Oral, nasal & subcutaneous treatments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Brandes et al, 2007 (1)[105] **Study design:** Two replicate, randomised, double-blind, single-attack, parallel group studies **Comparison:** Triptan vs NSAID **Setting:** Primary care practices, neurology clinics and headache clinics in the USA **Duration of follow-up:** 6 weeks	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-65 years. At least a 6 months history of migraine with or without aura as defined by IHS criteria. An average of 2 to 6 moderate or severe migraine episodes monthly during the 3 months preceding the screening visit. Could distinguish migraine episodes from other types of headache. Women had to be physically incapable of becoming pregnant, had to agree to practice adequate contraception during the study. Patients were eligible for the studies regardless of whether they were triptan-naïve. **Exclusion criteria:** 6 migraine attacks monthly during either of the 2 months before screening. Chronic daily headache (≥15 days per month of non-migraine headaches during each of the 3 months before screening). Uncontrolled hypertension (diastolic BP >95mmHg or systolic BP >160mmHg). Confirmed or suspected cardiovascular or cerebrovascular	**Group 1 Sumatriptan-naproxen sodium** **Group 2 sumatriptan 85mg** **Group 3 Naproxen sodium 500mg** **Group 4** Placebo (results not reported in this table) **All patients** Instructed to treat a migraine attack with study medication when pain intensity was moderate or severe. Patients were to treat a migraine attack within 6 weeks of the screening visit. One opportunity to re-screen if no migraine in 6weeks. Dosing regimens of migraine prophylaxis could not be changed during the 2 weeks prior to treatment, including the use of Calcium channel blockers, tricyclic antidepressants, Beta blockers or serotonergic medications for	**Headache response up to 2 hours**	**Group1:** 237/364 (65%) **Group 2**: 200/361 (55%) **Group 3:** 157/356 (44%) **p value** (Group 1 vs 2): 0.009	**Funding:** GlaxoSmithKline and Pozen Inc **Limitations:** Randomisation unclear. Allocation concealment unclear. **Additional outcomes:** Headache relief at 2 hours by severity of headache (moderate/severe). Absence of associated symptoms at 2 and 4 hours. Sustained absence of associated symptoms. Any vomiting to 24 hours after dosing. Use of rescue medication. Recurrence. **Notes:** <u>Pain severity scale</u> 0= none 1= mild
			Pain free at 2 hours	**Group1:** 125/364 (34%) **Group 2**: 90/361 (25%) **Group 3:** 53/356 (15%) **p value** (Group 1 vs 2): 0.009 (analysis was performed post hoc without adjustments for multiple comparisons)	
			Sustained pain-free at 24 hours	**Group 1:**90/364 (25%) **Group 2:**59/361 (16%) **Group 3:**37/356 (10%) **p value** (Group 1 vs 2): 0.009	
			Sustained	**Group1:** 174/363	

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	disease. History of cardiac arrhythmias requiring medication or clinically significant ECG abnormalities that in the investigators opinion, contraindicated study participation. Basilar or hemiplegic migraine. Current use or use within 3 months before screening of migraine prophylactic medication containing ergotamine, an ergot derivative or methysergide; use of a monoamine oxidase inhibitor within 2 weeks or preparations containing St. John's wort within 4 weeks before screening. Regular use of any anticoagulant or NSAID (except aspirin, ≤325 mg/d, for cardiovascular prophylaxis). **All patients** **N:** 1677 (randomised), 1441 (efficacy population) **Group 1** Sumatriptan-naproxen sodium **N:** 422 randomised. 370 took study medication. 364 included in primary efficacy analysis **Age (mean):** 40.3 (SD 11.4) **Gender F, n (%):** 322 (87) **Drop outs:** 58 (52 no study medication; 6 not evaluable)	any other indication. No NSAIDs (except aspirin ≤325mg/d, for cardiovascular prophylaxis); analgesics containing morphine, codeine or opioid derivatives; ergotamine containing compounds or serotonin agonists could be taken within 24h before treatment with study medication. No analgesics or acute migraine treatment could be taken within 6 hours before treatment with study medication. Rescue medication was permitted beginning 2 hours after dosing. Patients recorded on diary cards details about the migraine they treated with study medication and any use of study medication or concomitant medication. Pain severity was rated immediately before dosing; 0.5, 1 and 1.5 hours after dosing and hourly from 2 to 24 hours after dosing on a 4 point scale.	**headache response at 24 hours**	**Group2:** 127/362 **Group3:** 107/356	2= moderate 3= severe
			Incidence of serious adverse events	**Group1:** 0/370 **Group 2:** 1/365 (heart palpitations resulting in hospitalisation) **Group 3:** 0/361	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 sumatriptan 85mg **N:** 415 randomised. 365 took study medication. 361 included in primary efficacy analysis. **Age (mean):** 40.1 (SD 10.9) **Gender F, n (%):** 313 (86) **Drop outs:** 54 (50 no study medication; 4 not evaluable) **Group 3** Naproxen sodium 500mg **N:** 419. 361 took study medication. 356 included in primary efficacy analysis **Age (mean):** 39.4 (SD 11.3) **Gender F, n (%):** 311 (86) **Drop outs:** 63 (58 no study medication; 5 not evaluable) **Group 4** Placebo **N:** 421. 365 took study medication. 360 included in primary efficacy analysis **Age (mean):** 40.0 (SD 11.1) **Gender F, n (%):** 308 (84) **Drop outs:** 61 (56 no study medication; 5 not evaluable)				

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Brandes et al, 2007 (2)[105] **Study design:** Two replicate, randomised, double-blind, single-attack, parallel group studies **Comparison:** Triptan vs NSAID vs combination **Setting:** Primary care practices, neurology clinics and headache clinics in the USA **Duration of follow-up:** 6 weeks	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-65 years. At least a 6 months history of migraine with or without aura as defined by IHS criteria. An average of 2 to 6 moderate or severe migraine episodes monthly during the 3 months preceding the screening visit. Could distinguish migraine episodes from other types of headache. Women had to be physically incapable of becoming pregnant, had to agree to practice adequate contraception during the study. Patients were eligible for the studies regardless of whether they were triptan-naïve. **Exclusion criteria:** Six migraine attacks monthly during either of the 2 months before screening Chronic daily headache (≥15 days per month of non-migraine headaches during each of the 3 months before screening). Uncontrolled hypertension (diastolic BP >95mmHg or systolic BP >160mmHg). Confirmed or suspected cardiovascular or cerebrovascular disease. History of cardiac arrhythmias requiring medication or clinically significant ECG abnormalities that in the investigators opinion, contraindicated study participation. Basilar or hemiplegic migraine. Current use or use within 3 months before	**Group 1** Sumatriptan-naproxen sodium **Group 2 sumatriptan** 85mg **Group 3** Naproxen sodium 500mg **Group 4** Placebo (results not reported in this table) All patients Instructed to treat a migraine attack with study medication when pain intensity was moderate or severe. Patients were to treat a migraine attack within 6 weeks of the screening visit Patients recorded on diary cards details about the migraine they treated with study medication and any use of study medication or concomitant medication. Pain severity was rated immediately before dosing; 0.5, 1 and 1.5 hours after dosing and hourly from 2 to 24 hours after dosing on a 4 point scale.	**Headache response up to 2 hours**	**Group1:** 207/362 (57%) **Group 2:** 182/362 (50%) **Group 3:** 158/364 (43%) **p value (Group 1 vs 2):** 0.03	**Funding:** GlaxoSmithKline and Pozen Inc **Limitations:** Randomisation unclear. Allocation concealment unclear. **Additional outcomes:** Headache relief at 2 hours by severity of headache (moderate/severe). Absence of associated symptoms at 2 and 4 hours. Sustained absence of associated symptoms. Any vomiting to 24 hours after dosing. Use of rescue medication. Recurrence . **Notes:** Pain severity scale 0= none 1= mild 2= moderate 3= severe
			Pain free at 2 hours	**Group1:** 107/362 (30%) **Group 2:** 82/362 (23%) **Group 3:** 57/364 (16%) **p value (group 1 vs 2):** 0.02 (analysis was performed post hoc without adjustments for multiple comparisons)	
			Sustained freedom from pain 24 hours	**Group 1:**83/362 (23%) **Group 2**:51/362 (14%) **Group 3:**37/364 (10%) **p value (group 1 vs 2):** <0.001	
			Sustained headache response at 24 hours	**Group1:** 158/362 **Group2:** 121/362	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	screening of migraine prophylactic medication containing ergotamine, an ergot derivative or methysergide; use of a MAOI within 2 weeks or preparations containing St. John's wort within 4 weeks before screening. Regular use of any anticoagulant or NSAID (except aspirin, ≤325 mg/d, for cardiovascular prophylaxis). **All patients** **N:** 1736 (randomised), 1495 (took study medication as assigned), 1470 (included in primary efficacy analysis). **Group 1** Sumatriptan-naproxen sodium **N:** 433 randomised, 367 took study medication as assigned, 362 included in primary efficacy analysis **Age (mean):** 39.4 (SD 11.2) **Gender F:** 320 (87%) **Drop outs:** 71 (66 no study medication; 5 not evaluable) **Group 2** sumatriptan 85mg **N:** 434 randomised, 370 took study medication as assigned, 362 included in primary efficacy analysis **Age (mean):** 40.3 (SD 11.4) **Gender F:** 323 (87%) **Drop outs:** 72 (64 no study medication; 8 not evaluable)			**Group3:** 102/364	
			Incidence of adverse events	**Group1:** 0/367 **Group 2:** 0/370 **Group 3:** 0/371	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 3 Naproxen sodium 500mg **N:** 434 randomised, 371 took study medication as assigned, 364 included in primary efficacy analysis **Age (mean):** 40.4 (SD 11.6) **Gender F:** 329 (89%) **Drop outs:** 70 (63 no study medication; 7 not evaluable) **Group 4** Placebo **N:** 435 randomised, 387 took study medication as assigned, 382 included in primary efficacy analysis **Age (mean):** 40.6 (SD 10.7) **Gender F:** 345 (89%) **Drop outs:** 53 (48 no study medication; 5 not evaluable)				

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener et al, 2002[219] **Study design:** RCT **Comparison:** Triptan vs ergotamine +caffeine **Setting:** Outpatients **Duration of follow-up:** Up to 12 weeks.Follow up evaluations performed 7-14 days after treatment.	**Patient group:** Migraine with or without aura **Inclusion criteria:** Otherwise healthy patients who had experienced at least 1 migraine attack every 6 weeks but not more than 6 per month, for at least 1 year (defined by IHS criteria) with onset before age of 40. **Exclusion criteria:** Frequent nonmigrainous headaches (>6 per month on average); atypical migraine that had consistently failed to respond to treatment; migraine with prolonged aura; familial hemiplegic migraine; basilar migraine; migrainous infarction; known coronary artery disease; clinically significant arrythmias; heart failure; uncontrolled hypertension; peripheral vascular disease or Raynaud's syndrome; clinically significant active systemic, renal, hepatic, gastrointestinal, neurological, endocrine, metabolic or psychiatric disease; severe limitation of gastrointestinal misuse; regular excessive use of analgesics or ergotamine (intake on more than 2 days in 7); women who were pregnant, breastfeeding or at risk of pregnancy because of ineffective contraception; intolerance to Cafergot or its constituents, medications contraindicated with Cafergot.	**Group 1** Eletriptan 80mg (2 x 40mg tablets) + 2 placebo tablets **Group 2** Eletriptan 40mg (1 tablet) + 3 placebo tablets **Group 3** Cafergot (ergotamine tartrate 2mg, caffeine 200mg) + 3 placebo tablets **Group 4** Four Placebo tablets (results not reported in this table). Use of analgesics, antiemetics in the 6 hours before treatment, or sumatriptan or ergot derivatives in th 48 hours before treatment not permitted. 2nd dose permitted if no response within 2 hours or headache recurrence	**Headache response at 2 hours** Reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none) or 1 (mild)	**Group1:** 142/209 **Group 2:** 111/206 **Group 3:** 65/197 **p value:** <0.01 for all comparisons	**Funding:** Not reported **Limitations:** Groups not given for those who did not take treatment (n=204). **Additional outcomes:** Relief in reducing nausea, photophobia, phonophobia and vomiting 2 hours after treatment. Headache recurrence at 24 hours (defined as return of moderate or severe pain). Use of a second dose of treatment. Common adverse events. Patients withdrawing from study after 1 dose. Percentage of people stating they would take the same treatment again. **Notes:** Results relate to first dose only. Also reports baseline numbers for patients
			Pain free at 2 hours	**Group1:** 79/209 **Group 2:** 58/206 **Group 3:** 20/197 **p value:** <0.001 for all comparisons	
			Sustained Headache response at 24 hours Patients with headache response at 2 hours and neither recurrence nor use of rescue medications in 24 hours.	**Group1:** 107/210 **Group 2:** 84/209 **Group 3:** 55/201 **p values:** groups 1 or 2 to group 3: p<0.05	
			Sustained freedom from pain at 24 hours patients with pain free response at 2 hours and neither recurrence nor use of rescue medications in 24 hours.	**Group1:** 66/210 **Group 2:** 42/209 **Group 3:** 17/201 **p values:** groups 1 or 2 to group 3: p<0.01	
			Functional impairment relief at 2 hours - reduction of headache severity from grade 2 (activities severely impaired) or 3 (bed rest necessary) at baseline to	**Group1:** 130/209* (62%) **Group 2:** 107/206* (52%) **Group 3:** 61/197 (31%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients **N:** 937 randomised, 204 did not take treatment as no attack. Numbers by group given for those who took medication, not for all 937 randomised. Randomised in 2:2:2:1 sequence **Group 1** **N:** 214 **Age (mean):** 40±11 years **Gender F/M:** 193/21 **Drop outs:** NR **Group 2** **N:** 210 **Age (mean):** 40±11 years **Gender F/M:** 181/29 **Drop outs:** NR **Group 3** **N:** 203 **Age (mean):** 40±10 years **Gender F/M:** 175/28 **Drop outs:** NR **Group 4** – placebo, not reported here	within 24 hours. Results reported for 1st dose only. Rescue medication (other than sumatriptan or ergot derivatives) permitted from 2 hours after 2nd dose.	0 (able to work & function normally) or 1 (working, studying or house activities reduced)	**p value:** NR	with aura, without aura and those with & without aura. * calculated by NCGC
			Serious adverse events (not defined)	Numbers not reported. Study states incidence was similar across all groups with 2-5% of patients reporting treatment related serious adverse events.	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener et al, 2004[213] **Study design:** RCT / Crossover **Comparison:** Three arms – Aspirin vs Triptan (sumatriptan) vs NSAID (ibuprofen) **Setting:** Multicentre 16 outpatients departments **Duration of follow-up:** Two hours for assessment, 3 month period for attacks	**Patient group:** Adults with migraine with or without aura **Inclusion criteria:** Migraine meeting ICHD criteria. History of migraine of at least one year and between 1&6 attacks per month. **Exclusion criteria:** Participation in a study during 4 weeks prior to start of study; all other types of headache (including tension type headache); hypersensitivity to acetylsalicylic acid; salicylates; ibuprofen, NSAIDs or sumatriptan; peptic ulceration or gastric bleeding; haemorrhagic diathesis; disorders of kidney, liver, lung, heart or brain function; neurological disorders; hypertension, coronary heart disease and/or history of myocardial infarction; pregnant or lactating women or women of childbearing age not using contraception; drug or alcohol abuse and prohibited concomitant medication. **<u>All patients</u>** **N:** 356 randomised, 312 described as the study ITT population (took at least one dose & provided efficacy assessment); 192 described as per protocol population **Age (mean):** 38 (81% F) 79% migraine without aura **Drop outs:** 120 major protocol violations (drug intake later than 6hr after start of attack or discontinuation before all attacks	**Group 1** ASA 500mg (2 effervescent tablets) **Group 2** 400mg ibuprofen **Group 3** 50mg sumatriptan (thin gelatin encapsulated tablets) In all groups patients treated 3 migraine attacks during a study period of 3 months per patient. Patients instructed to leave a minimum of 48 hrs between consecutive study treatments. Medication only to be taken within 6hr of headache onset, when pain at least moderate or severe on a 4-point scale. Patients allowed to remedicate with any medication of their choice at any time during study, but encouraged to wait 2 hrs	**Headache response up to 2 hours** Reported at 2hrs: n (%)	**Group1:** 116/221 (52.5) **Group 2:** 127/211 (60.2) **Group 3:** 125/224 (55.8) **p value:** not significant	**Funding:** Bayer AG Germany **Limitations:** States double blind, but unclear if this is just between treatment and placebo, rather than active treatments. The tablets appear different. Crossover trial, but each patient treated a separate attack with a different drug therefore can be treated as a parallel study. Not clear what escape medication was used and by how many in each group – although encouraged to wait for 2 hours. Not all results reported. **Additional outcomes:** Outcomes also reported at 30mins, 1hr & 1hr30mins. NNT calculated for placebo adjusted response results (4 for all groups. Pain free at 24 hours (not reported). Recurrence of headache within 24 hours. Occurrence of nausea.
			Pain free at 2 hours n (%)	**Group1:** 60/221 (27.1) **Group 2:** 79/211 (33.2) **Group 3:** 83/224 (37.1) **p value:** not significant except ASA vs sumatriptan P=0.025	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	treated) **Group 1 – Acetylsalicylic acid** **N:** 222 **Age (mean(SD)):** 38.3 (12.2) **Drop outs: NR** 82.4% female 21.2% migraine with aura (78.8 without) **Duration of illness (yrs)**: with aura 19 (13.4) without aura 15 (11.3) **Group 2 - Ibuprofen** **N:** 212 **Age (mean):** 38.4 (11.8) **Drop outs: NR** 82.1% female 21.2% migraine with aura (78.8 without) **Duration of illness (yrs):** with aura 8.4 (13.9) without aura15.3(12.3) **Group 3 - Sumatriptan** **N:** 226 **Age (mean):** 38.2 (12.5) **Drop outs:** NR 80.5% female 20.4% migraine with aura (79.6 without) **Duration of illness (yrs):** Migraine with Aura 19.4 (14) Migraine without Aura 16 (12.7)	after study medication, or 12 hrs after for ergots and triptans.			Incidence of accompanying symptoms (photophobia, phonophobia & vomiting). Headache severity prior to use of escape medication. **Notes:** Predetermined randomisation code used. Sample size calculations based on headache response, 90% power P=0.05. 148 patients per treatment required. Reports ITT and per-protocol results (ITT reported here – everyone who treated at least 1 attack). Only people who treated all attacks included in per protocol analysis. Pregnant women excluded as were women of childbearing age not using contraception.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener et al, 2004[216] **Study design:** Double-blind, three arm, multicentre parallel group study **Comparison:** Triptan vs aspirin **Setting:** 42 centres in Germany **Duration of follow-up:** NR	**Patient group:** Males and females with migraine. **Inclusion criteria:** Migraine with or without aura as defined by the IHS 1988 criteria present for >1 year and a minimum average of 1 attack per month, but not more than 6 attacks per month. Able to comply with all study procedures, including the completion of diary cards, and to be able to distinguish non-migraine headache from typical migraine. At the time of the migraine attack, each of the following associated symptoms must be present: nausea, photophobia and phonophobia. Migraine headache must be of moderate or severe intensity and no aura present. **Exclusion criteria:** Participation in a study during the 30 days immediately prior to the start of the study, including the treatment of a second migraine attack, intake of analgesics or migraine drugs 24 hours before the administration of the study medication. Intake of compound analgesics, sumatriptan. Ergotamine tartrate or dihydroergotamine, codeine or barbiturates on > 10 days per month. Hypertension with diastolic BP >160mmHg. Coronary heart disease and/ or history of myocardial infarction, asthma of any origin, hypersensitivity to	**Group 1** 1 tablet sumatriptan 50 mg plus matching effervescent **Group 2** 1000mg effervescent ASA plus 1 placebo tablet **Group 3** Placebo (results not reported in this table) Patients took one dose of study medication for the treatment of a moderate or severe migraine headache within 6 hours of the start of the headache (or within 6 hours of waking if the headache was present on awakening), provided they had been free from any previous migraine for at least 24 hours. Rescue medication was permitted at any time during the course of the study, but patients were encouraged to wait until 2 hours after taking the study medication. Ergot derivatives and triptans were not permitted until 12 hours after intake of the study medication.	**Headache response up to 2 hours** (from grade 3 or 2 to grade 1 or 0) **Pain free at 2 hours**	**Group 1 (sumatriptan):** 66/135 (48.8%) * **Group 2 (ASA):** 72/146 (49.3%)* **p value:** NR **Group 1 (sumatriptan):** 33/135 (24.4%) **Group 2 (ASA):** 37/146 (25.3%) **p value:** NR	**Funding:** Bayer Vital GmbH & Co. KG, Germany **Limitations:** Allocation concealment unclear. **Additional outcomes:** Use of rescue medication. Adverse events. Headache recurrence. Percentage of patients assessing the medication as good or excellent. Remission of accompanying symptoms. **Notes:** Verbal rating scale of pain: Grade 3= severe Grade 2= moderate Grade 1= mild Grade 0= no pain

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	salicylates, urticaria or other allergic diatheses, hypersensitivity to sumatriptan and drug intake according to DSMIIIR (alcohol, drug abuse, or dependence, also in medical history). **All patients** **N:** 516 (randomised), 435 (safety population, 433 (ITT) **Drop outs:** 81 patients did not take medication; 2 did not return diary **Group 1 (sumatriptan)** **N :** No. randomised NR; 135 (efficacy analysis); 96 per protocol analysis **Age (mean (SD)):** 43.7 (12.1) **M:F:** 17.8: 82.2 **Weight (kg):** 71 (14.3) **Height (cm):** 169 (8.1) **Drop outs:** NR **Migraine with aura:** Yes: 23 (17%), No: 109 (80.8%), No remarks: 3 (2.2%) **Group 2 (ASA)** **N:** No. randomised NR; 146 (efficacy analysis); 102 per protocol analysis **Age (mean):** 41.8 (11.8) **M:F:** 88.4:11.6 **Weight(kg):** 68 (11.9) **Height (cm):** 167 (7.6) **Drop outs:** NR				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Migraine with aura: Yes: 28 (19.2%), No: 117 (80.1%), No remarks: 1 (0.7%) **Group 3 (placebo)** **N:** No. randomised NR; 152 (efficacy analysis); 106 per protocol analysis **Age (mean):** 41.9 (11.7) **M:F:** 83.6: 16.4 **Weight(kg):** 69 (13.7) **Height (cm):** 169 (7.9) **Migraine with aura:** Yes: 31 (20.4%), No: 116 (76.3%), No remarks:5 (3.3%)				

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, AE=Adverse events, ASA= acetylsalicylic acid (aspirin)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Dowson et al, 2000[233] **Study design:** Crossover RCT **Comparison:** Triptan vs antiemetic + paracetamol **Setting:** UK primary care practices **Duration of follow-up:** 6 months	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-65. Migraine began before age 50. Suffered from migraine for at least 1 year. History of at least 2 moderate or severe migraine attacks every 12 weeks, with a gap of at least 24 hours without headache between each attack. Not pregnant or breastfeeding. Using adequate contraception during the study. Capable of communicating well with study investigators and of giving informed consent. Before taking study medication, patients had to have been free of all migraine symptoms for at least 4 days and were not allowed to take any analgesics for any other existing conditions within 24 hours of a treated attack. **Exclusion criteria:** Cardiovascular conditions. Chronic renal/hepatic disease. Hypertension. Known sensitivity to either of the trial treatments. Those who had tried either treatment in the past and found it ineffective. **All patients** **N:** 204 recruited, 4 no migraine attack. 161 used at least 1 treatment; 120 (efficacy I population) used both treatments **Age (mean):** 42.8 (range: 18-62) **M/F:** 111/120 **Drop outs:** 39 (failed to attend clinic for 2nd visit, took excluded medication, defaulted on protocol).	**Group 1 -** Sumatriptan (50mg) + 2 placebo tablets **Group 2 -** Domperamol (10mg domperidone +500mg paracetamol) + Placebo capsule Each treatment used once for one attack, then crossover. **All patients** Clinical history, eligibility for entry and vital signs were measured at visit one. Thereafter, telephone contact was made with patients at 4-weekly intervals or after the first treated migraine attack. The second clinic visit was made at week 13 (or after the second migraine attack) when vital signs, adverse events and study compliance were assessed. Patients had to wait until a migraine attack was moderate to severe in intensity (i.e. sufficient to impair or disturb normal activity) before taking the study medication.	**Headache response up to 2 hours** (reduction in pain from 'severe' or 'moderate' to 'mild or no pain')	**Group 1**: 39/117 (33.3)%* **Group 2:** 43/118 (36.4)%* **p value:** NS * Calculated by NCGC	**Funding:** Servier Laboratories Ltd **Limitations:** Randomisation not described. Allocation concealment not described. High discontinuation rate. **Additional outcomes:** Reduction in pain from severe/moderate to mild/no pain within 4 hours of treatment. Relief of nausea and vomiting after 2 and 4 hours. Use of rescue medication 4-72 hours after treatment with study medication (sumatriptan and its analogues and ergotamine preparations not permitted). Adverse events (none serious). **Notes:** Patients were allowed to continue using tricyclic antidepressants and certain prophylactic medications (pizotifen, clonidine, beta-blockers or calcium channel blockers) for migraine prevention, as long as these had been used for at least 3 months and were kept constant throughout the study. Pain severity: 4 point scale.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Freitag et al, 2008[287] **Study design:** RCT **Comparison:** Triptan vs paracetamol vs combination **Setting:** 10 centres in the USA **Duration of follow-up:** 2 months	**Patient group:** Adults with migraine. **Inclusion criteria:** At least a 6 month history of migraine with or without aura according to the IHS criteria. ≥18 years old. Ability to distinguish between migraine attacks and other headache types. **Exclusion criteria:** > 6 migraine attacks per month. > 10 headache days per month. History of hemiplegic or basilar migraine. Daily/almost daily (>3/7 days) use of NSAIDs, COX-2 inhibitors or other analgesics; monoamine oxidase inhibitors or propanolol. History of, or clinical evidence of, IHD, coronary artery vasospam (including Prinzmetal's variant angina), or other significant underlying cardiovascular disease or uncontrolled hypertension or clinical evidence of significant pulmonary, renal, hepatic, endocrine, neurologic (other than migraine), psychiatric, or any other condition that would pose an additional risk or interfere with optimal participation in the study, or if they had demonstrated hypersensitivity to or experienced a serious adverse event in response to rizatriptan, acetaminophen, or any of their inactive components.	**Group 1 (Rizatriptan + acetaminophen)** Rizatriptan 10 mg and acetaminophen 1000 mg (500mgx 2 tablets) Route: oral **Group 2 (Acetaminophen)** Placebo to match rizatriptan (0 mg x 1 tablet) and acetaminophen 1000 mg (500 mg x 2 tablets) Route: oral **Group 3 (Rizatriptan)** Rizatriptan 10 mg (1 tablet) and placebo to match acetaminophen 1000 mg (0 mg x 2 tablets) Route: oral **All patients:** Treated a single attack of migraine within four hours from the onset of pain if the attack met the following criteria: migraine pain was moderate (grade 2) or severe (grade 3); migraine pain did not spontaneously resolve; and, migraine was not preceded by any prohibited concurrent medication. If the	**Headache response up to 2 hours** (pain relief-Grade 0 or 1)	**Group 1:** 43/48* (90%) **Group 2:** 30/43*(70%) **Group 3:** 33/43* (77%) **Group 1 vs 2:** **OR:** 3.71 **95% CI:** 1.20-11.54 **p value:** 0.018 **Group 1 vs 3:** **OR:** 2.49 **95% CI:** 0.77-8.08 **p value:** 0.128	**Funding:** Merck Assisted Studies Program of Merck & Co., Inc. **Limitations:** Allocation concealment not described. **Additional outcomes:** Use of other medication taken 24h before and 24h after the use of study medication. Use of rescue medication. Absence of associated symptoms at 2hours. Total migraine freedom. **Notes:** *Calculated by NCGC Randomisation: computer-generated allocation schedule to 1 of 4 treatment groups (1:1:1:1 ratio). Blinding: double-blind. <u>Pain scale</u> Grade 3: severe
			Pain free at 2 hours	**Group 1:** 23/48*(54%) **Group 2:** 11/43*(26%) **Group 3:** 17/43*(40%) **Group 1 vs 2:** **OR:** 3.48 **95% CI**:1.41-8.56 **p value:** 0.007 **Group 1 vs 3:** **OR:** 1.77 **95% CI:** 0.76-4.09 **p value:** 0.182	
			Sustained pain free at 24 hours	**Group 1:** 15/48* (32%) **Group 2:** 7/43*(16%) **Group 3:** 10/43* (23%) **Group 1 vs 2:** **OR:** 2.37 **95% CI:** 0.85-6.59 **p value:** 0.097	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients **N:** 200 (randomised), 18, no qualifying headache but study also reports 173 treated a qualifying headache **Female:** 152 (87.9%) **Race, N (%)** White: 137 (79.2%) Black: 27 (15.6%) Asian: 2 (1.2%) Hispanic: 7 (4.0%) **Age (mean):** 43.1 (SD 10.9) 20-68yrs **Drop outs:** 33 (8 loss to follow up, 18 discontinued treatment, 2 withdrew consent) **Group 1** (Rizatriptan+acetaminophen) **N:** 55 randomised; 6 no qualifying headache **Age (mean):** 41.5 **Female:** 41 (85.4%) **Race, N (%):** White 37 (77.1%), Black 8 (16.7%), Asian 0 (0%), Hispanic 3 (6.3%) **Drop outs:** 7 (1 loss to follow up, 6 discontinued treatment) **Group 2** (Acetaminophen) **N:** 48 randomised, 3 no qualifying headache **Age (mean):** 42.0 **Female:** 38 (88.4%) **Race, N (%):** White 37 (84.4%), Black 4 (9.3%), Asian 1(2.3%), Hispanic 2 (4.6%) **Drop outs:** 5 (2 loss to follow up, 3	patient awoke with a migraine headache that met the treatment criteria, the patient could use the study medication within 4 hours after awakening. Each patient was to treat a qualifying migraine attack within 2 months of randomisation. All patients were to ingest 3 tablets to treat one attack. Patients were allowed to use additional analgesic or anti-emetic rescue medication 2hours after taking study medication for a non-responsive or recurrent headache. The study consisted of 2 visits: visit 1 (pre-study/randomisation) and visit 2 (post-study).		**Group 1 vs 3:** **OR:** 1.57 **95% CI:** 0.61-4.03 **p value** 0.349	Grade 2: moderate Grade 1: mild Grade 0: no headache <u>Functional Disability</u> Grade 3: unable to perform daily activities, requires bed rest Grade 2: daily activities severely impaired Grade 1: daily activities mildly impaired Grade 0: able to perform daily activities Modified intention-to-treat (mITT): all randomised patients who had at least one pain severity rating within 2h after the initial dose.
			Sustained headache response at 24 hours	**Group 1:** 30/48* (62%) **Group 2:** 18/43*(42%) **Group 3:** 23/43* (53%)	
			Functional health status (absence of functional disability)	**Group 1:** 31/48*(65%) **Group 2:** 21/43* (49%) **Group 3:** 27/43* (62%)	
			Incidence of serious adverse events	No serious adverse events	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	discontinued treatment) **Group 3** (Rizatriptan) **N:** 48 randomised, 2 no qualifying headache **Age (mean):** 44.3 **Female:** 35 (83.3%) **Race, N (%):** White 33 (76.7%), Black 10 (23.3%), Asian 0 (0%), Hispanic: 0 (0%) **Drop outs:** 5 (2 loss to follow up, 3 discontinued treatment, 1 withdrew consent)				

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Goldstein et al, 2005[330] **Study design:** RCT **Comparison:** Paracetamol, aspirin+caffeine vs Triptan (sumatriptan) **Setting:** 8 sites (investigative sites – patients self-administered as outpatients) **Duration of follow-up:** 4 hours for assessment, no mention of time between clinic visits	**Patient group:** Migraine sufferers (with or without aura) **Inclusion criteria:** Reported an average of 1-8 migraine episodes per month that satisfied IHS diagnostic criteria for migraine with or without aura, and were of at least moderate intensity if left untreated. Subjects had to be able to distinguish migraine from other headache types at the onset of an attack. **Exclusion criteria:** Subjects reporting vomiting during more than 20% of migraine episodes or who required bed-rest during more than 50% of migraine episodes. **All patients** **N:** 188 randomised (81% F) 171 took study medication **Age (mean):** 38.1 **Drop outs:** 18 (didn't have attack) **Group 1 – ACA** **N:** 69 **Age (mean):** NR **Avg no. attacks/month:** 3.8 **No. attacks with aura:** 0.3 **Usual pain intensity (%, without treatment):** Moderate 35.3, Severe 64.7	**Group 1 – AAC** (acetaminophen 500mg, aspirin 500mg, caffeine 130mg) 2 tablets **Group 2 – Sumatriptan succinate** (25mg per tablet) 2 tablets *(Group 3 – Placebo, results not analysed here)* Hard gelatine capsules. Patient instructed to take the study medication when the first symptoms usually recognised as the beginning of a migraine attack occurred.	**Headache response up to 2 hours** (2 hour results reported as %) Also recorded at 0.25, 0.5, 0.75, 1 1.5 3 and 4 hrs post dose	**Group1:** 84 (42/50) **Group 2:** 65 (30/46) **95% CI:** NR **p value:** ≤0.05	**Funding:** Bristol Myers Squibb **Limitations:** Age not know for groups separately – or for inclusion criteria. ITT analysis stated, but reported results don't reflect this. Outcome reporting bias: Stated time to meaningful pain relief was recorded, but not reported. **Additional outcomes:** Pain intensity difference (PID) / sum of PID (4 point scale). Pain relief (5 point scale). Associated symptoms. Sustained response defined as those who were responders by 2 hrs and remained with mild or no pain till 4 hours. Recurrence and rescue medication. Global evaluation on efficacy. **Notes:** Randomisation 2:2:1 ratio (1=placebo, not included here).
			Percentage reporting serious adverse events	0 in both groups	
			Functional disability (5 point scale, % with no functional disability at 4 hours) Also recorded at 0.25, 0.5, 0.75, 1 1.5, 2, and 3hrs post dose.	**Group1:** 81 (41/50) **Group 2:** 62 (29/46) **95% CI:** NR **p value:** 0.044	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Usual attack duration without treatment(hrs, mean): 35 **Usual drug therapy:** Prescription 27.9, OTC 35.3, both 36.8 **Drop outs: NR** **Group 2 - Sumatriptan** **N:** 67 **Age (mean):** NR **Avg no. attacks/month:** 3.4 **No. attacks with aura:** 0.6 **Usual pain intensity (%, without treatment):** Moderate 35.8, Severe 64.2 **Usual attack duration without treatment(hrs, mean):** 30.2 **Usual drug therapy:** Prescription 37.3, OTC 44.8, both 17.9 **Drop outs: NR**				Computer generated random number table.

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, ACA= acetaminophen, aspirin and caffeine

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Goldstein et al, 2006[331] **Study design:** RCT **Comparison:** Paracetamol + aspirin + caffeine vs ibuprofen **Setting:** NR, multicentre **Duration of follow-up:** 4 hours	**Patient group:** Adults with migraine **Inclusion criteria:** Migraine with or without aura meeting IHS diagnostic criteria for migraine with or without aura. At least 18 years old, in good general health and had experienced a migraine attack at least once every 2 months, but no more than 6 times monthly, during the prior 12 months. Untreated attacks of at least moderate pain intensity. **Exclusion criteria:** Patients whose headache symptoms may have been caused or aggravated by recent head or neck trauma. Patients with cluster headache, specific migraine variants or other serious non-migraine causes of headache were excluded. Those who reported using analgesic drug products for headache on more than 12 days per month. **All patients NR** **Group 1 – ACA** **N:** 669 **Age (mean):** 38.3 (78.8%F, 21.1% M) **Race (%):** White 74.3, Black 20.2, Asian 0.6, Hispanic 3.9, Other 1 **Migraine type (%):** 78.6 with aura, 21.4 without aura	**Group 1 –** ACA (acetaminophen 250mg, aspirin 250mg and caffeine 65mg) 2 tablets **Group 2 -** ibuprofen 200mg (2 tablets) ***Group 3 –*** *Placebo (results not analysed here)* Patients were instructed to take study medication if headache symptom profile met the criteria for migraine and was of at least moderate intensity. They were asked not to take rescue medication for at least 2 hours, if possible.	**Time to freedom from pain** Onset of meaningful pain relief (median, minutes) **Headache response up to 2 hours (% responders)** Assumed ITT therefore n values are number randomised	**Group1:** 128.4 **Group 2:** 147.9 **95% CI**: Gp1 120,142 Gp2 135,163 **p value: 0.036** **Group1:** 67% (448/669) **Group 2:** 62% (413/666) **p value:<0.046**	**Funding:** NR **Limitations:** Exact analysis unsure (possibly ITT) **Additional outcomes:** Sum of pain relief at 2 and 4 hours. Pain intensity difference from baseline. Percentage pain free at 3 and 4 hours (in graphical form for other time-points). 4 hour weighted difference from baseline. Associated symptoms. **Notes:** Randomisation on 3:3:1 ratio (1 = placebo, not included here). Sample size based on one outcome for 665 patients per group for 90% power.

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Usual pain without treatment (%): Mild 0, Moderate 20, Severe 80 **Usual pharmacological treatment (%):** None 0.3, OTC 57, Prescription 20.6, both 22.1 **Drop outs:** 36 lost to follow up, 32 no headache **Group 2 - Ibuprofen** **N:** 666 **Age (mean):** 38.4 (81.5% F, 18.5% M) **Race (%):** White 76.6, Black 18.0, Asian 0.9, Hispanic 4.2, Other 0.3 **Migraine type (%):** 78.8 with aura, 21.2 without **Usual pain without treatment (%):** Mild 0.2, Moderate 17.7, Severe 82.1 **Usual pharmacological treatment (%):** None 0.6, OTC 55.1, Prescription 21.2, both 23.1 **Drop outs:** 38 lost to follow up, 27 no headache, 3 excluded				

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, ACA= acetaminophen, aspirin and caffeine, IHS=International headache society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Lainez et al, 2007[464] **Study design:** Randomised crossover study **Comparison:** Triptans vs ergotamine+ caffeine **Setting:** Outpatients Du**ration of follow-up:** Not reported	**Patient group:** Adults with an acute migraine attack **Inclusion criteria:** Migraine with or without aura, according to IHS criteria; between 1 & 6 attacks per month for > 1 year; diagnosed with migraine before the age of 50; aged 18 to 65. **Exclusion criteria:** Prolonged aura, familial hemiplegic migraine, migrainous infarction or vertebrobasilar migraine; Raynaud's phenomenon linked to migraine; cardiac ischemia or arrhythmias; uncontrolled hypertension; arteriosclerosis; clinically relevant abnormal findings during baseline physical examination & laboratory tests; any physical condition that might alter the pharmacokinetics of the drug; those unable to distinguish between migrainous and non-migrainous headaches; patients receiving treatment with beta-blockers, monoamine oxidase inhibitors, lithium, macrolide antibiotics, tetracyclines or antiretroviral drugs. **All patients** **N:** 272, only 229 took first study drug **Drop outs:** 43 **Group 1** **N:** 114, 104 treated 1 attack and had	**Group 1** 1st attack: Almotriptan (12.5mg) 2nd attack Ergotamine (2mg) + caffeine (200mg) **Group 2** 1st attack: Ergotamine (2mg) + caffeine (200mg) 2nd attack Almotriptan (12.5mg) 2 attacks treated in each group (one for each treatment). Both treatments encapsulated to maintain blinding. Second study drug not to be taken until 7 days had passed after 1st study drug. Rescue medication (excluding ergots and triptans) permitted for persistent moderate to severe migraine pain 2 hours after study medication. Recurrence medication (study medication for that attack) permitted for patients who initially responded to	**Pain relief at 2 hours** - reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none) or 1 (mild)	**Almotriptan:** 105*/182 (57.7%) **Ergotamine+caffeine:** 81*/182 (44.5%) **p value:** <0.01	**Funding:** not reported **Limitations:** Method of randomisation and allocation concealment unclear. Numbers randomised to each group not given. 7 day gap between first and second treatments but patients could use other medication for attacks in between – not stated how close to the second attack this would be. **Additional outcomes:** Pain relief at 90 minutes. Sustained pain relief and no adverse events. Percentage of people pain free at 2 hours after both agents. Percentage of people not pain free at 2 hours with either agent. Nausea, vomiting, photophobia & phonophobia. Number of serious adverse events, but not by drug.
			Pain free at 2 hours	**Almotriptan:** 38*/182 (20.9%) **Ergotamine+caffeine:** 25*/182 (13.7%) **p value:** <0.05	
			Sustained pain free at 24 hours (defined as pain free at 2 hours with no recurrence or use of rescue medication at 24 hours)	**Almotriptan:** 37*/182 (20.3%) **Ergotamine+caffeine:** 21*/182 (11.5%) **p value:** <0.05	
			Use of rescue medication	**Almotriptan:** 70*/182 (38.5%) **Ergotamine+caffeine:** 88*/182 (48.4%) **p value:** <0.05	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	≥1 assessment of pain intensity 89 treated 2 attacks and had ≥1 assessment of pain intensity **Age (mean±SD):** 33.15±8.8 **Gender F/M:** 97/17 **Drop outs:** NR **Group 2** **N:** 115, 107 treated 1 attack and had ≥1 assessment of pain intensity 93 treated 2 attacks and had ≥1 assessment of pain intensity **Age (mean±SD):** 33.84 ±10.1 **Gender F/M:** 102/13 **Drop outs:** NR	medication but experienced a recurrence or worsening of their migraine during the first 48 hours after taking study medication. Patients permitted to continue prophylactic medication with calcium antagonists, valproic acid or serotonin reuptake inhibitor. The dose had to be stable for at least 3 months before study entry.			**Notes:** Results relate to patients who treated 2 attacks and had ≥ 1 pain assessment outcome. ACA reported. * calculated by NCGC

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, ACA=available case analysis, IHS=International headache society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Le Jeune et al, 1999[484] **Study design:** RCT **Comparison:** Aspirin + antiemetic vs ergotamine+ caffeine **Setting:** Outpatients assumed **Duration of follow-up:** 3 months at latest	**Patient group:** Adults with migraine with or without aura **Inclusion criteria:** Migraine with or without aura according to IHS criteria, aged 18 to 65, history of migraine for at least 1 year, first attack before the age of 50, 1 to 6 moderate or severe attacks per month, at least 3 attacks in the last 3 months. **Exclusion criteria:** Known intolerance or contraindication to any study drug, pregnant or lactating women, women at risk of pregnancy with no adequate contraception. **All patients** **N:** 296 **Drop outs:** 28 **Group 1** **N:** 151 **Age (mean±SD):** 37±11 **Gender F/M:** 127/24 **Drop outs:** 15 **Group 2** **N:** 145 **Age (mean±SD):** 37±11 **Gender F/M:** 122/23 **Drop outs:** 13	**Group 1-** One sachet of calcium carbasalate 1,144.8mg (equivalent to 900mg acetylsalicylic acid) plus 10mg metoclopramide and 1 placebo tablet of ergotamine+ caffeine. 15 days after treatment of 1st attack return visit to investigator. Another treatment pack of same treatment given. **Group 2 -** One tablet of ergotamine (1mg) plus caffeine (100mg) and 1 placebo sachet. Another treatment pack of same treatment given. Concomitant treatment with salicylates, ergotamine tartrate, NSAIDs, macrolides, heparin, vitamin K antagonists, neuroleptic or antiepileptic drugs not allowed during the study. Migraine prophylaxis not allowed unless started at least 3 months before inclusion and without any modifications throughout study.	**Headache relief at 2 hours after 1st attack**	**Group1:** 73/134 **Group 2:** 48/132 **p value:** <0.003	**Funding:** NR **Limitations:** Randomisation and allocation concealment unclear. **Additional outcomes:** Severity of 1st and 2nd attacks for headache, nausea and vomiting. Number of patients experiencing at least 1 adverse event. Number of patients experiencing specific adverse events. **Notes:** ITT population defined as all randomised patients who took the study drug. Headache relief: reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none) or 1 (mild). Patients given diaries to record results.
			Headache relief at 2 hours after 2nd attack	**Group1:** 69/115 **Group 2:** 52/117 **p value:** <0.02	
			'Cure' at 2 hours after 1st attack (defined as 'complete relief' unclear if this means pain free or all symptoms)	**Group1:** 27/134 **Group 2:** 11/132 **p value:** <0.006	
			'Cure' at 2 hours after 2nd attack (defined as 'complete relief' unclear if this means pain free or all symptoms)	**Group1:** 28/115 **Group 2:** 20/117 **p value:** not significant	
			Use of rescue medication within 24 hours of 1st attack	**Group1:** 49/134 **Group 2:** 61/132	
			Use of rescue medication within 24 hours of 2nd attack	**Group1:** 38/115 **Group 2:** 53/117	
			Recurrence of migraine at 24 hours after initial headache relief after 1st attack	**Group1:** 61/134 **Group 2:** 44/132	
			Recurrence of migraine at 24 hours after initial headache relief after 2nd attack	**Group1:** 56/115 **Group 2:** 46/117	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, 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: Misra et al, 2007[562] **Study design:** RCT **Comparison:** Triptan vs NSAID **Setting:** Tertiary care teaching hospital **Duration of follow-up:** 1 month	**Patient group:** Men and women with migraine **Inclusion criteria:** >12 years. Diagnosis on the basis of IHS criteria. <8 attacks/ month **Exclusion criteria:** Mild (grade 1) headache. Headache with recurrent vomiting. > 8 attacks per month. Pregnant or lactating mothers. Those on oral contraceptives. History of drug allergy. Intractable hypertension. Renal/ hepatic failure. Coronary artery disease. Pulmonary, psychiatric or other neurological diseases **All patients** **N:** 165 (randomised), 155 (treated) **Age (mean):** 30.5 range 16-58 **Gender F/M:** 106/49 **Drop outs:** 10 **Group 1 (rizatriptan)** **N:** 57 **Age (mean±SD):** 29.15±8.7, 36 F **No. of attacks:**4.6±0.13 **Duration (months):** 60.8±60.7 **Functional disability:** I: 3, II: 28, III: 21, IV: 1 **Severity of headache:** Moderate: 28, Severe: 25 **Duration of attack (hours):** 17.0±10.3	**Group 1 (rizatriptan)** Rizatriptan 10mg **Group 2 (ibuprofen)** ibuprofen 400mg **Group 3 (placebo)** Not reported in this table **All patients** Advised to take study medication if the headache was moderate to severe. Rescue medication piroxicam 20mg was advised if moderate to severe headache persisted 2h after initial medication.	**Headache response up to 2 hours** (severity reduced to grade 1 or 0) **Freedom from pain at 2 hours** **Functional disability at 2 hours** 0=normal, I=daily activity mildly impaired, II=daily activity moderately impaired, III=daily activity severely impaired, IV= inability to perform daily activities requiring bed rest **Severe adverse events**	**Group1:** 39/53 (73%) **Group 2:** 28/53 (53.8%) **p value:** 0.0001 **Group1**: 20/53 (37.7%) **Group 2:** 16/53 (30.8%) **p value:** 0.38 **Group1:** Before treatment: 2.38±0.63 2h after treatment: 1.04±0.98 Z value: -5.75 **p value:** 0.0001 **Group 2:** Before treatment:2.29±0.87 2h after treatment:1.27±1.10 Z value: -5.57 **p value:** 0.0001 **Group1:** 0 **Group 2:** 0	**Funding:** NR **Limitations:** Allocation concealment not reported. Efficacy of treatments based on 2 or more attacks; unclear how many attacks were treated (possible double counting but n values imply averages were used). **Additional outcomes:** Headache score. Associated symptom score. 24 hour headache relapse. Use of rescue medication. Adverse events. **Notes:** Headache severity Grade I= mild Grade II= moderate Grade III= severe

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs:4 **Group 2 (ibuprofen)** **N:** 55 **Age (mean±SD):** 30.5±10.6, 38 F **No. of attacks:**4.2±1.2 **Duration (months):** 65.7±68.3 **Functional disability:** I: 10, II: 21, III: 17, IV: 4 **Severity of headache:** Moderate: 28, Severe: 24 **Duration of attack (hours):** 13.6±8.8 **Drop outs:** 3 **Group 3 (placebo)** **N: 53** **Age (mean±SD):** 31.78±9.9, 40 F **No. of attacks:**4.5±1.4 **Duration (months):** 63.1±57.0 **Functional disability:** I: 4, II: 22, III: 23, IV: 1 **Severity of headache:** Moderate: 31, Severe: 19 **Duration of attack (hours):** 14.8±10.9 Drop outs: 3				

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Myllyla et al, 1998[577] **Study design:** RCT **Comparison:** Triptan vs NSAID **Setting:** Patients' homes 5 neurological centres in Finland (one hospital department and 4 neurology clinics) **Duration of follow-up:** NR	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-65 years. Met diagnostic criteria for migraine with or without aura as defined by the IHS. History of migraine for >1 year. >1 but <4 attacks per month, characterised by severe or moderate headache. **Exclusion criteria:** NR **All patients** **N:** 154 (unclear if this is no. randomised), 141 (available for analysis) **Group 1(sumatriptan)** **N:** 46 **Age (mean):** 40 ±10.0 **Gender F/M:** 39/7 (85%/15%) **Migraine, No. (%):** Without aura: 37 (80%), With aura: 2 (4%), With and without aura: 7 (15) **Drop outs**: NR **Group 2 (tolfenamic acid)** One patient in this group was randomised twice, demographic	**Group 1 (sumatriptan)** Sumatriptan 100mg (Imigran) **Group 2 (tolfenamic acid)** tolfenamic acid rapid release 200mg (Clotam Rapid) **Group 3 Placebo** (results not reported in this table) **All patients** Run-in period: 1 migraine attack treated at home with usual medication, followed by 2 successive attacks with trial medication. Medicine for 3 attacks was provided in order to be able to replace an incompletely recorded attack. 1st dose to be taken at the first symptoms of an attack. If symptoms had not improved, patient allowed an extra dose of test medicine after1	**Headache response up to 2 hours** (grades 3 and 2 to grades 1 and 0)	**Attack 1** **Group1:** 33/42 (79%) **Group 2:** 33/43 (77%) **p value:** 0.85 **95% CI:** -22%, 18% Attack 2 Group 1: 25/39 (64%) Group 2: 30/43 (70%) p value: NS	**Funding:** A/S GEA Farmaceutisk Fabrik **Limitations:** Some treated attacks were mild. Allocation concealment not described. **Additional outcomes:** Use of rescue medication. Headache severity at 2 hours. Extra dose of test medicine after 1 hour. Good or excellent effect. Associated symptoms. Recurrent headache. Headache relief at 2 hours across all attacks. Headache severity at 2 hours across all attacks. **Notes:** Randomisation: computer-generated; blocks of 6. In each block, 2 patients were assigned to placebo, 2 to R-TA, and 2 to sumatriptan. Complete blocks were
			Pain free at 2hours	**Attack 1** **Group 1:** 21/42(50%) **Group 2:** 16/43 (37%) **p value:** NS Attack 2 Group 1: 10/39 (26%) Group 2: 7/43 (16%) p value: NS	
			Severe adverse events	**Group 1:** 0 **Group 2:** 3 (1 patient had chest pressure, paraesthesia and flushing; 1 patient had fatigue; 1 patient had headache).	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	data of this patient was only used once in the calculations **N:** 47 **Age (mean±SD):** 39±8.3 **Gender F/M:** 42/4 (91%/9%) **Migraine, No. (%):** Without aura: 34 (74%), With aura: 2 (4%), With and without aura: 10 (22%) **Drop outs:** NR **Group 3(placebo)** **N:** 48 **Age (mean±SD):** 39±9.5 **Gender F/M:** 45/3 (94%/6%) **Migraine, No. (%):** Without aura: 31 (65%), With aura: 4 (8%), With and without aura: 13 (27%)	hour. Escape medication permitted after 2 hours (paracetamol, ASA, another NSAID, prochlorperazine or diazepam). 48 hours was required between the treatments of 2 successive attacks.			assigned to centres, and patients were entered in ascending sequential order of patient number at each centre. Double-blind. <u>Headache severity</u> 0= no pain 1= mild 2= moderate 3= severe pain Note if subgroup results reported.

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: The Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group, 1992[785] **Study design:** Double-blind, double-dummy, equally randomised, parallel-group design **Comparison:** Triptan vs aspirin + antiemetic **Setting:** 37 centres including neurology departments, private clinics and GP surgeries in Austria, Denmark, FR Germany, France, New Zealand, Sweden, Switzerland, UK	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-65. At least a 1 year history of 1-6 severe or moderately severe migraine attacks per month. Ability to recognise early signs of an attack. Not taking prophylactic medication. Fulfilled the IHS criteria for migraine with or without aura. **Exclusion criteria:** Participation in a previous sumatriptan trial. History of narcotic or ergotamine abuse or regular requirement of these drugs. Existing alcohol or drug abuse. Hypersensitivity to, intolerance of, or contradiction for taking aspirin plus metoclopramide. Lactation. Pregnancy. Inadequate contraceptive measures. History suggestive of IHD, uncontrolled hypertension, serious psychiatric illness or other systemic disease. Need for continuing migraine prophylaxis. Participation in >3 clinical trials within the previous 3 years. **All patients** **N:** 382 (randomised), 358 (treated an attack), 355 (evaluable for at least 1 migraine attack) **Group 1 (sumatriptan)** **N:** No. randomised not reported, 172	**Group 1** Sumatriptan 100mg dispersable tablet **Group 2** 3 soluble 300mg aspirin tablets plus one 10mg metoclopramide tablet **All patients** Patients treated up to 3 migraines at home with study medication over a 3-month period and visited the clinic monthly. At the first visit patients gave details of their migraine history and any relevant clinical history and underwent a physical and neurological examination. A blood sample was taken for haematology and biochemistry test, a urine specimen was obtained for analysis, and a baseline, 12-lead ECG was recorded. At this point, all migraine prophylaxis was discontinued for at least 2	**Headache response up to 2 hours** (from grade 3 or 2 to grade 0 or 1) 3 attacks; attack 1 only reported **Pain-free at 2 hours** 3 attacks; attack 1 only reported **Functional health status** (% of patients able to resume their usual activities within 6 hours)	**Group 1:** 74/133 (56%) **Group 2:**62/138 (45%) **p value:** 0.078 **Group 1:** 35/133 (26%) **Group 2:** 19/138(14%) **p value:** <0.001 **Group 1:** 50% **Group 2:** 30% **p value:** 0.003 Denominator unclear	**Funding:** Glaxo **Limitations:** Allocation concealment not described. Unexplained high drop-out rate. **Additional outcomes:** Headache relief for attacks 2 and 3. Proportion of patients pain-free at 2 hours. Incidence of nausea, vomiting, photophobia and/or phonophobia. Requirement for rescue medication at 2 hours. Duration of migraine attack. Time to complete recovery. Interruption of normal activity. Effect of migraine type on relief. Effect on relief of the interval between onset of attack and taking medication. Recurrence of headache within 48 hours. Onset of headache improvement.

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Duration of follow-up: 48h washout period; monthly visits for max. of 3 months	treated an attack **Age (mean±SD):** 42±12 **Gender F/M:** 129/43 **Migraine type:** Without aura: 126, With aura: 28, Both: 18 **Median duration of migraine history, months:** 240 **Frequency of headache**: <1 attack/ month: 4, 1-3 attacks/month: 113, Weekly: 55, Daily: 0 **Drop outs:** NR **Group 2 (aspirin + metoclopramide)** **N:** No. randomised not reported, 183 treated an attack **Age (mean±SD):** 39±11 **Gender F/M:** 154/29 **Migraine type:** Without aura: 129, With aura: 32, Both: 22 **Median duration of migraine history, months:** 216 **Frequency of headache:** <1 attack/ month: 4, 1-3 attacks/month: 127, Weekly:52, Daily: 0 **Drop outs:** NR	weeks prior to use of the study medication. Details of each attack were recorded on a diary card. Not permitted to take the test medication within 24 hours of any ergotamine-containing preparation. Rescue medication permitted (not containing ergotamine, aspirin or metoclopramide). Instructed to leave a minimum interval of 48 hours between consecutive study treatments to ensure that a new attack and not a recurrence was treated each time.			Adverse events. Patients' comments on treatment. **Notes:** Headache severity scale 0= no pain 1= mild pain 2= moderate pain 3= severe pain Note if subgroup results reported. Randomisation: blocked (n=6), each block containing equal allocations to the 2 treatment combinations. Complete blocks were allocated to centres and patients were assigned in order of registration for the study.

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Schoenen et al, 2008 [705] **Study design:** Double-blind, double-dummy, crossover study **Comparison:** Triptan + NSAID vs triptan + placebo **Setting:** outpatients 8 centres in Belgium **Duration of follow-up:** 60 days	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-65 years. Minimum 12 months' history of migraine with or without aura according to IHS criteria. Experienced 2-6 attacks in each of the 2 months preceding trial entry. Migraine onset before age 50 years. **Exclusion criteria:** Pregnancy. Currently on NSAID regimen. Unable to distinguish between migraine and non-migraine headaches. History or evidence of substance abuse or addiction. Any concurrent illness, including dermatological disease, likely to jeopardise trial participation. **All patients** N: 112 (randomised) 90 (ITT) **Group 1 (almotriptan + aceclofenac / almotriptan + placebo)** **N:** 57 **Age mean (SD):** 37.65 (10.91) **BMI, mean (kg/m²):** 23.08 (3.47) **Gender F (%):** 51 (89%) **Time since 1st migraine attack, mean SD (years):** 17.72 (12.46) **Age at first migraine attack, mean SD**	**Group 1 (almotriptan, aclofenac / almotriptan, placebo)** Oral almotriptan 12.5mg + aclofenac 100mg **Group 2 (almotriptan, placebo / almotriptan, aclofenac)** almotriptan 12.5 mg + placebo **All patients** Asked to treat moderate or severe attacks. One migraine attack treated with each combination. Washout period of at least one week between the two attacks. Any existing prophylactic migraine treatment, except NSAIDs was permitted provided there was no change to the patient's regimen during the study. Patients must not have taken NSAIDs or any other acute anti-migraine treatment within 24h prior to study treatment. Two similar tablets taken by each patient per attack.	**Headache response up to 2 hours** (headache relief at 1 hour) % of attacks **Pain free at 2 hours** % of attacks **Remaining pain-free 24 hours** after treatment % of attacks **Serious adverse events**	**Group 1:** 35.5% **Group 2:** 38.2% **p value:** NS **Group 1:** 40.7% **Group 2:** 29.1% **p value:** 0.007 **Group 1:** 31.4% **Group 2:** 19.8% **p value:** 0.007 **Group1:** 0 **Group 2:** 0	**Funding:** NR **Limitations:** Allocation concealment unclear. Selective outcome reporting- some outcomes reported in graph only but no figures provided. **Additional outcomes:** Pain free at 0.5,1&2 hours. Prevalence of allodynia in the overall patient population and across the 2 migraine attacks. The influence of migraine attack severity on allodynia prevalence at baseline. Influence of allodynia and pain intensity at time 0 on headache relief rates at 1 and 2 h, and on 2h and sustained pain-free rates. Adverse events. Headache recurrence. Migraine associated symptom relief. 2 hour pain relief (graph only). **Notes:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	(years):20.5 (9.92) **No. of patients with 3-5 attacks per month over previous 2 month (%):**32 (56) **Drop outs:** NR **Group 2 (almotriptan + placebo / lmotriptan + aclofenac)** **N:** 33 **Age mean (SD):** 38.33 (10.12) **BMI, mean (kg/m²):** 24.80 **Gender F (%):** 26 (79) **Time since 1st migraine attack, mean SD (years):**16.24 (11.92) **Age at first migraine attack, mean SD (years):**22.57 (11.48) **No. of patients with 3-5 attacks per month over previous 2 month (%):** 24 (73) **Drop outs:** NR				Randomisation: 2:1 ratio Crossover trial, but treated as a parallel group study for analysis – one attack treated with each medication. Double-blind.

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Smith et al, 2005[743] **Study design:** Multicentre, randomised, double-dummy, double-blind, placebo-controlled 4 arm study **Comparison:** Triptan vs NSAID vs combination **Setting:** 32 centres in the USA **Duration of follow-up:** 24-72 hours	**Patient group:** Adults with migraine **Inclusion criteria:** ≥18 years. Migraine with or without aura according to IHS criteria (1988 and 2004). History of at least 2, but not more than 6 migraine attacks per month during the preceding 12 months. A history of tolerating oral treatment with a 5-HT agonist (triptans or ergotamine derivatives) for migraine. **Exclusion criteria:** NR **All patients** **N:** 1138 (randomised) 166 (not treated), 972 (treated), 965 (efficacy population) **Group 1 (sumatriptan 50mg+naproxen sodium 500mg)** **N:** 251 **Age, mean (SD):** 42.5 (11.0) **Gender F/M:** 235/16 **Migraine duration (years):** 21.0 **Migraine type:** With aura(%): 8, Without aura (%): 77, With/without aura (%): 15 **Drop outs:** 0 **Group 2 (sumatriptan 50mg)**	**Group 1 (triptan + NSAID)** One sumatriptan 50mg E capsule and one tablet of naproxen sodium 500mg. **Group 2 (triptan)** One sumatriptan 50mg E capsule and one placebo tablet (matching the naproxen sodium tablet). **Group 3 (NSAID)** One placebo capsule (matching the sumatriptan 50mg E capsule) and one tablet of naproxen sodium 500mg. **Group 4 (placebo)** One placebo capsule and one placebo tablet (results not reported in this table). **All patients** Instructed to treat a single migraine headache of moderate or severe pain intensity. Following onset of a moderate to severe migraine attack, subjects completed study diary cards just prior to taking study medication. Additional diary card assessments were	**Headache response up to 2 hours**	**Group 1:** 163/250* (65%) **Group 2:** 111/226* (49%) **Group 3:** 114/248* (46%) **P value (group 1 vs group 2):** <0.01 **P value (group 1 vs group 3):** <0.01	**Funding:** Pozen Inc. **Limitations:** Randomisation and allocation concealment: NR. **Additional outcomes:** Use of rescue medication. Pain response at 30 mins, 1 hour and 4 hours. Pain free at 30 mins, 1 hour, 4 hours. Headache recurrence. Migraine-associated symptom responses. Adverse events. **Notes:** *Calculated by NCGC <u>Headache severity scale</u> 0= no headache pain 1= mild headache pain 2= moderate headache pain 3= severe headache pain
			Pain free at 2 hours	**Group1:** 85/250 *(34%) **Group 2:** 46/226*(20%) **Group 3:** 45/248 *(18%) **p value (group 1 vs group 2):** ≤0.01 **p value (group 1 vs group 3):** ≤0.01 **p value (group 1 vs group 2):** ≤0.01	
			Sustained headache response at 24 hours	**Group1:**115/250 *(46%) **Group 2:** 66/226* (29%) **Group 3:**62/248 *(25%) **p value (group 1 vs group 2):** <0.01 **p value (group 1 vs group 3):** <0.01 **p value (group 2 vs group 3):** <0.01	
			Serious adverse events	**Group1:** 0 **Group 2:** 0 **Group 3:** 0	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 229 **Age (mean):**41.2 **Gender F/M:** 208/21 **Migraine duration (years):** 21.5 Migraine type: With aura(%): 8, Without aura (%):79, With/without aura (%): 12 **Drop outs:** 3 **Group 3 (naproxen sodium 500mg)** **N:** 250 **Age (mean):**42.1 **Gender F/M:** 223/27 **Migraine duration (years):** 19.6 **Migraine type:** With aura(%): 10, Without aura (%): 73, With/without aura (%): 18 **Drop outs:** 2 **Group 4 (placebo)** **N:** 242 **Age (mean):** 41.2 **Gender F/M**: 214/28 **Migraine duration (years):** 20.0 **Migraine type:** With aura(%): 11, Without aura (%): 71, With/without aura (%): 19 **Drop outs**: 0	subsequently recorded at 15 minute intervals for up to 2 hours after dosing, and at 30 minute intervals between 2 and 4 hours after dosing. Rescue medication was permitted no sooner than 2 hours after dosing.			

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Tfelt-Hansen et al, 1995[780] **Study design:** Double-blind, randomised, 3 parallel group study **Comparison:** Triptan vs aspirin + antiemetic **Setting:** Patients' homes. 68 centres in Belgium, France, Denmark and the Netherlands **Duration of follow-up**: 8 weeks	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-65 years. Met IHS criteria for migraine with or without aura. History of migraine of >1 year. 2-6 attacks per month within the last 3 months. **Exclusion criteria:** NR **All patients** **N:** 421 (randomised), 385 (treated 1 attack), 327 (treated 2 attacks) **Drop outs:** NR **Group 1(sumatriptan)** **N:** 139, 122 had data for 1 attack, 105 treated 2nd attack **Age (mean):** 39 (18-58) **Gender F/M**: 108/31 **Group 2_(LAS+MTC)** **N:** 145, 137 had data for 1 attack, 120 treated a 2nd attack **Age, mean (range):** 40 (18-62) **Gender F/M:** 113/32 **Group 3 (Placebo)** **N:** 137, 126 t had data for 1 attack, 102 treated a 2nd attack **Age, mean (range):** 39 (18-63) **Gender F/M**: 106/31	**Group 1(sumatriptan)** Oral sumatriptan 100mg **Group 2 (LAS+MTC)** 1620mg lysine acetylsalicylate (equivalent to 900mg of aspirin) and 10mg of metoclopramide. **Group 3 (Placebo)** Results not reported in this table. Two consecutive attacks with moderate or severe headache, grade2-3 on the severity scale were evaluated. Patients were treated at home over a period of 8 weeks with a monthly control visit. Rescue medication was allowed (except for ergot alkaloids or morphinomimetic drugs) if the headache was inadequately controlled after 2 hours.	**Headache response up to 2 hours**	**1st attack** **Group1:** 63/119 (53%) **Group 2**: 76/133 (57%) **p value:** 0.50 **95% CI:** +17 to -8 2nd attack Group1: 56/102 (55%)* Group 2: 51/ 119(43%)* p value: 0.08	**Funding:** NR **Limitations**: Randomisation: unclear Allocation concealment: unclear. **Additional outcomes**: Use of rescue medication. Headache recurrence within 24 h after an initial decrease or disappearance at 2h. Adverse events. Relief of nausea. Good or excellent effect as rate by patients. **Notes:** <u>Headache severity</u> 0= no pain 1= mild 2= moderate 3= severe
			Pain free at 2 hours	**1st attack** **Group1:** 36/122 (30%) **Group 2:** 29/135 (22%) **P value:** NS 2nd attack Group1: 35/105 (33%) Group 2: 28/119 (24%) P value: NS	
			Serious adverse events (ITT group)	**Group1:** 1 **Group 2:** 2	
			Adverse events necessitating premature withdrawal from the trial	**Group1:** 4 (3.2%) **Group 2:** 1 (0.7%)	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, 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: Touchon et al, 1996[798] **Study design:** Randomised crossover study **Comparison:** Triptan vs dihydro-ergotamine **Setting:** Outpatient **Duration of follow-up:** Not reported	**Patient group:** Adults with migraine **Inclusion criteria:** Men and women aged 18-65, at least 1 year history of 1 to 6 migraine attacks per month, able to differentiate migraine attacks from other types of headache, IHS criteria for migraine with or without aura, usually experienced frequent and disabling migraine attacks with sever/moderate headache. **Exclusion criteria:** Lactation, pregnancy or inadequate contraception, history suggestive of ischemic heart disease, uncontrolled hypertension or other systemic disease, drug or alcohol abuse, contraindications to the use of dihydroergotamine, hypersensitivity to or intolerance of sumatriptan or dihydroergotamine. **All patients** **N:** 317, 289 treated 1st attack, 266 treated 2nd attack as well **Drop outs:** 51 **Group 1** **N:** No. randomised NR, 145	**Group 1** 1st attack Sumatriptan & placebo DHE 2nd attack Dihydroergotamine (DHE) & placebo Sumatriptan **Group 2** 1st attack DHE & placebo Sumatriptan 2nd attack Sumatriptan & placebo DHE 2 attacks treated in each group (1 per treatment) <u>Drugs</u> Sumatriptan: 6mg subcutaneous injection into thigh from pre-filled syringe with auto injector device. Dihydroergotamine (DHE) nasal spray (1 spray of 0.5mg in each nostril). Patients taking DHE had the option to take a 2nd dose after 30 minutes 1st if headache not completely relieved. To maintain blinding patients in Sumatriptan group took a second dose of placebo DHE.	**Headache response at 2 hours** reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none) or 1 (mild)	Data not reported. States Sumatriptan significantly better than DHE **p value:** <u>≤</u> 0.001	**Funding:** Glaxo Wellcome **Limitations:** Details on randomisation and allocation concealment not provided. No mention of a washout period. Event rates not provided, calculated from percentages. Patients on DHE permitted to take a 2nd dose if inadequate headache relief, patients on Sumatriptan not permitted to take 2nd dose. **Additional outcomes:** Nausea, vomiting, photophobia & phonophobia relief at 2 hours. 'meaningful' (undefined) relief of attack, rating of treatment efficacy by patients (5 point
			Pain free at 2 hours reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none)	Data not reported. States Sumatriptan significantly better than DHE **p value:** <u>≤</u> 0.001	
			Sustained headache response at 24 hours patients with headache relief at 2 hours and neither recurrence nor use of rescue medications in 24 hours.	**Sumatriptan:** 144*/266 (54%) **DHE:** 104*/266 (39%) **p values:** <0.001 * number calculated by NCGC	
			Use of rescue medication	**Sumatriptan:** 74*/266 (28%) **DHE:** 112*/266 (42%) **p values:** <0.001 * number calculated by NCGC	
			Use of 2nd dose of DHE (or placebo if using active Sumatriptan)	**Sumatriptan:** 146*/266 (55%) **DHE:** 226*/266 (85%) **p values:** <0.001 * number calculated by NCGC	
			Relief of clinical	Numbers unclear.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	treated 1st attack, 133 treated 2nd attack as well **Age (mean±SD):** 42±10 (n=133)* **Gender F/M:** 119/14 (n=133)* **Drop outs:** NR **Usual severity of headache:** moderate 37, severe 96 (n=133)* **Group 2** **N:** No. randomised NR, 144 treated 1st attack, 133 treated 2nd attack as well **Age (mean±SD):** 42±10(n=133)* **Gender F/M:** 111/22 (n=133)* **Drop outs:** NR **Usual severity of headache:** moderate 32, severe 101 (n=133)* * relates to patients who treated 2 attacks only	Patients instructed to prepare both treatments (active & placebo) then to administer within 1 minute of each other. Rescue medication permitted if migraine symptoms not relieved after two hours. Ergotamine containing medications, DHE or Sumatriptan not permitted as rescue medications. Prophylactic medication excluding oral DHE permitted provided dosage remained unchanged during study.	**disability** – reduction of functional ability from 2 (functional/working ability severely impaired) or 3 (bed rest required) to 0 (able to function normally) or 1 (functional/working ability impaired to some degree)	Reports 63% of patients in both groups were severely disabled or required bed rest pre-treatment. Reduction in disability significantly less in DHE group at all time points. **p values:** <0.001	scale). Number of adverse events. Patients withdrawing from study due to adverse events. **Notes:** Outcome data relates to all patients who completed treatment for 2 attacks.

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IHS=International Headache Society, DHE=dihydroergotamine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Winner et al, 1996[857] **Study design:** RCT **Comparison:** Triptan vs dihydro-ergotamine **Setting:** In patient clinic Dura**tion of follow-up:** 24 hours	**Patient group:** Migraine with or without aura. **Inclusion criteria:** Migraine with or without aura according to IHS criteria for at least 1 year; 1 to 6 moderate or severe attacks per month in the preceding 6 months; duration of migraine to be treated less than 12 hours, excluding aura; resolution of all previous migraine events within 72 hours with no permanent neurologic dysfunction; screening diastolic blood pressure of 90mmHg or less. Premenopausal women who were not surgically sterile or using an acceptable method of birth control were required to have negative results of a serum pregnancy test immediately before treatment. **Exclusion criteria:** History of chronic tension type or cluster headache, hemiplegic, aphasic or basilar migraine; duration of aura longer than 60 minutes; active psychiatric or neurologic disorders other than migraine; peripheral occlusive vascular disorders, including coronary artery disease; current use of macrolide antibiotics; significant hepatic or renal impairment; history of repeated treatment failures with hypersensitivity to sumatriptan,	**Group 1** Sumatriptan (6mg) succinate injected subcutaneously into lateral aspect of thigh. **Group 2** Dihydroergotamine (DHE) (1mg) mesylate injected subcutaneously into lateral aspect of thigh. Patients receiving prophylactic treatment for migraine were permitted no change in the medication for at least 2 weeks before study dosing: <u>Prophylactics in Sumatriptan group</u> Calcium channel blockers: 9 Beta blockers: 16 Tricyclic derivatives: 21 <u>Prophylactics in DHE group</u> Calcium channel blockers: 14 Beta blockers: 18 Tricyclic derivatives: 28 Use of any form of ergot alkaloid or sumatriptan prohibited in 72 hours preceding drug administration. Use of antiemetics and narcotic	**Headache relief at 2 hours** - reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none) or 1 (mild)	**Group 1:** 128*/150 (85.3%) **Group 2:** 106*/145 (73.1%) **p value:** <0.001	**Funding:** Sanchez Pharmaceuticals **Limitations:** Method of randomisation not reported and no mention of allocation concealment. Nurse administering treatment was not blinded to interventions. Unclear if investigator was blinded to patient characteristics, they were blinded to treatment. **Additional outcomes:** Pain relief at 3 & 4 hours. Improvement in functional status at 3 & 4 hours. Recurrence of headache at 24 hours; nausea; emesis; number of adverse events; physician's global evaluation of drug effectiveness. Proportion of patients pain free at 24 hours (unclear if efficacy population).
			No receiving 2nd dose of treatment – patients without relief after 2 hours received a second dose of study drug.	**Group 1:** 23/150 **Group 2:** 43/145 **p value:** NR	
			Improvement in functional status at 2 hours – 3 categories: Able to function normally; "Struggle to carry on"; "Too ill to do anything".	**Group 1:** 127*/150 (84.7%) **Group 2:** 99*/145 (68.3%) **p value:** <0.001	
			Improvement in functional status at 4 hours – 3 categories: Able to function normally; "Struggle to carry on"; "Too ill to do anything".	**Group 1:** 119*/150 (79.3%) **Group 2:** 104*/145 (71.5%) **p value:** NS Unsure of denominators at 24 hours	
			Improvement in functional status at 24 hours – 3 categories: Able to	**Group 1:** 121*/150 (80.7%) **Group 2:** 128*/145 (88.3%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	ergotamine or dihydroergotamine in any dosage form; known physical or psychological dependence on addictive agents; chronic use (>3 days/week) of opioid or other analgesic; use of serotonin reuptake inhibitors. **All patients** **N:** 310 **Drop outs:** 15 **Group 1** **N:** 158 **Age (mean):** 41.5 (22-55) **Functional status:** Able to function normally - 0; "Struggle to carry on" – approx 2 thirds; "Too ill to do anything" – approx 1 third **Drop outs:** 8 **Group 2** **N:** 152 **Age (mean):** 40.5 (20 to 63) **Functional status:** Able to function normally - 3; "Struggle to carry on" – approx 2 thirds; "Too ill to do anything" – approx 1 third **Drop outs:** 7	analgesics was prohibited in 24 hours preceding drug administration. At 60 minute assessment intramuscular prochlorperazine edisylate (10mg) or, if contraindicated, metoclopramide hydrochloride (10mg) could be given for emesis. No other medications permitted. Patients discharged 2 hours after treatment if pain relieved. Those without relief 1 hour after 2nd dose could be given rescue medication of physician's choice but not ergotamines, dihydroergotamine, sumatriptan or steroids.	function normally; "Struggle to carry on"; "Too ill to do anything". **Serious adverse events**	**p value 2:** NS Unsure of denominators at 24 hours **Group 1:** 0/150 **Group 2:** 0/145 **p value:** NS	**Notes:** * calculated by NCGC Patients attended pre-treatment screening then told to return to clinic when they next experienced a moderate or severe headache.

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