Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Dahlof et al, 1996[183] **Study design:** RCT (crossover trial) **Setting:** Gothenburg Migraine Clinic, Sweden **Duration of follow-up:** Evaluated 2 hours post dosing	**Patient group:** Adults with episodic tension type headache. **Inclusion criteria:** Aged between 18-70 years; Experienced episodic tension type headache (diagnosed according to IHS criteria) headache in association with or without migraine; Headache history of at least one year; 2-8 headache episodes per month. **Exclusion criteria:** Presence of gastric or duodenal ulcer, inflammatory bowel disease, nasal polyposis, utricaria, coagulation or platelet disorder; Cardiac, renal or hepatic failure; History of asthma; Hypersensitivity to paracetamol, aspirin or other analgesics; Ergotamine and/or analgesic dependence; Concomitant NSAID therapy or treatment with antiepileptics, chloramphenicol or probenecid; Pregnancy, lactation or insufficient contraception; Treatment with other investigational drugs within the previous three months. **All patients** **N:** 40(enrolled); 30 (completed	**Group 1 - Single oral dose of ketoprofen 25mg** **Group 2 - Single oral dose of ketoprofen 50mg** **Group 3 - Single oral dose of paracetamol 500 mg** **Group 4 - Single oral dose of paracetamol 1000 mg** **Group 5 - Placebo** Each patient was provided with the 5 study drugs, one to treat each of the five attacks of episodic tension type headache. A minimum interval of 72 hours between 2 attacks was considered sufficient to ensure the absence of carry over effect between successive attacks. No concomitant medication was allowed for 2 hours after intake of the study medication.	**Pain free at 2 hours** 100mm VAS and verbal scale % (number of patients/total number) **Pain intensity difference** Baseline to 2 hours after medication intake, 100 mm VAS	**Group 1:** 28% (8/29) **Group 2:** 32% (9/29) **Group 3:** 17% (5/29) **Group 4:** 17% (5/29) **Group 5:** 17% (5/29) **Group 1:** intermediate between ketoprofen 50 mg and placebo‡ **Group 2:** -31.8±24.6 **Group 3:** no detectable difference from placebo‡ **Group 4:** no detectable difference from placebo‡ **Group 5:** -17.1±25.4 2vs5 (at 2 hours) 0.025	**Funding:** NR **Limitations:** Unclear randomisation and allocation concealment. Unclear blinding of participants, care administrators and investigators. No mention of duration of study and follow up, unclear as to whether enough time had been allowed for each of the drugs to take effect. Loss to follow up was 25%. No reasons for loss to follow up discussed. Order of dropout not mentioned, not clear what groups they were from. **Additional outcomes:** Change in nervousness/tension, muscle stiffness in the neck and shoulders. Treatment giving best relief as reported by patient. Proportion of patients requiring rescue medication. Adverse events in each group (abdominal pain, asthenia, chills, malaise, pain, dizziness etc) not

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	study, treated 5 attacks) **N:** 29 (included in analysis) **M:** 13 (32.5%); F: 27(67.5%) **Age (mean ± SD):** M 48±6 (37-56), **F:** 42±8 (19-56) **Drop outs:** 11 [10 (discontinued prematurely); 1(major protocol violation)]				classified as serious. **Notes:** ITT analysis ‡ Data only presented in graphs Last study medication of 10 patients who dropped out reported: 6 Placebo, 2 Paracetamol 100 mg, 1 Paracetamol 500 mg and 1 Ketoprofen 50 mg.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, VAS=visual analogue scale

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diamond et al, 2000[202] **Study design:** RCT **Comparison:** NSAID vs placebo **Setting:** Multicenter study at 19 different sites in USA **Duration of follow-up: 6 hours**	**Patient group:** Adults with tension type headache. **Inclusion criteria:** 18 years or older; History of acute tension-type headaches as defined by IHS criteria; 3-15 tension type headaches every month for at least the previous year; Headaches had to be responsive 75% of the time at least to non-prescription-strength analgesics. **Exclusion criteria:** Known or suspected to be allergic to any of the study medications; Had a significant coexisting illness or medical condition that would compromise their ability to swallow, absorb, metabolize or excrete the study medication. **All patients** **N:** 385 (for all three arms); 331(treated attack) **Age (mean, range):** 37 (18-73) **Drop outs:** 30 before treatment (9 inappropriate enrolment, 14 protocol violation, 2 treatment of non-qualifying headaches, 5 concurrent caffeine consumption). **Group 1** **N:** 99 **Age (mean, range):** 37 (19-72) **Drop outs:** 0 (after attack treated) **Group 2** **N:** 48 **Age (mean, range):** 36 (19-61) **Drop outs:** 0 (after attack treated)	**Group 1 - Ibuprofen 400mg** **Group 2 - Placebo** Participants were given a single dose of study medication to take home and instructed to use it for the treatment of a moderate intensity tension-type headache within a two month period. Participants rated baseline pain intensity before dosing. They were advised to wait 2 hours before taking any rescue medication. Seen within 1 week at the clinic, assessments were reviewed for completeness and consistency by a staff member and study co-ordinator.	**Time to freedom from pain** Median time to onset of meaningful improvement, minutes	**Group1:** 161 **Group2:** 279	**Funding:** Procter and Gamble Company, Cincinnati, Ohio, USA. **Limitations:** Unclear randomisation and allocation concealment. No details provided regarding blinding of participants and investigators. No data provided on use of concomitant medication **Additional outcomes:** Participants overall evaluation of the medication. Pain relief scores. Percentage of participants who experienced complete relief with each medication. **Notes:** Participants with occasional migraine (less than two per month) included as long as they could differentiate between migraine and tension-type headaches. 4 arm trial with participants randomised in ratio of 2:2:1:1 to [Ibuprofen 400mg +Caffeine 200mg]: Ibuprofen 400mg: Caffeine200 mg: Placebo.
			Median time to onset of perceptible improvement, minutes	**Group1:** 69 **Group2:** 88	
			Incidence of serious adverse events	None	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, IHS=International headache society

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener et al, 2005[224] **Study design:** RCT **Setting:** Outpatient clinics, Germany **Duration of follow-up:** Unclear	**Patient group:** Adults with episodic tension type headache and/or migraine with or without aura **Inclusion criteria:** 18-65 years old; Headaches had to meet IHS criteria for episodic tension-type headache and/or migraine with or without aura; Headaches should have been experienced for at least 12 months with a minimum of two headache episodes in the previous 3 months. **Exclusion criteria:** Patients treating their headache with prescription analgesics or migraine drugs, requiring higher single doses of non-prescription analgesics to treat their headache than indicated in the patient information leaflet, normally treated with non-prescription analgesic in effervescent tablet form, headaches occurred on more than 10 days per month or lasted untreated normally less than 4 hours; Close association between the occurrence of headache and menstruation (menstrual migraine); Concomitant treatment with prescription-only and/or non-prescription analgesics, antidepressants or antipsychotic medication (within the previous 4 weeks before study enrolment), anti-rheumatic or anti-inflammatory drugs that may influence the headache symptoms (within the previous 4 days), drugs containing acetyl salicylic acid (above a daily dose of 100mg/day), paracetamol or caffeine; Migraine prophylaxis or administration of drugs that influence headache symptoms; Drug overuse connected with headache; Pregnancy and lactation; Gastrointestinal ulcers, pathologically increased bleeding tendency, glucose-6-phospahate dehydrogenase deficiency, hypersensitivity to paracetamol, caffeine, ASA, salicylates and other antiinflamatory drugs, bronchial asthma, concomitant treatment with anticoagulants, chronic or recurrent gastrointestinal symptoms, Gilbert's syndrome and hyperthyroidism.	**Group 1 - Acetylsalicylic acid (ASA) 2 tablets of 500mg** **Group 2 -** Paracetamol 2 tablets of 500 mg **Group 3 – Placebo 2 tablets** Patients took trial medication as a single dose when headache occurred and when they would normally have taken their usual analgesic. Patients were allowed to use rescue medication 4 hours after the administration of the trial medication if their pain remained and had document details of time, dose and type of drug used.	**Pain intensity difference at 2 hours** Least square mean, mean difference (95% CI)	**Group1:** 40.7, -4.0, (-7.5, -0.6) **Group 2:** 39.5, -5.2 (-8.7, -1.7) **Group 3:** 24.6, -20.1 (-24.6, -15.7)	**Funding:** Boehringer Ingelheim Pharma GmbH & Co. KG, Vertriebslinie Thomae, Germany **Limitations:** Includes patients suffering both from migraine and tension type headaches. No mention of any other therapies used. **Additional outcomes:** Time to 50% pain relief. Time until reduction of pain intensity to 10mm on VAS. Percentage of patients with 50% pain relief at least after 30min, 1, 2, 3 and 4 hours evaluated on VAS. Weighted sum of pain intensity difference (SPID). Global assessment of efficacy and
			Functional health status and health related quality of life Percentage of patients with no impairment of daily activities at 2 hours post medication intake	**Group1:** 48.4% **Group 2:** 48.65 **Group 3:** 30.5%	
			Incidence of serious adverse events (n)	**Group1:** 0 **Group 2:** 1 **Group 3:** 0	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients **N:** 1983 (for six arms of the trial) **Group 1 Acetylsalicylic acid (ASA)** **N:** 296 (randomised); 276(treated), 252(ITT) **Age (median, range):** 38, 18-69 **Drop outs:** 57 [20(not treated), 13(discontinued), 24(excluded for no VAS/not reliable)] **Group 2 Paracetamol** **N:** 284(randomised), 275(treated), 251(ITT) **Age (median, range):** 39, 18-70 **Drop outs:** 60[9(not treated), 27 (discontinued), 24 (excluded for no VAS/not reliable)] **Group 3 Placebo** **N:** 146(randomised), 138 (treated), 128 (ITT) **Age (median, range):** 37, 18-67 **Drop outs:** 24[8 (not treated), 6(discontinued), 10 (excluded)]				tolerability by the patient. **Notes:** Trial was a six arm trial with the other three groups being Acetylsalicylic acid + Paracetamol + Caffeine, Acetylsalicylic acid + Paracetamol and Caffeine

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, ETTH=episodic tension type headache

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Friedman et al, 1987[295] **Study design:** RCT **Setting:** Multicentre study **Duration of follow-up: 4 hours**	**Patient group:** Adults with tension type headache. **Inclusion criteria:** Specific diagnosis of tension headache (as defined in Monograph 6 of the National institute of Neurological Diseases and Blindness), characterised by an average of six attacks per month for the three months preceding the study; History of previous episodes for at least 1 year; Age between 18-65 years; Motivation to participate in the study and demonstrated willingness to cooperate. **Exclusion criteria:** If participants' use of drugs, health status or lifestyle interfered with their treatment responses or increased their risk of adverse drug reactions (e.g. drug hypersensitivity, history of organic or structural head/neck disease, hypertension/hypotension, serious medical disorder, pregnancy, routine performance of potentially hazardous tasks). **All patients** **N:** 212 (enrolled for all 3 arms of the trial) **Age (range):** 19-64 years **Drop outs:** 14 (failure to comply with study requirements) **Group 1 – Acetaminophen + Codeine** **N:** 65 (randomised); 1(required additional analgesic medication) **Age (mean):** NR **Drop outs:** Unclear **Group 2 - Placebo** **N:** 67(randomised); 5(required additional analgesic medication) **Age (mean):** NR **Drop outs:** Unclear	**Group 1 -** Acetaminophen with codeine **Group 2 -** Placebo Participants were given two identical capsules to be taken at the onset of their next tension headache, if it seemed typical of previous attacks. They were to evaluate at five designated times over the next four hours the level of pain, tension, and muscle stiffness and the amount of pain relief.	**Pain free at 2 hours** Percentage of patients reporting complete relief of pain at 2 hours **Incidence of serious adverse events**	**Group1:** 24.6% (16/65) **Group 2:** 11.9% (8/67) **P value:** 1vs 2, p<0.05 None	**Funding:** Sandoz Inc., East Hanover, NJ, USA **Limitations:** Unclear randomisation and allocation concealment. Blinding of participants and investigators unclear. Number and reasons for loss to follow up not reported per group. **Additional outcomes:** Mean patient self rating scores for tense/uptight, muscle stiffness, pain relief and pain severity. Physicians' global evaluations. **Notes:** 3 arm trial also comparing Fioricet (acetaminophen + caffeine + butalbital) vs (acetaminophen +codeine) vs placebo. Multicentre (10 centres).

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Kubitzek et al, 2003[458] **Study design:** RCT **Setting:** 22 primary care centres in Germany **Duration of follow-up:** 6 hours post dosing; 1 month for taking medication.	**Patient group:** Adults with episodic tension type headache who regularly used over the counter medication. **Inclusion criteria:** History of episodic tension type headache (as defined by the IHS criteria) with onset before the age of 50; Had at least 10 previous episodes lasting between 30 min and 7 days, but averaging less than 180 days per year and less than 15 days of headache per month; Headache lasts at least 1 hour if left untreated. **Exclusion criteria:** Patients who typically experienced nausea or vomiting, photophobia, phonophobia; history of chronic tension type headache, migraines, cluster headaches, headaches secondary to extra-or intracranial pathologies or associated with drug withdrawal; hypersensitivity to NSAIDs or related drugs; asthma, urticaria, acute rhinitis following treatment with acetylsalicylic acid; history of peptic ulcer, gastrointestinal bleeding/gastrointestinal disease; Patients reporting lack of efficacy with for OTC headache remedies; chronic drug use or abuse habit; continuous treatment with prescription doses of analgesics, NSAIDs, tranquilisers, muscle relaxants or anticoagulants; concomitant medication which might confound pharmacological effects of study drugs. **All patients** **N:** 684 (randomised); 620(used study drug); 504 (completed study) **Drop outs:** 116 (prematurely discontinued, 109 due to use of rescue medication) **Group 1**	**Group 1 Diclofenac 12.5mg tablets** **Group 2 Diclofenac 25mg (2 x 12.5mg tablets)** **Group 3 Ibuprofen 400mg (2x200 mg tablets)** **Group 4 Placebo** Single dose study. Patients experiencing headache within a month took the study drug at least 30 min after onset of pain, when pain was at least moderate. Rescue medication (paracetamol 500mg) could be taken 2 hours after taking study drugs.	**Pain free at 2 hours** Percentage of patients reporting complete relief at 2 hours; n (%)	**Group1:** 29 (18.1%) **Group 2:** 35 (22.6%) **Group 3:** 33 (21.9%) **Group 4:** 12 (7.8%) **P values:** 1vs4, 2vs4, 3vs4= p<0.01	**Funding:** Novartis Consumer Health SA, Nyon, Switzerland. **Limitations:** Unclear randomisation and allocation concealment. Blinding of investigators not reported. No details of concomitant medication or other therapies. **Additional outcomes:** Time to rescue medication. Overall evaluation of efficacy by patient. Time weighted sum of pain intensity differences from baseline (SPID). Time interval weighted sum of the pain relief score (TOTPAR).
			Pain intensity difference	**P values:** 1vs4, 2vs4, 3vs4=p<0.01 at all time pints 1 hour post dosing.	
			Incidence of serious adverse events	None	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 171 (randomised), 160 (treated) **Age (mean, SD):** 42.3(14.9) **Drop outs:** NR **Group 2** **N:** 171 (randomised), 156 (treated) **Age (mean, SD):** 42.1 (14.5) **Drop outs:** NR **Group 3** **N:** 172(randomised), 151(treated) **Age (mean, SD):** 44.7 (15.0) **Drop outs:** NR **Group 4** **N:** 170(randomised), 153(treated) **Age (mean, SD):** 39.9 (13.7) **Drop outs:** NR				**Notes:** Trial also compared diclofenac to ibuprofen

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, TTH=tension type headache, IHS=international headache society

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Mehlisch et al, 1998 [549] **Study design:** RCT **Setting:** Outpatient clinics, USA **Duration of follow-up:** Evaluated 4 hours post dose; Study lasted two weeks to 1 month	**Patient group:** Adults with a history of tension type headache. **Inclusion criteria:** 18 years or older; Reported at least 1 year history of tension headache episodes (according to IHS criteria); Average frequency of ≥1 but not more than 10 episodes per month. **Exclusion criteria:** Pregnancy and lactation; Women enrolled had to be naturally or surgically sterile or using a medically acceptable means of birth control; Experienced migraine, post-concussion or cluster headaches in the past year; Had significant medical conditions; Had abnormal laboratory findings with potential to jeopardise their health or interfere with the results of the study; History of chronic use of analgesics, NSAIDS, tranquilisers or muscle relaxants, drug or alcohol dependence; Known hypersensitivity to NSAIDS or acetaminophen; Treated with an investigational new drug within the previous 30 days. **All patients** **N:** 737 (enrolled), 703 (given study medication), 631 (included in efficacy analysis). **Drop outs:** 72 (5 protocol violation, 67 did	**Group 1:Ketoprofen 25 mg** Tablet/gelcap formulation taken orally with 4 ounces of water. **Group 2: Ketoprofen 12.5 mg** Tablet/gelcap formulation taken orally with 4 ounces of water. **Group 3: Acetaminophen 1000 mg** Tablet/gelcap formulation taken orally with 4 ounces of water. **Group 4: Placebo** Tablet/gelcap formulation taken orally with 4 ounces of water. All medications were to be taken when experiencing a sustained tension headache that was at least moderate in intensity. Time to meaningful pain relief was scored by starting a stopwatch at the time of dosing and stopping it when he individual perceived	**Time to meaningful pain relief** hours:mins (median) Log-Rank with letter codes indicating no statistically significant difference between groups sharing the same letter code; A indicates most effective treatment, B the next most effective treatment, etc.	**Group1:** 0:56 **95% CI:** 0:49,1:02 **Log-Rank:** A **Group2:** 1:07 **95% CI:** 0:59,1.18 **Log-Rank:** AB **Group3:** 1:05 **95% CI:** 1:00,1:21 **Log-rank:** BC **Group4:** 1:25 **95% CI:** 1:07,1:44 **Log-Rank:** C	**Funding:** Pharmaceutical company (SCIREX Corporation, Austin, USA and Bayer AG, Consumer Care, Germany) **Limitations:** Unclear randomisation and allocation concealment. 10.8% loss to follow up; unclear which groups the drop outs were from. Protocol violation not defined. Unclear whether study investigators were blinded to participants exposure to intervention and confounding factors. **Additional outcomes:** SPRID (4-hour sum of pain relief intensity differences). TOTPAR (Total pain relief at 2 and 4 hours). SPID (2 and 4 hour sum of pain intensity difference). **Notes:**
			Pain intensity difference (mean± SD) Baseline to 2 hours after medication intake measured on a scale rating pain intensity as 0=none, 1=mild, 2=moderate, 3=severe.	**Group1:** 4.87±2.07 **Group2:** 4.73±1.98 **Group3:** 4.58±2.11 **Group4:** 4.45±2.11	
			Functional health status and health related quality of life (Change in functional ability impairment across treatment groups from baseline)	No demonstrable difference among groups	

	not record data properly). **Group 1 Ketoprofen 25 mg** **N:** 156 **Age (mean ± SE):** 30.6 ± 0.8 **M/F:** 34/66% **Drop outs:** NR **Group 2 Ketoprofen 12.5 mg** **N:** 158 **Age (mean ± SE):** 31.1 ± 0.8 **M/F (%):** 30/7% **Drop outs:** NR **Group 3 Acetaminophen 1000 mg** **N:** 166 **Age (mean ± SE):** 32.2 ± 0.7 **M/F (%):** 29/71% **Drop outs:** NR **Group 4 Placebo** **N:** 151 **M/F (%):** 35/65% **Age (mean ± SE):** 32.2 ± 0.8 **Drop outs:** NR	meaningful pain relief. Functional ability impairment ratings were recorded at baseline and at 1 hour post dosing on a 4 point scale ranging from 0=none to 3=severe. If study medication was not taken within 30 days of dispensing medication, subjects were asked to return to the clinic and their participation was terminated.	**Incidence of serious adverse events**	**Group1:** 2/156 **Group2:** 4/158 **Group3:** 2/166 **Group4:** 1/151	Concomitant use of medications which could confound the assessment of study drug efficacy and safety was prohibited beginning 4 hours prior to intake of study medication to end of assessment period.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Packman et al, 2000 [602] **Study design:** RCT **Setting:** Headache clinic **Duration of follow-up:** Three hours	**Patient group:** Inpatients aged >12 with moderately severe TTH. **Inclusion criteria:** Age over 12 years; History of episodic TTH defined by IHS criteria; Onset of headaches before 50 years; reporting at headache clinic within 1 hour of onset of moderately severe headache. **Exclusion criteria**: Habituated to analgesics; History of migraine (on average >1 migraine per month over the past 6 months); Menstrual headaches; Allergic hypersensitivity or contraindications to aspirin, NSAIDs or acetaminophen. **All patients** **N:** 154 M/F: 37/117 **Age (mean ± SD):** 39.6± 11.8 **Drop outs:** 0 **Group 1 Ibuprofen** **N:** 60 M/F:14/46 **Age (mean± SD):** 38.5± 10.4 **Group 2 Acetaminophen** **N:** 62 M/F: 15/47 **Age (mean± SD):** 41.2± 12.6 **Group 3 Placebo** **N:** 32 M/F: 8/24 **Age (mean± SD):** 38.3± 12.4	**Group 1Ibuprofen 400mg (2x200 mg liquigels)** Liquigel formulation: encapsulating solubilised ibuprofen in a soft gelatin shell formed by spreading a molten gelatin mass into two lubricated ribbons that shape the liquigel. Ibuprofen is then injected through a wedge in the gelatine mould. **Group 2 Acetaminophen 1000mg (2x500mg caplets)** **Group 3 Placebo** **All patients:** Single dose study. Participants had to rate headache pain as at least moderately severe on a 4 point categorical pain rating scale confirmed by a score of at least 66mm on a 100 mm visual analogue pain scale. Time of perceptible first pain relief and meaningful relief was recorded by patients using two stopwatches started at the time of dosing.	**Time to meaningful pain relief** minutes (median time) Percentage who experienced first perceptible pain relief as well as meaningful pain relief by 30 min	**Group1:** 39 **Group2:** 53 **Group3:** >180 **Group1:** 20% (12/60) **Group2:** 2% 1/62) **Group3:** 0%	**Funding:** Whitehall-Robins Healthcare, Madison, NJ. **Limitations:** Unclear randomisation and allocation concealment. Small sample size for placebo group. Study conducted in specialised headache clinic: may not be generalisable to population. Blinding of participants and investigators unclear. **Additional outcomes:** Sum of pain relief intensity difference scores for 3 hours (SPRID3). Pain relief intensity difference (PRID) at 2 and 3 hours. Time to first perceptible relief. **Notes:** Qualifying subjects stratified by sex before randomisation.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, TTH=tension type headache.

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Pini et al, 2008[631] **Study design:** RCT (Crossover trial) **Setting:** 8 outpatient headache centres in Italy **Duration of follow-up:** 4 hours for each headache attack, to treat a total of three attacks	**Patient group:** Adults with history of tension-type headache (TTH) **Inclusion criteria:** Diagnosis of episodic TTH according to ICHD-II criteria, modified in the single following criterion: absence of nausea, vomiting, photophobia and phonophobia (to exclude subjects with migraine headaches); Mean frequency of 4-14 days with TTH per month; History of response to treatment of TTH with over the counter pain killers; Daily consumption of at least two cups of coffee; Adequate contraception in women of fertile age; Medical history and physical examination inconsistent with organic disorders associated with headaches. **Exclusion criteria:** Known hypersensitivity or allergy to paracetamol or naproxen; Chronic headache, either recurrent or continuous; Concomitant use/overuse of NSAIDS or other analgesics; treatment with antiplatelet or anticoagulant drugs; History of migraine or post-traumatic headache; History of alcohol abuse, drug dependency,	**Group 1 - Paracetamol 1000mg+Caffeine 130mg (in sachets)** **Group 2 - Naproxen sodium 550 mg (in soft gel capsule)** **Group 3 - Placebo (sachets and soft gel capsules)** Each patient was randomly allocated to one of the study treatment sequences to treat the next three consecutive TTH attacks: PCF-NAP-PLA NAP-PLA-PCF PLA-PCF-NAP PCF-PLA-NAP NAP-PCF-PLA PLA-NAP-PCF [PCF paracetamol 1000mg+caffeine 130mg, NAP naproxen sodium 550mg, PLA placebo]. TTH attacks treated with the trial medication had to be separated from each other by at least 48 hours. Patients also received rescue medication (ibuprofen 600mg) to be taken 2 hours after administration of the trial medication if the pain persisted.	**Incidence of serious adverse events** (reported as severe adverse events by patients)	**Group 1:** 3 (1.3%) **Group 2:** 5 (2.3%) **Group 3:**13 (5.8%)	**Funding:** Angelini Farmaceutici, ACRAF SpA (Rome, Italy) **Limitations:** Details of blinding of investigators not provided. Number lost to follow up in each group not detailed. **Additional outcomes:** Total pain relief at 2 and 4 hours (TOTPAR) Sum of pain intensity difference (SPID) at 2 and 4 hours. **Notes:** No serious adverse events were recorded by the study investigators.

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	or psychiatric disease; History of coagulation disorders, peptic ulcer disease, pancreatic disease, clinically significant renal or hepatic disease, blood hypertension, mild/moderate kidney or liver disease, Gilbert's syndrome. **All patients** **N:** 111(enrolled); 99 (took at least one treatment); 12 [excluded 2(did not fulfil inclusion criteria), 10 (did not take study medication; 93(Per protocol population and ITT population). **Age (mean ± SD):** 35.1±10.19 years **M/F (%):** 40.4/59.6% **Headache duration in years (mean± SD):** 22.2±9.09 **Drop outs:** 18				

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, TTH=tension type headache, ICHD=International classification of headache disorders

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Prior et al, 2002[641] **Study design:** RCT **Setting:** Outpatient clinics **Duration of follow-up:** 6 hours	**Patient group:** Adults with history of tension type headache **Inclusion criteria:** 18 years or older; History of acute tension-type headaches of at least moderate intensity that met at least two of the following characteristics (a pressing, tightening, non-pulsating quality, possible inhibition but not prohibition of activity, bilateral or variable location, not aggravated by physical activity) derived from the IHS diagnostic criteria; Headache required treatment with over-the-counter analgesics and occurred between four and ten times per month; Headache was not associated with nausea, vomiting, photophobia, phonophobia or auras; History of response to treatment of acute tension-type headaches with over the counter analgesics; Medical history, physical and neurologic examination inconsistent with organic disorders associated with headaches. **Exclusion criteria:** History of any of the following: Migraine or cluster headaches; Recurrent sinus headaches; Withdrawal headaches from substances such as caffeine or nicotine; Headaches related to food or excess alcohol; Headaches due to other underlying pathology or related to head or neck trauma; Alcohol abuse, drug dependency, or psychiatric disease; Use of daily NSAIDs, other analgesics, low dose aspirin prophylaxis, anti-coagulants or psychotropics; Continuous daily headaches; Headaches unresponsive to treatment with over the counter analgesics; Headaches related to menses; sensitivity or allergy to acetaminophen, aspirin, or NSAIDs; peptic ulcer disease, inflammatory bowel disease, gastrointestinal bleed, unstable clinically significant cardiovascular disease, clinically significant renal or hepatic disease, coagulation disorders, unstable diabetes, pancreatic disease, uncontrolled hypertension, seizures, cerebral vascular ischaemia, infarct, haemorrhage or central nervous system disease, unstable	**Group 1: Naproxen 375mg orally** **Group 2: Acetaminophen 1000mg orally** **Group 3 Placebo** Single dose placebo controlled study Participants were required to be experiencing an acute tension-type headache of at least moderate severity before ingesting the study medication. Participants were to record in a diary the date and time of ingestion, pain intensity before treatment and pain intensity and pain relief after treatment recorded at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 and 6 hours.	**Time to meaningful pain relief** minutes (median)	**Group1:** 138.5 **Group2:** 131.5 **Group3:** 178.5	**Funding:** McNeil consumer & Specialty Pharmaceuticals, Fort Washington, PA. **Limitations:** Unclear allocation concealment. Placebo group had a lower percentage of women at baseline. No information on type of rescue medication or dosing. Pain relief measurement is subjective and could be influenced by the fact that some of the participants were known to the study investigators. **Additional outcomes:** sum of pain intensity difference (SPID) weighted from baseline. Maximum pain intensity difference from baseline (MAXPID) occurring over the observation period. TOTPAR (time interval weighted sum of the
			Pain free at 2 hours Percentage of participants with headaches completely resolved at 2 hours (n)	**Group1:** 31.5% (93) **Group2:** 36.8% (112) **Group3:** 25.9% (78)	
			Headache response at up to 2 hours Percentage of participants with pain reduced to mild or none at 2 hours (n)	**Group1:** 61.7%(182) **Group2:** 65.1% (198) **Group3:** 55.1% (166)	
			Pain intensity difference	Results reported in graph	
			Incidence of serious adverse events	None	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	metabolic disease, current malignancy or active tuberculosis and prior gastrointestinal surgery which could influence absorption, metabolism or excretion of study medication. **All patients** **N:** 963 (enrolled); 915 (took study medication); 900 (completed the study) **Drop outs:** 63 **Group 1** **N**: 321 (randomised); 295(completed trial) **Age (mean):** 34.6 years **Drop outs:** 26 **Group 2** **N:** 321 (randomised); 304 (completed trial) **Age (mean):** 33.2 years **Drop outs:** 17 **Group 3** **N:** 321(randomised); 301(completed trial) **Age (mean):** 33.8 years **Drop outs:** 20				pain relief scores). Maximum pain relief (MAXPAR) that occurred during the observation period. **Notes:** Participants were allowed to use rescue medication after one hour if their pain remained at or returned to the level before treatment.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, IHS=International headache society

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Sargent et al, 1988[696] **Study design:** RCT **Setting:** Four study centres (Headache clinics/research centres) across USA **Duration of follow-up: 6 hours**	**Patient group:** Adults with tension type headache **Inclusion criteria:** Confirmed diagnosis of recurrent muscle contraction headaches characterised by a moderate to severe degree of steady or intermittent headache pain and a sensation of increased muscle tension in the posterior neck, occipital, frontal or temporal areas; frequency of recurrent headaches of 4 to 12 per month, average of one to three per week; history of symptoms for at least 3 months. Patient should be able to distinguish between a migraine and a muscle contraction headache, according to the symptoms defined by the National Institute of Neurological Diseases and Blindness. **Exclusion criteria:** Severe daily headaches of any type including those caused by structural intracranial or extra cranial disease; serious medical illness or illness with pain as a prominent symptom; history of bleeding problems or anticoagulant therapy within 4 weeks of the start of the study. **All patients** **N:** 161 (enrolled); 137 (received trial medication) **Group 1** **N:** 64 (randomised) ; 63 (included in efficacy analysis) **Age (mean, range):** 40 (21-73) **Drop outs:** 1(insufficient headache data) **Group 2** **N:** 73 (randomised); 71 (included in efficacy analysis) **Age (mean, range):** 39 (20-62) **Drop outs:** 2 (1 insufficient headache data, 1 protocol violation)	**Group 1- Naproxen sodium 275 mg capsules orally** **Group 2 Placebo** Sufficient trial medication was dispensed for four headache episodes at the first visit; Patients were to take two capsules (either naproxen or placebo) for each headache episode. Rescue medications could be taken if pain was not adequately controlled. Concomitant use of antidepressants was allowed but not corticosteroids, analgesics, anti-inflammatory agents or muscle relaxants.	**Pain intensity difference** (mean)	**Group1:** 7.2 (1 hour post dose), 14.1 (2 hours post dose) **Group2:** 4.0(1 hour post dose), 5.8 (2 hours post dose) **P values:** 1vs 2 at 1 hour post dose = 0.013 1vs2 at 2 hours post dose =<0.001	**Funding:** Syntex Laboratories, Inc. **Limitations:** Randomisation and allocation concealment unclear. Blinding of participants and investigators not detailed. No mention of other therapies used to alleviate pain. **Additional outcomes:** Sum of pain intensity differences (SPID). Use of rescue medication.
			Incidence of serious adverse events [Complaints reported as severe by patients]	**Group1:** 3 (one GI, two CNS complaints) **Group 2**: 16 (7 GI, 5 CNS and 4 other)	

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Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Schachtel et al, 1988[700] **Study design:** RCT **Setting: NR** **Duration of follow-up: 2 hours**	**Patient group:** Adults with history of tension type headache and previous response to non-prescription analgesic **Inclusion criteria:** Adult subjects with a diagnosis of muscle contraction headache who reported history of satisfactory relief of headaches from a non-prescription analgesic (aspirin, acetaminophen, ibuprofen); Not receiving treatment from a physician; history of at least moderately severe muscle contraction headaches occurring at least twice a month during the past year. **Exclusion criteria:** History of migrainous headache or hypersensitivity to ibuprofen or aspirin; use of any drugs including analgesics, tranquilisers and mood-altering agents within 4 hours preceding the headache evaluation. **All patients** **N:** 70 (randomised) **Group 1** **N:** 35 **Age (mean, range):** 20.1 (18-23) **Drop outs:** NR **Group 2** **N:** 35 **Age (mean, range):** 21.2 (19-38) **Drop outs:** NR	**Group 1 - Ibuprofen 400 mg orally** **Group 2 - Placebo orally** Both groups completed a headache diary when they experienced a muscle contraction headache and had to swallow single dose of study medication, complete efficacy evaluations at 15, 30, 45, 60, 90, 120 minutes after dosing and note the occurrence of side effects.	**Pain intensity difference** (at various times post dose)	**Group1:** 12.6±11.1 (30 mins) 21.1±14.0 (45mins) 28.9±18.1 (60mins) 37.6±19.6 (90 mins) 43.7±20.5 (120 mins) **Group 2:** 1.8±4.1 (30 mins) 2.7±6.0 (45 mins) 3.5±6.9(60 mins) 3.7±8.4 (90mins) 3.5±8.2 (120 mins) **P values:** 1vs 2 at all time points was statistically significant. P<0.001	**Funding:** Whitehall laboratories Inc. **Limitations:** Unclear randomisation and allocation concealment. Blinding of participants and investigators not described. Details of follow up and assessment not provided. No mention of other therapies used to alleviate pain. No mention of comorbidities. **Additional outcomes:** Headache pain relief scores.
			Incidence of serious adverse events	None	

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Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Steiner et al, 1998[760] **Study design:** RCT **Setting:** Outpatient clinic s **Duration of follow-up:** 72 hours after headache attack	**Patient group:** Adults with episodic tension type headache (ETTH) **Inclusion criteria:** 18-65 years; Healthy except ETTH (with or without peri-cranial muscle disorder) diagnosed by the IHS criteria. **Exclusion criteria:** Suffering from other headaches including migraine; Pregnant, at risk of pregnancy or breastfeeding; Presently or previously had evidence of peptic ulceration or gastrointestinal haemorrhage; History of alcohol or medication misuse; Otherwise ill, physically or mentally; Taking regular medication. **All patients** **N:** 453 (randomised); 348 (treated at least one attack of ETTH); 9(excluded for taking treatment <1 hr or >12hr after onset); 339 (intention to treat population ITT) **Drop outs:** 39 (protocol violation) **Group 1 Ketoprofen (25mg)** **N:** 109(treated at least one attack of ETTH); 107 (included in ITT analysis) **Age (median, range):** 42(18-74) **Drop outs:** Unclear **Group 2 (Acetaminophen 1000 mg)** **N:** 123(treated at least one attack of ETTH);119 (included in ITT analysis) **Age (median, range):** 39(18-64)	**Group 1 Ketoprofen 25mg orally** **Group 2 Acetaminophen 1000 mg orally** **Group 3 Placebo** After baseline assessment, patients were issued with a medication pack for one attack. Pack had 2 bottles, 1 containing ketoprofen or matching placebo and the other acetaminophen or matching placebo with instructions on the correct use of the trial medication and in completion of diary cards. Trial medication from both bottles was taken at home between 1 and 12 hours of onset of an otherwise untreated attack; headache intensity had to be at least moderate subjectively. Allowed three months in which to treat an attack; were considered dropouts if they did not.	**Pain free at 2 hours** Percentage of patients experiencing total relief at 2 hours	**Group 1:** 27% (28/102) **Group 2:** 22% (25/116) **Group 3:** 16% (18/ 112)	**Funding:** NR **Limitations:** Unclear randomisation and allocation concealment. Unclear if double blinded or not; details not reported Numbers and reasons for dropout according to groups not provided. Unclear how patients were monitored at home; no details of rescue medication/ concomitant therapy provided. Unclear if randomisation was done prior to screening patients for inclusion as exclude patients for not fulfilling inclusion criteria after randomisation. **Additional outcomes:** Patients' global assessment at 2 hours. Pain relief at 4 hours.
			Functional health status and health related quality of life	**Group 1:** 75% normal at 2 hrs 88% at 4 hrs **Group 2:** 68% normal at 2 hrs 78% at 4 hrs **Group 3:** 53% normal at 2 hrs 68% at 4 hrs	
			Incidence of serious adverse events	No serious adverse events were reported	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: Unclear **Group 3 Placebo** **N:** 116 (treated at least one attack of ETTH);113 (included in ITT analysis) **Age (median, range): 42 (20-67)** **Drop outs:** Unclear				

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Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Steiner et al, 2003[761] **Study design:** RCT **Setting:** GP surgeries **Duration of follow-up:** 4 hours	**Patient group:** Aged over 16 with episodic tension type headache **Inclusion criteria:** 16-65 years; Met IHS diagnostic criteria for episodic tension-type headache but not for migraine; Had no other serious physical or mental illness or contraindications to study treatment. **Exclusion criteria:** Women who were pregnant or who might become pregnant; Concomitant use of antidepressants or drugs known to interact with study medication. **All patients** **N:** 638 (randomised); 542 (took study medication) **Drop outs:** 96 (did not take study medication) **Group 1** **N:** 126 (randomised);111 (took study medication, included in ITT) **Age in years, mean (SD):** 39.9 (11.8) **Drop outs:** 15 **Group 2** **N:** 128(randomised); 103 (took study medication, included in ITT) **Age in years, mean (SD):** 41.0(12.3) **Drop outs:**25	**Group 1:Aspirin 500mg** **Group 2: Aspirin 1000mg** **Group 3: Paracetamol 500mg** **Group 4: Paracetamol 1000mg** **Group 5: Placebo** Each participant received a diary card and one dose of trial medication with instructions to treat an attack of episodic tension-type headache occurring within 8 weeks of enrolment. Headache had to be moderate in intensity and the study medication could not be used for a headache associated with a cold, influenza, other viral infection or hangover. Rescue medication was	**Pain free at 2 hours**: Percentage of participants recording 'total relief' or 'some worth while effect' at 2 hrs post dose	**Group 1:** 70.3% (78/111) **Group 2:** 75.7% (78/103) **Group 3:** 63.8% (67/105) **Group 4:** 71.2% (79/111) **Group 5:** 54.5% (49/112) **p values:** 1vs5: 0.011; 2vs5: 0.00009 3vs5: 0.014; 4vs5: 0.007 2vs4: 0.275; 1vs3: 0.19	**Funding:** Bayer AG, BG Consumer Care, Germany **Limitations:** Unclear randomisation and allocation concealment. Patients were not monitored at home. Unclear how groups were followed up. Blinding of investigators unclear. Reasons for loss to follow up unclear. **Additional outcomes:** Use of rescue medication at 2 hours. Global evaluation analysis. Sum of pain intensity difference scores (SPID). Notes:
			Pain intensity difference	**P values:** 2vs5: 0.0001 (2 hrs); significant at each time point from 30 min to 2 hours 4vs5: 0.0058 and 3vs5: 0.0018;(at 2 hrs); not significant at any time point prior to 2 hrs	
			Functional health status Return to normal function by 1 hr	**Group1:** NR **Group 2:** 41.7% **Group 3:** NR **Group 4:** 26.1% **Group 5:** 19.6%	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 3 **N:** 128 (randomised); 105 (took study medication, included in ITT) **Age in years, mean (SD):** 39.7 (11.4) **Drop outs:** 23 **Group 4** **N:** 128 (randomised); 111 (took study medication, included in ITT) **Age in years, mean (SD):** 38.4 (11.8) **Drop outs:** 17 **Group 5** **N:** 128(randomised); 112 (took study medication, included in ITT) **Age in years, mean (SD):** 40.6 (11.4) **Drop outs:** 16	permitted after two hours of medication intake.		**p-values:** 2vs5: 0.0003 2vs4: 0.012 4vs5:0.16	5 arm trial with 2 different doses of aspirin and paracetamol. Participants were recruited from the UK general population by advertisement in GP surgeries and local newspapers.
			Incidence of serious adverse events	None	

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