| Study details | Patients | Interventions | Outcome measures | Effect size | Comments |
|---|---|---|---|---|---|
| **Author & Year:** El Amrani, 2002[254]<br><br>**Study design:** RCT<br><br>**Setting:** NR (16 European centres; France, Belgium, Netherlands)<br><br>**Comparison:** Sodium valproate vs placebo<br><br>**Duration of follow-up:** 2 weeks | **Patient group:** Males aged 18-70 and post menopausal women<br><br>**Inclusion criteria:** Patients with episodic or chronic cluster headache according to IHS, with 1-3 attacks per day.<br><br>**Exclusion criteria:** Drug or alcohol abuse, liver or kidney disease, psychiatric disorders, intake of antidepressants, neuroleptics and contraindications to sodium valproate including abnormal hepatic trans-aminases. No prophylactic treatment should have been used in the 2 weeks prior to first visit or in preceding 4 weeks in the case of lithium prophylaxis<br><br>**<u>All patients</u>**<br>**N:** 96<br>**Drop outs:** 6 (see limitations)<br><br>**<u>Group 1 SV</u>**<br>**N:** 50<br>**Age (mean):** 47.0+/-11.3<br>**Drop outs:** 4 (8%)<br>**Sex (M/F):** 44 (88%)/6 (12%)<br>**Chronic cluster headache:** 11 (22%)<br>**Episodic cluster headache:** 37 (74%)<br>**Unspecified:** 2 (4%)<br>**Mean duration of previous cluster** | **Group 1 Sodium valproate 500mg release tablets**<br>Dose: 1-2g/ day. Day 1-3 patients received 2 tablets (1g/ day) in the evening. From day 4-8 according to clinical status one tablet could be added on the morning. From day 9 onwards a fourth tablet was added so the dose remained unchanged from day 9-15.<br><br>**Group 2 - Placebo tablet identical to intervention in shape and colour**<br><br>**Both groups:** Run-in period of 7 days after first visit. Patient recorded attacks in a diary. If the number of attacks was between 7-21 the patient was randomised and treated for 2 weeks with assessments at the end of each week. | **Responder rate (mean, SD)**<br>(> 50% reduction in average number of attacks between run-in week and last week of treatment) | **Group1:** 25/50* (50%)<br>**Group 2:** 29/46* (62%)<br>**p value:** 0.23 | **Funding:** Sanofi research department<br><br>**Limitations:**<br>Recruitment stopped early (due to slow recruitment).<br>Discrepancy in dropouts: reported as 6, but figure adds up to 8.<br>Baseline characteristics not balanced between groups: intervention group had lower % of attack-free days, shorter duration of attacks and shorter mean duration of present episode.<br><br>**Additional outcomes:**<br>Mean duration of attacks.<br><br>**Previous medication tried?**<br>NR<br><br>**Notes:**<br>*calculated by NCGC<br>Analysed on an ITT basis (states sodium valproate n= 50, placebo n=45)<br>Patients blindly assigned to treatment according to a randomisation list by balanced blocks of four that |
| | | | **Percentage of attack free days (mean, SD)** | **<u>Run in</u>**<br>**Group1:** 18.3 (17.4)<br>**Group 2:** 12.2 (5.15)<br>**<u>Last week</u>**<br>**Group1:** 45.4 (33.4)<br>**Group 2:** 50.2 (35.5)<br>**p value:** 0.496 | |
| | | | **Pain intensity (Per week) [100mm VAS scale used] (mean, SD)** | **<u>Run in</u>**<br>**Group1:** 5.7 (1.6)<br>**Group 2:** 5.8 (1.4)<br>**<u>Last week</u>**<br>**Group1:** 4.9 (2.2)<br>**Group 2:** 5.3 (1.8)<br>**p value:** 0.2680 | |
| | | | **Percentage of patients using rescue medication**<br>Number of patients (%) using **sumatriptan** | **<u>Run in</u>**<br>**Group1:** 22/50* (44)<br>**Group 2:** 25/46* (54)<br>**<u>Last week</u>**<br>**Group1:** 18/50 *(35.5)<br>**Group 2:** 24/46* (51.6)<br>**p value:** 0.31 | |
| | | | **Percentage of patients using rescue medication**<br>Number of patients (%) | **<u>Run in</u>**<br>**Group1:** 6/50* (12)<br>**Group 2:** 14/46* (30)<br>**<u>Last week</u>** | |

| Study details | Patients | Interventions | Outcome measures | Effect size | Comments |
|---|---|---|---|---|---|
| | **period (days) episodic:** 46.8+/-35.4<br>**Mean duration of present episode (days) episodic:**12.1+/-6.3<br>**Number attacks in run-in week:**<br>**% of attack free days:** 18.3+/-17.4<br>**Maximum duration of attacks (hh:min):** 1:50+/-1:42<br><br>**<u>Group 2 Placebo</u>**<br>**N:** 46<br>**Age (mean):** 43.6+/-11.5<br>**Drop outs:** 2 (4.3%)<br>**Sex (M/F):** 40 (87%) /5 (11%)<br>**Chronic cluster headache:** 6 (13%)<br>**Episodic cluster headache:** 36 (78%)<br>**Unspecified:** 3 (7%)<br>**Mean duration of previous cluster period (days) episodic:** 62.4+/-46.5<br>**Mean duration of present episode (days) episodic:** 48.4+/-38.8<br>**Number attacks in run-in week:** 12.0+/-6.4<br>**% of attack free days:** 12.2+/-15.5<br>**Maximum duration of attacks (hh:min):** 2:21+/-2:19 | | using **oxygen**<br><br>**Adverse events (%) not classified as serious** | **Group1:** 6/50* (12.9)<br>**Group 2:** 15/46* (32.3)<br>**p value:** 0.13<br><br>**Group1:** 20/50* (40)<br>**Group 2:** 13/46 (28)<br>**p value:** NR<br><br>Most common were nausea or vomiting and somnolence | had been predefined by sanofi research department. Patients authorised to use s.c. sumatriptan (max 6mg b.i.d, with at least 1 hour between 2 injections and oxygen inhalation at flow of 7L/ min |

*Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, RCT= randomised controlled trial, s.c= subcutaneous, b.i.d= twice daily, mg= milligrams, min= minutes, hh=hours, ITT= intention to treat, IHS=International Headache Society*

| Study details | Patients | Interventions | Outcome measures | Effect size | Comments |
|---|---|---|---|---|---|
| **Author & Year:**<br>Leone et al, 1996[488]<br><br>**Study design:**<br>RCT pilot<br><br>**Setting:**<br>Headache centre, of a neurological institute 1994-1995<br><br>**Comparison:**<br>Melatonin vs placebo<br><br>**Duration of follow-up:**<br>2 weeks | **Patient group:** Adults with cluster headache<br><br>**Inclusion criteria:** Patients to have suffered at least one previous cluster period and all cluster periods to have lasted one month. Episodic cluster headaches entered into the study between 2nd and 10th day after beginning a cluster period.<br><br>**Exclusion criteria:** Drug or alcohol abuser, patients with liver of kidney disease, psychiatric disorders, or those taking antidepressants or antipsychotic medications.<br><br>**All patients**<br>N: 20<br><br>**Group 1 Melatonin**<br>**N:** 10<br>**Age (mean):** 38.4<br>**Drop outs:** NR<br>**Sex (M/F):** 9/1<br>**Mean duration of previous cluster periods (days):** 5019<br>**Entered study**: days after beginning cluster period: 5.93<br><br>**Group 2 Placebo**<br>**N:** 10 | **Group 1- melatonin**<br>Single oral dose of 10 mg melatonin in the evening for 2 weeks<br><br>**Group 2 – placebo** for 2 weeks<br><br>**Both groups -** One week run-in period without prophylaxis preventative treatment, then patients randomly assigned to treatment groups. | **Number of daily attacks**<br>mean (SD)<br>n= NR assumed 10 in each group | **Run in**<br>**Group1:** 3.3 (1.12)<br>**Group 2**: 2.39 (1.01)<br>**1st week treatment period**<br>**Group1:** 1.89 (1.51)<br>**Group 2:** 2.7 (0.86)<br>**2nd week treatment period**<br>**Group1:** 1.5 (1.7)<br>**Group 2:** 2.50 (0.86)<br>**Group 1 p value:** <0.03<br>**Group 2 p value:** 0.7 (not stated whether after 1st or 2nd week) | **Funding:** NR<br><br>**Limitations:**<br>2 chronic cluster headache patients continued preventative treatment.<br>Outcomes for "responders" and "non-responders" but no definition of responder.<br>Randomisation and allocation concealment NR.<br><br>**Additional outcomes:**<br>Headache frequency significantly lower in the 1st (p=<0.03) and 2nd (p=0.1) weeks of treatment than the run-in week.<br><br>**Previous medication tried?** NR<br><br>**Notes:**<br>Acute treatment allowed throughout the study.<br>All figures reported unclear due to formatting of text. |
| | | | **Daily numbers of analgesics consumed**<br>mean (SD)<br>n= NR assumed 10 in each group | **Run in**<br>**Group1**: 2.57 (1.16)<br>**Group 2:** 2.06 (0.95)<br>**1st week treatment period**<br>**Group1:** 1.49 (1.35)<br>**Group 2:** 2.49 (0.78)<br>**2nd week treatment period**<br>**Group1:** 1.16 (1.41)<br>**Group 2:** 2.37 (0.87)<br>**p value:** (If no p-value: Sig/Not sig/NR) | |
| | | | **Consumption of abortive medications**<br>mean (SD) | **Run in**<br>**Group1:** NR | |

| Study details | Patients | Interventions | Outcome measures | Effect size | Comments |
|---|---|---|---|---|---|
| | **Age (mean):** 34.4<br>**Drop outs:** NR<br>**Sex (M/F):** 6/4<br>**Mean duration of previous cluster periods (days):** 4212<br>**Entered study:** days after beginning cluster period: 4.42 | | n= NR assumed 10 in each group | **Group 2:** NR<br>**1st week treatment period** P=0.07 (t test)<br>**2nd week treatment period** P=<0.03<br>Does not state which group the p values refer to. | Mean age of group 2 stated as 344 in paper- we have assumed it to be 34. |

*Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, RCT= randomised controlled trial, ITT= intention to treat, IHS=International Headache Society*

| Study Details | Patients | Interventions | Outcome measures | Effect size | Comments |
|---|---|---|---|---|---|
| **Author & Year:** Leone et al, 2000[487]<br><br>**Study design:** RCT<br><br>**Setting:** Outpatients, Italy<br><br>**Comparison** Verapamil (calcium channel blocker) vs placebo<br><br>**Duration of follow-up:** 2 weeks | **Patient group:** 18-60 yr olds with episodic cluster headache<br><br>**Inclusion criteria:** 18-60 years, diagnosis of episodic cluster headache according to IHS. At least one cluster period lasting at least a month before the study, being in a cluster period for not more than 10 days and expected duration remainder of cluster period not less than 20 days (as suggested by length of past periods)<br><br>**Exclusion criteria:** Liver or kidney disease, cardiopathology contraindicating verapamil administration, psychiatric disorder, antidepressants or antipsychotics, drugs or alcohol abuse, and previous adynamic ileus.<br><br>**<u>All patients</u>**<br>**N:** 30<br>**Drop outs:** 0<br><br>**<u>Group 1</u>**<br>**N:** 15<br>**Age (mean):** 44+/-8<br>**Sex (m/f) (%):** 13(86)/2 (14)<br>**Drop outs:** 0<br>**Illness duration (years) mean:** 16+/-11<br>**Duration of previous cluster period (days), mean:** 50+/-18<br>**Current cluster period (days), mean:** 4+/-2<br>**Previous verapamil (y/n)(%):** 5 (33)/10 (66)<br><br>**<u>Group 2</u>**<br>**N:** 15 | **Group 1 verapamil** 360 mg/ day (120 mg t.i.d)<br>For 2 weeks<br><br>**Group 2 placebo**<br>Placebo t.i.d For 2 weeks<br><br>**Both groups**<br>5 days run-in with no prophylaxis. | **Responder rate**<br>>50% reduction in frequency | **Group1:** 12/15<br>**Group 2:** 0/15<br>**p value:** NR | **Funding:** NR<br><br>**Limitations:**<br>Randomisation and allocation concealment not described (states double blind and double dummy).<br>Dropouts NR.<br>Baseline characteristics unbalanced:<br>intervention group had shorter duration of cluster period, not significant.<br>50% of intervention group had received verapamil previously compared to 25% of the placebo group.<br><br>**Previous medication tried:** Details in patient information (re. verapamil).<br><br>**Additional outcomes:** N/A |
| | | | **Number of attacks per day**<br>Mean (SD) | **<u>Run in</u>**<br>**Group1:** 1.92 (0.87)<br>**Group 2:** 1.37 (0.8)<br>**p value:** <0.008<br>**<u>1st week treatment</u>**<br>**Group1:** 1.1 (1.02)<br>**Group 2:** 1.7 (1.12)<br>**p value:**NR<br>**<u>2nd week treatment</u>**<br>**Group1:** 0.6 (0.88)<br>**Group 2:** 1.65 (1.01)<br>**p value:** <0.001 | |
| | | | **Number of abortive agents used per day**<br>Mean (SD) | **<u>Run in</u>**<br>**Group1:** 1.8 (0.79)<br>**Group 2:** 1.0 (0.77)<br>**p value:** <0.0001<br>**<u>1st week treatment</u>**<br>**Group1:** 1.0 (0.96)<br>**Group 2:** 1.2 (0.92)<br>**p value:** NR<br>**<u>2nd week treatment</u>**<br>**Group1:** 0.5 (0.87)<br>**Group 2:** 1.2 (1.03)<br>**p value:** <0.004 | |
| | | | **Adverse events**<br>(Constipation, vertigo, nausea, asthenia, swelling). All mild, none required suspension of treatment. | **Group1:** 13<br>**Group 2:** 5<br>**p value:** NR | |

| Study Details | Patients | Interventions | Outcome measures | Effect size | Comments |
|---|---|---|---|---|---|
| | **Age (mean):** 43+/-10<br>**Sex (m/f)(%):** 14 (93)/1 (7)<br>**Drop outs:** 0<br>**Illness duration (years) mean:** 15+/-10<br>**Duration of previous cluster period (days), mean:** 93+/-92<br>**Current cluster period (days), mean:** 4+/-2<br>**Previous verapamil (y/n):** 3 (20)/12 (80) | | | | |

*Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, RCT= randomised controlled trial. s.c= subcutaneous, b.i.d= twice daily, t.i.d=three times a day, mg= milligrams, min= minutes, hh=hours. ITT= intention to treat*

| Study Details | Patients | Interventions | Outcome measures | Effect size | Comments |
|---|---|---|---|---|---|
| **Author & Year:** Monstad et al, 1995[570]<br><br>**Study design:** RCT<br><br>**Setting:** 35 neurology departments in 11 countries<br><br>**Comparison**: Sumatriptan (serotonergic modulator) vs placebo<br><br>**Duration of follow-up:** 1 week | **Patient group:** Men and women with chronic or episodic cluster headache, 18-65 years<br><br>**Inclusion criteria:** History of chronic or episodic cluster headache according to IHS. Experienced cluster headaches with a duration of 30 minutes or longer and their cluster period was expected to continue for another 5 weeks. Attack frequency of at least one per day.<br><br>**Exclusion criteria:** Abused or regularly used narcotic analgesic drugs, currently or within the last year abused ergotamine, evidence of alcohol abuse. Women not using adequate contraceptive measures, pregnant or breast feeding. History suggestive of ischaemic heart disease, epilepsy, hepatic, renal or heart disease or serious psychiatric illness.<br><br>**<u>All patients</u>**<br>**N:** 217 (see note*)<br>**Drop outs:** 1 (unclear)<br><br>**<u>Group 1 sumatriptan</u>**<br>**N:** 89<br>**Age (mean):** 40+/-10<br>**Drop outs:** NR<br>**M:F:** 78:11<br>**Type of cluster headache (%):**<br>**Episodic:** 45 (51) **Chronic:** 44 (49)<br>**Frequency of attacks during period:** | **Group 1: Sumatriptan (oral)** 100 mg t.i.d for 7 days- at 7am, 3pm and 11pm.<br><br>**Group 2: Placebo (oral)**<br><br>**Both groups:** Underwent observation week and completed diary cards about details of their headaches. Patients who experienced a minimum of 7 attacks during observation were issued with s.c. sumatriptan to treat their next attack. Patients returned to clinic to discuss their response to s.c. sumatriptan and were assigned to either oral sumatriptan or placebo group.<br><br>Details of all attacks during 7 day treatment period recorded on diary cards. Patients rated severity of headache. | **Responder rate** 50% reduction in number of attacks | **Group1:** 20/89 (23%)<br>**Group 2:** 17/79 (22%)<br>**p value:** 0.88 | **Funding:** NR<br><br>**Limitations:**<br>Allocation concealment NR.<br>Baseline characteristics unbalanced: Placebo group had a shorter usual duration of cluster headache, less people with very severe pain (average severity) and shorter duration of attacks without medication.<br>One patient who used s.c. sumatriptan did not continue into the study, one patient entered the study who had not self administered s.c. sumatriptan first.<br><br>**Additional outcomes:**<br>50% reduction in number of severe or very severe attacks.<br>Duration of attack.<br><br>**Previous medication tried:**<br>167/168 patients included in the analyses undertook injection of s.c. sumatriptan to treat one attack prior to receiving study drug. No other details reported.<br><br>**Notes:**<br>Responder rate and number of attacks per day requiring |
| | | | **Number of attacks per day requiring rescue medication** During study treatment week. | **Group1:** 1<br>**Group 2:** 1<br>**p value:** NR | |
| | | | **Adverse events** (all nausea/ vomiting, malaise/fatigue or dizziness/vertigo) mild | **Group1:** 19/89 (21%)<br>**Group 2:** 8/79 (10%)<br>**p value:** NR | |

| Study Details | Patients | Interventions | Outcome measures | Effect size | Comments |
|---|---|---|---|---|---|
| | **1-3/day:** 76; **4-6/day:** 11<br>**>6/day:** 2<br>**Average severity of attacks (%): moderate pain:** 2 (2), **severe pain:** 38 (43), **very severe pain:** 49 (55)<br>**Usual duration of attacks (minutes) (%): 30-60:** 25 (28); **60-90:** 26 (29); **90-180:** 33 (37)<br>**Medication always used (%):** 5 (6)<br><br>**<u>Group 2 - placebo</u>**<br>**N:** 79<br>**Age (mean):** 40+/-10<br>**Drop outs:** NR<br>**M:F:** 71:8<br>**Type of cluster headache (%): Episodic** 45 (57); **Chronic:** 34 (43)<br>**Frequency of attacks during period (%): 1-3/day:** 68 (86); **4-6/day:** 10 (13); **>6/day:** 1 (1)<br>**Average severity of attacks (%): moderate pain:** 2 (2.5); **severe pain:** 38 (48); **very severe pain:** 39 (49)<br>**Usual duration of attacks, minutes (%): 30-60:** 29 (37); **60-90:** 22 (28); **90-180:** 20 (25)<br>**Medication always used (%):** 8 (10) | | | | rescue medication carried out on ITT population.<br>*of 217 recruited into study only 168 used the autoinjector device.<br>Initial dose of 6 mg s.c. sumatriptan in sumatriptan naive patients before dispensing oral sumatriptan to patients.<br>Any prophylactic medication withdrawn at least 1 week before entry into the study.<br>Patients allocated after using s.c. sumatriptan using computer generated randomisation code.<br>Rescue medication allowed from 5 minutes after onset (oxygen or simple analgesics). |

*Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, RCT= randomised controlled trial. s.c= subcutaneous, b.i.d= twice daily, t.i.d=three times a day, mg= milligrams, min= minutes, hh=hours. ITT= intention to treat, IHS=International Headache Society*

| Study details | Patients | Interventions | Outcome measures | Effect size | Comments |
|---|---|---|---|---|---|
| **Author & Year:** Pageler et al, 2011[606]<br><br>**Study design:** RCT<br><br>**Setting:** Multicentre, 6 supra regional specialised headache centres.<br><br>**Comparison:** Frovitriptan vs placebo<br><br>**Duration of follow-up:** Run-in period of 4-7 days, treatment period of 14 days, follow-up of 7 days | **Patient group:** Adults with episodic cluster headache aged 18-65 years<br><br>**Inclusion criteria:** Patients suffering from Episodic cluster headache according to IHS. Patients suffers from at least a second phase of cluster headache, duration since onset of current episode at least 1 week, expected duration at least 6 weeks after start of screening, demonstrated response to oxygen inhalation, attack frequency between 1 attack every other day and 8 attacks per day at visit 2.<br><br>**Exclusion criteria:** Change of concomitant prophylactic treatment one month prior to visit 1, concomitant prophylactic medication with corticosteroids, civamide or botulinum toxin A, previous treatment within 24 hours prior to beginning the study or concomitant treatment with other triptans including treatment of acute attacks with s.c. ergotamine, sumatriptan or ergotamine derivatives or other 5HT receptor agonists.<br><br>**Group 1**<br>**N:** 5<br>**Age (mean):** NR<br>**Drop outs:** NR<br><br>**Group 2**<br>**N:** 6<br>**Age (mean):** NR<br>**Drop outs:** NR | **Group 1 - frovitriptan 5mg**<br><br>**Group 2 - placebo** | **Headache cluster frequency (per week)**<br>mean (SD) | **Run in**<br>**Group1:** 14.8 (7.3)<br>**Group 2:** 16.2 (9.9)<br>**Treatment period**<br>**Group1:** 14.1 (6.8)<br>**Group 2:** 10.1 (10.1)<br><br>**Group 1 95% CI:** 3.4, 24.9<br>**Group 2 95% CI:** -0.5, 20.7<br>**Group 1 p value:** 0.6095 | **Funding:** NR<br><br>**Limitations:**<br>Study prematurely discontinued after 13 months by the sponsor due to infeasibility: 11 patients enrolled instead of the planned 80 patients- slow recruitment.<br>**A**ll patients included conducted major protocol violations.<br><br>**Additional outcomes:**<br>Attack duration (minutes).<br>Quality of life "Placebo treated patients performed better than frovitriptan for nearly all scores".<br><br>**Previous medication:** Implied that previous medication used, but not explicitly stated which ones were tried.<br><br>**Notes:**<br>States all analysis undertaken on ITT basis, however data for Headache cluster frequency (per week) reported frovitriptan n=4 and placebo n=6<br>Paper was reported as a brief communication – lack of general detail (e.g. baseline characteristics). |
| | | | **Frequency of headache attacks per week**<br>Number of attacks | **Run in**<br>**Group1:** 15<br>**Group 2:** 16<br>**Follow up**<br>**Group1:** 11<br>**Group 2:** 3<br>**p value:** NR | |
| | | | **Response rate**<br>Reduction of the mean number of cluster headache attacks per week | **Group1:** 1/5<br>**Group 2:** 4/6<br>**p value:** NR | |

*Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, RCT= randomised controlled trial. s.c= subcutaneous, b.i.d= twice daily, mg= milligrams, min= minutes, hh=hours, ITT= intention to treat, IHS=International Headache Society*