealed

Blinding: double-blinded

Follow-up Period: 4 hours

Setting: Bryan/College Station, Texas

Participants: (n = 455) Men and women were recruited who were 18 years of age and older and had a history of muscle contraction headache (tight or pressing and associated with contraction of scalp, head, neck, or shoulder muscles). Entry into the study was restricted to those volunteers who presented with moderate-severe tension-type headaches, had an occurrence of at least twice a month during the previous year, and reported to be relieved satisfactorily by an over-the-counter analgesic agent.

Intervention: Participants received a single dose of either 400 mg of ibuprofen (n = 153), 1000 mg of acetaminophen (n = 151), or placebo (n = 151). All doses were administered in two identically appearing opaque capsules.

Outcomes: Headache Pain Intensity Scale and Headache Pain Relief Scale; each measured 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after administration of a single dose of treatment.

Patient follow-up: 100%; 455 or 455 participants

Main Results: Mean headache pain intensity difference scores from baseline were significantly greater at each time point after treatment with ibuprofen and acetaminophen compared with placebo and for ibuprofen compared to acetaminophen ($p < 0.01$). Significantly more participants experienced complete relief with each active treatment compared to placebo (63% for ibuprofen, 34% for acetaminophen, and 7% for placebo; $p < 0.01$) and significantly more participants treated with ibuprofen experienced complete relief than those who were treated with acetaminophen ($p < 0.01$). Participants treated with ibuprofen achieved complete relief significantly faster than those who received acetaminophen ($p < 0.001$).

Conclusions: The authors concluded that both ibuprofen 400 mg and acetaminophen 1000 mg were efficacious analgesics for treating tension-type headache. Specifically, ibuprofen 400 mg is significantly more effective than acetaminophen 1000 mg for treating this condition.

Extended Abstracts: Ibuprofen

Comments:

Limitations associated with the internal validity of this trial must be considered before making a clinical judgement. First, the design of the trial is questionable as the participants were made to wait in a room and only allowed to take part in quiet activities after receiving a single-dose of treatment. This is a confounding factor which the authors did not consider as the beneficial effects may not be due to treatment alone. Finally, patients who previously did not respond well to analgesics were excluded from the trial thus providing a potential bias.

In terms of the external validity, the trial was well-designed and incorporated thorough histories of patients to ensure they were acceptable candidates for self-care. The three treatment arms were also similar in characteristics however, the median ages were those of a young-adult. Thus, this limitation does not allow the data to be extrapolated to older populations, such as geriatric patients. Despite these points, this trial provides efficacy data for ibuprofen as compared to acetaminophen and placebo which can be applied to the algorithm and place in therapy.

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- 2) Van Gerven JMA et al. Self-medication of a single headache episode with ketoprofen, ibuprofen or placebo, home-monitored with an electronic patient diary. Br J Clin Pharmacol. 1996;42:475-481

Study Objective: The authors set out to investigate the efficacy of single-dose ketoprofen compared with ibuprofen and placebo using an electronic patient diary for tension-type headaches.

Methods:

Design: single-dose, randomized, placebo-controlled, parallel group design trial

Allocation: unconcealed

Blinding: double-blinded

Follow-up Period: 4 hours

Setting: outpatient setting (patient's home)

Participants: (n = 166) Volunteers over the age of 18 with episodic tension-type headache and no refractory headaches or contraindications to non-steroidal anti-inflammatory drugs (NSAIDs) were contacted by advertisements and selected by questionnaires.

Intervention: Patients received a single dose of either ketoprofen 25 mg, ketoprofen 50 mg, ibuprofen 200 mg, or placebo for treatment of a single headache occasion. The patients were home-monitored using an electronic patient diary. They were also allowed to use their personal analgesic medication as an 'escape', if headache relief was insufficient after at least 2 hours following ingestion of trial medication.

Outcomes: Visual Analogue Scales (VAS) of headache severity, five-item Headache Relief Rating (HRR) scales, and time to intake of 'escape' analgesics

Extended Abstracts: Ibuprofen

Patient Follow-up: 96%; 159 of 166 patients

Main Results: Headache (VAS and HRR) improved more with the 3 NSAIDs as compared to placebo; there was no statistical difference between the VAS scores of the 3 NSAIDs. After 4 hours, VAS and HRR scores were: 3% and 18% for placebo; 10% and 39% for ibuprofen 200 mg, 18% and 62% for ketoprofen 25 mg; and 28% and 55% ketoprofen 50 mg, respectively. The use of 'escape' analgesics occurred more often during treatment with placebo than with either ketoprofen 25/50 mg or ibuprofen 200 mg.

Conclusions: The authors concluded that the effects of ketoprofen were more pronounced than those of ibuprofen, there was no difference between ketoprofen 25 mg and 50 mg, and mild to moderate adverse events were reported more in the ketoprofen groups. As a result, they believe treatment of headache can start with ketoprofen 25 mg.

Comments:

There are some limitations in terms of the trial's internal validity that warrant discussion. First, the dose utilized for ibuprofen (200 mg) was sub-therapeutic as multiple sources cite a dose of 400-800 mg to be therapeutic. Second, results were self-reported by patients; a technique which heavily relies on the patients adhering to the study protocol. Finally, patients who did not have satisfactory relief from previous analgesic use were excluded from the study resulting in a selection bias.

The trial was well constructed in terms of the external validity as all 4 arms had similar characteristics and ranged anywhere from 20-73 years of age. However, the trial had a significantly larger proportion of females as compared to males.

Although the main aim of this trial was to determine the efficacy and safety of ketoprofen, it did provide data for the use of ibuprofen in a self-care setting. Thus its applicability to the algorithm and place in therapy holds value.

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- 3) Packman B et al. Solubilized Ibuprofen: Evaluation of Onset, Relief, and Safety of a Novel Formulation in the Treatment of Episodic Tension-type Headache. Headache. 2000;40(7):561-7

Study Objective: The authors of this trial set out to evaluate the relative efficacy of a single-dose ibuprofen liquiset compared with acetaminophen caplets and placebo.

Methods:

Design: single-dose, randomized, placebo-controlled, parallel group study

Allocation: unconcealed

Blinding: double-blind

Follow-up Period: 3 hours

Setting: Single site (study centre)

Extended Abstracts: Ibuprofen

Patients: (n = 154) Male and female patients over the age of 12 with a history of episodic tension-type headaches were recruited for the trial. Headaches had to be at least moderately severe and have responded to over-the-counter analgesics.

Intervention: Patients were required to report to the study centre within 1 hour of the onset of a moderately severe headache. Qualifying subjects then received either, 400 mg ibuprofen, 1000 mg acetaminophen, or placebo.

Outcomes: Categorical Pain Rating Scale, time to first perceptible relief, and time to meaningful relief.

Patient Follow-up: 100%; 154 of 154 patients

Main Results: Ibuprofen had a significantly earlier median time to relief than acetaminophen and placebo for first perceptible relief (39 minutes versus 47 minutes and 113 minutes) and meaningful relief (39 minutes versus 53 minutes and 180 minutes). Also, by the third hour after dosing, 75% of ibuprofen-treated subjects reported complete pain relief compared with 32% of those who received acetaminophen and 13% of those who received placebo

Conclusion: The authors concluded that the trial demonstrates a clinically relevant advantage for time to analgesic effects with the liquigel formulation of ibuprofen as compared to acetaminophen and placebo.

Comments:

There are limitations of this study which potentially affect its internal validity. First, the trial was financially supported by Whitehall-Robins Healthcare, producer of the brand name Advil® (ibuprofen), which elicits a conflict of interest. Second, the authors mention that pain intensity and relief were also measured at the time of rescue medication (if required); however, they fail to explain or mention the criteria for rescue medication. Finally, a main outcome for this study was to measure the time to perceptible and meaningful relief, however, this was a subjective measure which was not defined nor measured by any evidence-based scales.

With respect to the external validity, there are some limitations in terms of the treatment group demographics. First, this trial included a significantly higher proportion of females to males (117:37) in the patient population. As well, the placebo group had significantly less patients than both the ibuprofen and acetaminophen group (32:60 and 32:62, respectively). Finally, the trial did not include any patient over the age of 55 or under the age of 25, thus extrapolating the data from this trial to treat children/adolescents or geriatric patients is not feasible.

This trial does provide clinical value to the literature as it is the only one to examine the effect of solubilized ibuprofen in treating tension-type headaches. As a result, it can be utilized to augment the algorithm and place in therapy.

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- 4) Nebe J, Heier M, Diener, HC. Low-dose ibuprofen in self-medication of mild to moderate headache: a comparison with acetylsalicylic acid and placebo. Cephalalgia. 1995;15(6):531-5

Extended Abstracts: Ibuprofen

Study Objective: The intention of this trial was to determine the efficacy of ibuprofen 200 mg compared with acetylsalicylic acid 500 mg and placebo in patients who usually self-treated their headaches with over-the-counter medications.

Methods:

Design: three-fold crossover, double-dummy trial

Allocation: unconcealed

Blinding: double-blind

Follow-up Period: 150 minutes

Setting: outpatient and clinic

Patients: (n = 95) Males and females aged 18-70 years with 1-6 episodes of mild to moderate headache per month for at least 6 months were included. Patients were stratified as having either tension-type headache, migraine, or both.

Intervention: Patients were asked to treat 3 headache episodes in a cross-over fashion, each time with two oral formulations: one coated tablet containing either ibuprofen 200 mg or placebo and one tablet containing either acetylsalicylic acid 500 mg or placebo. The study medication was to be used after a wash-out period of 2 days and when the headache was mild. Rescue medication of the patient's choice could be taken 1 hour or more after the study medication.

Outcomes: Visual Analogue Scale (headache intensity),

Patient Follow-up: 68%; 65 of 95 patients (77 patients included in the intention-to-treat protocol)

Main Results: Ibuprofen 200 mg was found to be significantly superior to acetylsalicylic acid in decreasing headache intensity by 50% within 1 hour. The difference in pain reduction of ibuprofen and acetylsalicylic acid diminished past the 1 hour recording.

Conclusion: The authors concluded that self-medication of mild to moderate migraine attacks and tension-type headache episodes with ibuprofen 200 mg was at least equivalent to 500 mg acetylsalicylic acid and superior to placebo

Comments:

A considerable number of limitations exist which question the internal validity of this trial. First, the trial included patients who were not only experiencing tension-type headaches but also migraine attacks. These patients may or may not be candidates for self-care. Second, the trial had a significantly high drop-out rate (30 patients) which undermines the power of the study. The authors attempted to mitigate this with an intention-to-treat protocol. Finally, there is a potential conflict of interest associated with this study as it was supported by Bayer Inc.*

Extended Abstracts: Ibuprofen

With respect to the external validity, limitations exist that must be brought to light. Due to the patient population (median age 30 and majority females), the results from this study cannot be extrapolated to treat children/adolescents or geriatric patients. As well, this trial only included moderate tension-type headaches (and migraines) and does not provide data for mild or severe headaches. Finally, the sub-therapeutic dose of ibuprofen (200 mg) utilized in this trial cannot be extrapolated for therapeutic doses of ibuprofen (400-800 mg) in treating tension-type headaches.

Due to the numerous limitations of this trial, its application and inclusion towards the algorithm and place in therapy is limited.

Secondary/Tertiary Literature

- 5) MacGregor EA, Steiner TJ, Davies PTG. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache. British Association for the Study of Headache. 2010;3(1):1-53

Study Objectives: The purpose of these guidelines is to suggest management strategies for common headache disorders that have been found by specialists to work well. These guidelines are intended for all healthcare practitioners who manage headache.

Scope: The authors state that wherever evidence was available, the guidelines are based on it. However, where there is no formal evidence, the authors rely on expert opinion based on clinical experience.

Methods: N/A

Main Results: Initial measures for the treatment of tension-type headaches include non-pharmacological options such as, exercise and physiotherapy. Initial drug therapy includes aspirin 600-900 mg or ibuprofen 400 mg. Other NSAIDs (ketoprofen or naproxen) are sometimes indicated. Paracetamol appears to be less effective. If the frequency of headaches increases, long-term (3 week) naproxen therapy is indicated to avoid medication overuse headaches. For chronic tension-type headaches, amitriptyline is the therapy of choice.

Conclusions: The authors suggest the first step in treatment would be to reassure the patient of their symptoms, as it is important and often effective on its own. It is also important to treat any underlying contributory factors and to monitor for medication overuse headaches. When initiating over-the-counter analgesic drug therapy, the authors suggest it is appropriate for episodic tension-type headache occurring fewer than 2 days per week. They also advise that children and adolescents under the age of 16 years not use aspirin.

Comments:

A discussion of the internal and external validity of these guidelines is limited as they are not structured in the typical format and thus do not include an overview of the methods. With this in mind, there are a few limitations that should be addressed. First, without a search strategy it is impossible to decipher which trials were excluded and included which could result in a bias. However, the majority of the trials included do seem to be randomized controlled trials or expert opinion papers. Second, these guidelines fail to grade the evidence making this review less credible. Finally, the recommendations are

Extended Abstracts: Ibuprofen

not stratified according to age and caution must be exercised by clinicians when recommending therapy for vulnerable patient populations (ex. children, geriatrics, etc.).

As the authors have noted, these guidelines are based upon evidence derived from primary literature or expert opinion where such literature does not exist. As a result, this review provides a concise and valuable summary of treatment principles for healthcare practitioners and is applicable for the self-care algorithm and place in therapy.

- 6) Bendsten L et al. EFNS Guideline on the Treatment of Tension-Type Headache. Europe an Journal of Neurology 2010, 17: 1318–13 25

Study Objectives: The aim of the authors is to provide evidence-based or expert recommendations for the different treatment procedures in tension-type headache.

Scope: N/A

Methods:

Each author was responsible for performing an independent literature search (MedLine, Science Citation Index, and Cochrane Library) using the key word *tension-type headache*. Trials published in English and conducted amongst adult patients (aged 18 and older) that distinguished tension-type headaches from migraines were considered. For drug treatments, randomized placebo-controlled trials and trials comparing different treatments were considered. For non-drug treatments, controlled trials were considered. The authors also incorporated a review book and treatment recommendations from the British Association for the Study of Headache.

A total of four drafts were written by the chairmen of the task force; whereby after each draft, each member discussed changes via email. All recommendations had to be agreed upon by all members of the task force unanimously. The background of the research strategy, reaching consensus, and definitions of the recommendation levels were adapted from an earlier EFNS review.

Main Results:

With respect to ibuprofen, the authors found that doses of 800 mg, 400 mg, and 200 mg were more effective than placebo. Amongst the NSAIDs, ibuprofen was found to have the most favourable side effect profile. Five trials have compared the efficacy of different NSAIDs, however, it is not possible to clearly demonstrate the superiority of any particular drug.

Other agents (paracetamol, aspirin, and other NSAIDs) have been studied, where a majority of the trials have demonstrated improved efficacy as compared to placebo and only a select few have found no difference. Five studies reported NSAIDs to be significantly more effective than paracetamol whilst 3 studies could not demonstrate a difference.

Conclusions:

The authors concluded that simple analgesics and NSAIDs are the mainstay in the acute treatment of tension-type headaches. Specifically, ibuprofen 400 mg may be recommended as drug of choice amongst the NSAIDs because of a favourable side effect profile. They also noted that paracetamol 1000 mg is probably less effective than NSAIDs but has a better side effect profile.

Extended Abstracts: Ibuprofen

This review also cautions to avoid the frequent and excessive use of analgesics to prevent the development of medication-overuse headaches. Furthermore, the authors place into context the results of the aforementioned trials in terms of the respective degree of efficacy displayed in each. The EFNS task force suggests the efficacy demonstrated in these trials to be modest and accept there may be room for better modalities in the acute treatment of episodic tension-type headaches.

Comments:

There are many strengths to this systematic review in terms of its internal validity. The search strategy and method are clearly defined; the majority of the trials are randomized, placebo-controlled trials; and the recommendations have been graded according to their evidence and assigned levels. One limitation of this guideline is that the authors did not provide a summary of the trials included which could potentially discredit this study. However, when examining the references, it seems only randomized, placebo-controlled or head-to-head trials were utilized thus enhancing the power of this review.

Similarly, minor are the limitations for the external validity of this trial. Of note, the authors specify only trials including patients greater than 18 years of age were considered for this review. As a result, data cannot be extrapolated for the treatment of children and adolescents.

This systematic review provides and adds evidence-based value to the literature. While presenting a thorough description of the literature, the authors also delve into the gray and fill-in any gaps in the treatment of tension-type headaches. As a result, this review is influential in the self-care algorithm and place in therapy.

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- 7) Manzano S, Doyon-Trottier E, Bailey B. Myth: Ibuprofen is superior to acetaminophen for the treatment of benign headaches in children and adults. CJEM 2010;12(3):220-222

Study Objectives: The intention of this article was to review the evidence supporting the concept that ibuprofen is superior to acetaminophen for the treatment of benign headaches.

Scope: The authors identified 415 articles of which 44 were reviewed in their entirety. Five of these trials were randomized controlled trials while the others were comprised of case reports, editorials, or narrative reviews.

Methods: A literature search was performed which included articles that compared acetaminophen to ibuprofen; used pain reduction as a primary outcome measure (irrespective of the type of pain scale used); and were conducted on children, adolescents, and/or adults with headaches. The authors searched Ovid MedLine and Ovid Embase for randomized controlled trials, meta-analyses, and reviews while also conducting bibliographic reviews of these papers. The clinicians' search strategies were based on the work of other authors and are available upon request.

Main Results: For tension headache in adults and children, this review cited a single randomized controlled trial which demonstrated a faster first perceptible relief and a faster subjective meaningful relief with ibuprofen as compared to acetaminophen and placebo. Similarly, the authors found only 1 randomized controlled trial for tension headaches in adults. This trial exhibited significantly lower pain intensity scores and a significantly higher proportion of patients with complete pain-free status with ibuprofen than with acetaminophen.

Extended Abstracts: Ibuprofen

Conclusions: Although ibuprofen is considered more effective than acetaminophen for the treatment of benign headaches, the authors believe there is minimal evidence in the literature to support this belief. They infer there that there are only 2 trials that have demonstrated a superiority of ibuprofen in the treatment of tension-type headaches.

Comments:

In light of these conclusions, limitations of this paper need to be acknowledged. First, the authors fail to mention the reasoning as to why only 44 of the possible 415 trials were included in this review, thus allowing for the possibility of selection bias. Also, the power of this review is questionable as the author's state to only have found 2 trials comparing the efficacy of ibuprofen and acetaminophen. This extended abstract identified several which is supported by the aforementioned EFNS guidelines.

A strength of this trial with respect to the external validity is the inclusion criteria. The literature search included all age groups as children, adolescents, and/or adults with headaches were incorporated. A pitfall of the inclusion criteria for this trial was that the authors included all types of headaches (migraine, tension, and high-altitude), which can skew the results and question the power as some of the patients may or may not be candidates for self-care.

Due to these substantial limitations, this trial does not add value to the literature. As a result, it will not be considered for the tension-type headache algorithm or place in therapy of ibuprofen.

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- 8) Verhagen AP et al. Is Any One Analgesic Superior for Episodic Tension-type Headache? J Fam Pract. 2006;55(12):1064-72.

Study Objectives: The aim of this review was to describe and assess the data from randomized controlled trials concerning the efficacy and tolerability of analgesics for the treatment of acute episodes of Tension-type headache in adult patients.

Scope: Only randomized controlled trials (41) including analgesic medicine used in the treatment or management of tension headache conducted among adult patients (aged 18 years or older), with reasonable criteria designed to distinguish tension headache from migraine were selected for this review.

Methods: The authors conducted a literature search of Medline, EMBASE, and The Cochrane Controlled Trials Register with the search terms tension-type headache, tension headache, stress headache, or muscle contraction headache. Two authors independently rated the quality of the trials using the Delphi list. Disagreements were solved through the means of consensus or the inclusion of a third author.

Main Results: 1) NSAIDs were found to be more efficacious than placebo in treating short-term pain relief while the occurrence of adverse events indicated no significant difference. 2) Pooled results of high-quality and low-quality trials displayed a beneficial effect of acetaminophen compared to placebo while the relative risk for the number of patients reporting adverse events was not significant. 3) Pooled results of high-quality and low-quality studies showed a significant difference in short-term pain relief in favour of NSAIDs while the occurrence of adverse effects was not significant. 4) A comparison between different NSAIDs found no difference in short-term pain relief while an analysis of adverse events found naproxen, zomepirac, and aspirin to be the most causative agents.

Extended Abstracts: Ibuprofen

Conclusions: The authors state that although all non-narcotic analgesics have displayed efficacy against tension-type headaches, ibuprofen's generally favourable side-effect profile make it a reasonable first choice. However, the clinicians believe that many of the included trials had methodological shortcomings and as a result only 35% of the studies were considered to be of high-quality.

Comments:

This systematic review is well-designed and offers many strengths while encompassing only minor limitations. With respect to the internal validity, the authors did an excellent job of providing a chart that outlines how trials were selected for this review and which ones were excluded and why. Furthermore, the authors provide an in-depth review of the included trials to supplement this paper. The validity of the study is quite strong as only randomized control trials were included which were comprised of 10,363 patients. A discussion of the external validity finds that the results of this review can be applied to a large proportion of patients as adults from the age of 18 through 87 were included. One pitfall was that the conclusions of this review cannot be generalized to treating children/adolescents.

This article not only reviews efficacy data but also provides an analysis of safety profiles for the multiple treatment modalities. Due to the high value provided by this systematic review, it is influential in comprising the algorithm for tension-type headaches and place in therapy for ibuprofen.