Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Afshari et al, 2012[9] **Study design:** RCT **Comparison:** Topiramate vs valproate **Setting:** Hospital neurology clinic in Iran **Duration of follow-up:** 12 weeks	**Patient group:** People with migraine aged 18 to 65 **Inclusion criteria:** Aged 18 to 65 at time of entry; diagnosis of migraine (with or without aura) according to IHS criteria; a history of migraine for at least 6 months; 4 to 10 migraines per month; each attack separated by a pain-free interval of at least 48 hours; age at onset <50 years; females of child bearing age group that are neither pregnant or lactating and are ready to use reliable methods of contraception during the study; the concomitant migraine prophylactics withdrawn 1 month prior to entry into trial. **Exclusion criteria:** Experienced headaches other than migraine; had migraine onset after the age of 50; overused migraine treatments (>8 treatment days per month of ergots, NSAIDs or triptans; using other migraine medications; alcohol or other drug dependency; history of hemiplegic, ophthalmoplegic, or basilar migraine; patients with serious medical conditions such as cardiovascular diseases, significant heamatological diseases, severe liver or kidney diseases, and malignancy.	**Group 1 -** Topiramate 25 mg/d for first week, then 50 mg/d until end of study **Group 2** - Sodium valproate 200 mg/d for first week then 400mg/d until end of study Washout and baseline phase Eligible participants kept a diary, documenting frequency of the number, duration and severity of attacks in the preceding 4 weeks, associating symptoms, adverse events experienced during the entire treatment period and symptomatic medication. Concomitant medications Participants permitted to take symptomatic medications such as NSAIDs, acetaminophen, ergotamine, triptans or opioids.	**Migraine frequency** Mean +SD for last 4 weeks of treatment phase Baseline mean +SD migraine frequency in 4 weeks prior to treatment phase **Migraine severity** Mean +SD in last 4 weeks of treatment phase Baseline mean +SD migraine severity in 4 weeks prior to treatment phase	Group 1: 3.0+1.9 (n=28) Group 2: 3.6+1.8 (n=28) Group 1: 6.8+2.0 Group 2: 7.5.0+1.9 Group 1: 5.2+1.5 (n=28) Group 2: 6.3+1.9 (n=28) Group 1: 8.6+1.7 Group 2: 8.6+1.7	**Funding:** Kermanshah University of Medical Sciences **Limitations:** Unclear allocation concealment (though study reports it was double blinded). No headache data for 12/40 (30%) patients in topiramate group and 8/36 (22%) patients in sodium valproate group. **Additional outcomes:** Duration of each episode and patients' weight for 1st, 2nd and 3rd 4 week periods, MIDAS and HIT Scores for baseline and 2nd 4 week period.

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	All participants **N:** 76 randomised, (100 screened). **Drop outs:** 20 **Group 1** **N:** 40 **Age (mean):** 32.1 +10.2 **Drop outs:** 12 (moved away (2), adverse events (2), did not believe in efficacy of medication (8)) **Group 2** **N:** 36 **Age (mean):** 29.2 +9.6 **Drop outs:** 8 (moved away (0), adverse events (6), did not believe in efficacy of medication (2))				

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

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Apostol et al, 2008[41] **Study design:** RCT (phase 3) **Comparison:** Antiepileptic vs placebo **Setting:** Multicentre study (38 centres in US) **Duration of follow-up:** 12 weeks	**Patient group:** People aged 12 to 17 with migraine **Inclusion criteria:** Aged 12 to 17 at time of randomisation; initial migraine (classified based modified IHS diagnostic criteria) at least 12 months before screening; >3 * <12 migraines per month; weighed between 35 and 100kg; practicing an accepted form of birth control; had normal screening laboratory results; **Exclusion criteria:** History of encephalopathy, hepatitis, pancreatitis or urea cycle disorder; pregnant or nursing, history of cluster headaches; >15 headaches on any type per month; medication non-compliance; substance abuse within the last 6 months; allergic reaction to valproate; taking headache medication >10 days per month; used valproate or an investigational drug within the last 30 days; had failed >2 'adequate' regimens of prophylactic antimigraine medications. **All participants** **N:** 305 randomised, ITT = 299, (504 screened, 436 entered baseline phase). **Drop outs:** 39 **Group 1** **N:** 75 (ITT for efficacy = 73, safety analysis =75)	**Group 1 -** Divalproex (DVPX) extended release (ER) 1000mg/d **Group 2 -** Divalproex (DVPX) extended release (ER) 500mg/d **Group 3 -** Divalproex (DVPX) extended release (ER) 250mg/d **Group 4 -** Placebo Washout and baseline phase Eligible participants entered into washout period up to 2 weeks (if needed). This followed by 4 week baseline phase. Participants permitted to take NSAIDs and/or acetaminophen throughout baseline and treatment phase but not on a daily basis. Participants randomised after baseline phase. Titration During titration phase participants on 1000mg/d received 500mg/d, participants on 500mg/d or 250mg/d received 250mg/d.	**Migraine frequency** Change in mean +SD per 4 weeks during treatment phase	**Group 1:** -1.8+1.76 (n=73) **Group 2:** -2.0+1.84 (n=74) **Group 3:** -1.7+1.84 (n=81) **Placebo:** -1.9+2.18 (n=71)	**Funding:** Abbott **Limitations:** Unclear randomisation and allocation concealment. Only 305 out of 436 participants in the 4 week baseline phase that came after screening were randomised; no explanation given as to why. Unclear if those administering care were kept blind to treatment. Unclear why 1 of the 4 groups had more participants than the others (i.e. 75, 74, 83, 73). This group also had 1 person withdrawn because blinding was broken. **Additional outcomes:** Median 4 week frequency of migraines at baseline and treatment phases and median change in this frequency, change from baseline in metabolic and
			Baseline mean +SD migraine frequency in 3 months prior to screening	**Group 1:** 17.3+6.84 **Group 2:** 18.0+7.02 **Group 3**: 16.6+7.02 **Placebo:** 16.7+7.62	
			Migraine days Change in mean +SD per 4 weeks during treatment phase	**Group 1:** -3.1+3.61 (n=73) **Group 2:** -2.2+3.18 (n=74) **Group 3:** -2.8+2.91 (n=81) **Placebo:** -2.8+3.02 (n=71)	
			Responder rate (Number of participants who had a >50% reduction in mean monthly migraine frequency during treatment phase)	**Group 1:** 37/72 (51%) **Group 2:** 27/74 (36%) **Group 3:** 33/81 (41%) **Placebo:** 33/71 (46%)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Age (mean±SD): 14.33 +1.66 **Drop outs:** 13 (lost to follow-up (3), adverse events (7), withdrew consent (1), non-compliance (1), other reasons (1)) **Group 2** **N:** 74 (ITT for efficacy = 74, safety analysis =74) **Age (mean±SD):** 14.1 +1.56 **Drop outs:** 12 (lost to follow-up (5), lack of efficacy (3), withdrew consent (1), non-compliance (3)) **Group 3** **N:** 83 (ITT for efficacy = 81, safety analysis =82) **Age (mean±SD):** 14.2 +1.69 **Drop outs:** 9 (lost to follow-up (5), lack of efficacy (3), withdrew consent (1), non-compliance (3), never took study drug (1)). Some participants reported >1 reason for discontinuing treatment. **Group 4** **N:** 73 (ITT for efficacy = 71, safety analysis =73) **Age (mean±SD):** 14.2 +1.50 **Drop outs:** 6 (lost to follow-up (4), lack of efficacy (1), adverse event (1))	Concomitant medications Certain medications known to have an interaction with DVPX, most psychotropic medications, and anticoagulants and antiplatelet agents were prohibited. Stimulant medications for the treatment of attention deficit hyperactivity disorder were allowed (except pemolinie) provided subjects were on a stable dose and the medication did not affect headache symptoms			reproductive endocrine parameters. **Notes:** 504 participants screened, 436 entered baseline phase, 305 randomised. No explanation or criteria as to why the 231 participants in baseline phase did not make it to randomisation. Results include data averaged over entire randomised treatment period including titration. The efficacy data set was an intention-to-treat data set that included all data from randomised subjects who received the study drug and provided at least 1 headache evaluation during the experimental phase.

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

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Brandes et al, 2004, MIGR-002 Study Group[106] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** Multicentre study (52 North American clinical centres) **Duration of follow-up:** 26 weeks	**Patient group:** People aged >12 with migraine **Inclusion criteria:** Established history of migraine with or without aura (IHS criteria) for at least 6 months before screening; aged 12 to 65 years; have between 3 and 12 migraines, but not more than 15 headache days (migraine or nonmigraine experience for at least 30 minutes) per 28 days during the prospective baseline phase; women had to be post menopausal, surgically incapable of bearing children or practicing a medically acceptable method of birth control for at least 1 month before study entry. **Exclusion criteria:** Experiencing headaches other than migraine, episodic tension or sinus headaches; failure to respond to >2 adequate previous preventative migraine regimens; onset of migraine after age 50 years; overuse of analgesics or specific acute migraine treatments (Examples of overuse: >8 treatment episodes of ergot-containing medications or triptans a month, >6 treatment episodes of potent opioids a month); requirement to use: beta blockers, tricyclic antidepressants, antiepileptics, calcium channel blockers,	**Group 1 -** Topiramate 200mg/d Median daily dose actually taken = 150.2mg/d (69.2% achieved target dose) **Group 2 -** Topiramate 100mg/d Median daily dose actually taken = 85.6mg/d (85.8% achieved target dose) **Group 3 -** Topiramate 50mg/d Median daily dose actually taken = 46.5mg/d (97.4% achieved target dose) **Group 4 -** Placebo 85.1% achieved target dose Washout and baseline phase Eligible participants entered into washout period up to 14 days. This followed by 28 day prospective baseline phase during which headache and medication record information completed by participants. Rescue medication permitted during this time. Participants randomised after baseline phase.	**Migraine frequency** Mean +SD monthly during treatment phase	**Group 1:** (baseline 5.1+2.0) 3.0+2.2 (n=117) **Group 2:** (baseline 5.8+2.6) 3.5+3.5 (n=120) **Group 3:** (baseline 5.4+2.4) 4.1+3.6 (n=117) **Placebo:** (baseline 5.6+2.2) 4.5+2.9 (n=114)	**Funding:** Johnson and Johnson Pharmaceuticals **Limitations:** Fewer participants reached their target dose and the mean dose taken was less than prescribed dose with Topiramate 200mg/d group than others. No table of results given. Only 53% of participants completed the treatment regimen. **Additional outcomes:** Mean migraine duration; specific adverse events.. **Notes:** All results reported using Intention to Treat population (ITT). Intention to treat population described as the randomised participants who had at least 1 post-baseline efficacy
			Responder rate Proportion of participants with >50% reduction in migraine frequency during treatment phase	**Group 1:** 55*/117 (47%) **Group 2:** 59*/120 (49%) **Group 3:** 46*/117 (39%) **Placebo:** 26*/114 (30%) p values compared to placebo: Group 1 p<0.001, Group 2 p<0.001, Group 3 p=0.01	
			Migraine days Change in mean number of monthly days during treatment phase. Baseline data – +SD, end data - Least square means +SEM.	**Group 1:** (baseline 6.1+2.54) -2.9+0.32 (n=117) **Group 2:** (baseline 6.9+3.00) -2.6+0.31 (n=120) **Group 3:** (baseline 6.4+2.88) (n=117) change value not reported but study states not sig. **Placebo:** (baseline 6.7+2.84) -1.3+0.32 (n=114) p values compared to	

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	mono-amine oxidase inhibitors, NSAIDs daily, magnesium supplements at high doses (e.g. 600mg/d), riboflavin at high doses (e.g. 100mg/d), corticosteroids, local anaesthetics, botulinum toxin or herbal preparations such as feverfew of St John's wort; history of nephrolithiasis, participants who had taken topiramate for more than 2 weeks or had participated in a topiramate trial; participants who had received and experimental drug or used an experimental device within 30 days of screening. **All participants** **N:** 483 randomised, ITT for efficacy = 468, (693 screened for inclusion) **Drop outs:** 228 **Group 1** **N:** 121 (ITT = 117) **Age (mean):** 39.1+12.71 **Drop outs:** 51 (4 didn't provide post baseline efficacy data & lost to follow-up; 47 withdrew because: participant choice (5), lost to follow up (3), adverse events (25), lack of efficacy (12), other (2)). **Group 2** **N:** 122 (ITT = 120) **Age (mean):** 39.1+12.58	Titration Topiramate doses started at 25mg/d and increased by 25mg weekly (for a total of 8 weeks) until participants reached assigned dose or maximum tolerated dose, whichever was less. Participants then received that amount for 18 weeks in 2 divided daily doses. In event of tolerability problems participants were given the opportunity to reduce study medication by a maximum of 2 dose levels during entire 26 week treatment phase. Rescue medications Rescue medications permitted included aspirin acetaminophen, NSAIDs, ergot derivatives, triptans and opioids.		placebo: Group 1 p<0.001, Group 2 p<0.003, Group 3 p NS	assessment. Results include data averaged over entire randomised treatment period including titration. For participants discontinuing early, the mean monthly migraine frequency during the entire double-blind treatment phase and cumulative monthly periods were computed according to the migraine periods observed before discontinuing. * calculated by NCGC Previous preventive medications used or years used not reported.
			Acute medication use Change in mean number of days requiring rescue medication during treatment phase. Baseline data – +SD, end data - Least square means +SEM.	**Group 1:** (baseline 5.8+2.52) -2.2+0.29 (n=117) **Group 2:** (baseline 6.2+2.52) -2.1+0.29 (n=120) **Group 3:** (baseline 5.7+2.72) value not reported but study states not sig (n=117) **Placebo:** (baseline 5.8+2.67) -1.0+0.29 (n=114) p values compared to placebo: Group 1 p<0.001, Group 2 p<0.003, Group 3 p NS	
			Migraine intensity Change in mean severity during treatment phase. Baseline data – +SD, end data - Least square means +SEM.	**Group 1:** (baseline 2.3+0.39) -0.1+0.04 (n=117) **Group 2:** (baseline 2.2+0.37) -0.2+0.04 (n=120) **Group 3:** (baseline 2.3+0.38) -0.1+0.04 (n=117) **Placebo:** (baseline 2.2+0.45) -0.1+0.04 (n=114) p values compared to	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 59 (2 didn't provide post baseline efficacy data & lost to follow-up; 57 withdrew because: participant choice (6), lost to follow up (4), adverse events (32), lack of efficacy (11), other (4)). **Group 3** **N:** 120 (ITT = 117) **Age (mean):** 39.0+12.09 **Drop outs:** 61 (3 didn't provide post baseline efficacy data & lost to follow-up; 58 withdrew because: participant choice (8), lost to follow up (9), adverse events (20), lack of efficacy (15), other (6)). **Group 4** **N:** 120 (ITT = 114) **Age (mean):** 39.3+11.96 **Drop outs:** 57 (6 didn't provide post baseline efficacy data & lost to follow-up; 51 withdrew because: participant choice (7), lost to follow up (6), adverse events (14), lack of efficacy (21), other (3)).			placebo: Group 1 p=0.46, Group 2 p<0.04, Group 3 p=0.61	

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

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener et al, 2004, MIGR-003 Study[225] **Study design:** RCT **Comparison:** Anitconvulsant vs beta-blocker vs placebo **Setting:** Tertiary care headache centres Multicentre study (61 centres in 13 countries) **Duration of follow-up:** 26 weeks	**Patient group:** People aged 12-65 with migraine **Inclusion criteria:** Aged between 12 and 65 years old, 3 to 12 migraine periods and no more than 15 headache (including migraine) days, history of migraine with or without aura (according to IHS criteria) for at least 1 year. **Exclusion criteria:** Failed more than 2 previous 'adequate' regimens of prophylactic medications for recurrent migraine; history of asthma; bradyarrhythmia; uncontrolled diabetes; other limitations with using beta-blockers; **All participants** **N:** 575 randomised, ITT for efficacy = 568, (761 screened for inclusion) **Drop outs:** 215 **Group 1** **N:** 144 (ITT=143) **Age (mean):** 42.6+11.29 **Drop outs:** 79 (1 didn't provide post baseline efficacy data; 78 withdrew because: participant choice (8), lost to follow up (1), adverse events (63), lack of efficacy (2), other (4)).	**Group 1 -** Topiramate 200mg/d Median daily dose actually received for randomised period (i.e. titration & maintenance) 124.2mg/d. Target dose achieved in 53%. **Group 2 -** Topiramate 100mg/d Median daily dose actually received for randomised period (i.e. titration & maintenance) 87.9mg/d Target dose achieved in 87%. **Group 3 -** Propranolol 160mg/d Median daily dose actually received for randomised period (i.e. titration & maintenance) 129.6mg/d Target dose achieved in 78%. **Group 4** Placebo Median daily dose actually received for randomised period (i.e. titration & maintenance) 165.5mg/d (based on algorithm used for 200mg/d topiramate group) Washout and baseline phase Study starts with up to 14 day washout period during which migraine preventive medications were discontinued. Followed with a 28 day baseline phase during which participants' headache and medication	**Migraine frequency** Change in mean +SD per 28 days (least square mean +SEM)	**Group 1:** (baseline 5.3+2.24) -1.1+0.22 (n=143) **Group 2:** (baseline 4.9+1.97) -1.6+0.22 (n=139) **Group 3:** (baseline 5.1+2.17) -1.6+0.21 (n=143) **Group 4:** (baseline 5.2+2.24) -0.8+0.21 (n=143)	**Funding:** Johnson and Johnson Pharmaceuticals **Limitations:** Unclear randomisation and allocation concealment, unclear. Only 63% of participants completed the treatment regimen. Group using Topiramate 200mg/d had a much higher dropout rate than other groups. **Additional outcomes:** Change in average monthly migraine duration, change in migraine attack rate (distinct from migraine periods – attacks calculated irrespective of headache duration using an algorithm "suggested by a regulatory agency"), treatment emergent adverse events,
			Migraine days Change in mean +SD per 28 days (least square mean +SEM) Any calendar day the subject had a headache of at least 30 minutes duration.	**Group 1:** (baseline 6.2+2.76) -1.3+0.25 (n=143) **Group 2:** (baseline 5.8+2.21) -1.8+0.25 (n=139) **Group 3:** (baseline 6.1+2.70) -1.9+0.25 (n=143) **Group 4:** (baseline 6.1+2.60) -1.1+0.24 (n=143)	
			Acute medication use Change in the number +SD of days of rescue medication use (least mean square +SEM)	**Group 1:** (baseline 5.5+2.62) -0.9+0.21 (n=143) **Group 2:** (baseline 5.0+2.21) -1.5+0.21 (n=139) **Group 3:** (baseline 5.4+2.54) -1.6+0.21 (n=143)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 141 (ITT=139) **Age (mean):** 39.8+10.88 **Drop outs:** 47 (2 didn't provide post baseline efficacy data; 45 withdrew because: participant choice (5), lost to follow up (0), adverse events (37), lack of efficacy (1), other (2)). **Group 3** **N:** 144 (ITT=143) **Age (mean):** 40.6+11.13 **Drop outs:** 42 (1 didn't provide post baseline efficacy data; 41 withdrew because: participant choice (3), lost to follow up (1), adverse events (29), lack of efficacy (3), other (5)). **Group 4** **N:** 146 (ITT=143) **Age (mean):** 40.4+10.11 **Drop outs:** 47 (3 didn't provide post baseline efficacy data; 44 withdrew because: participant choice (7), lost to follow up (1), adverse events (15), lack of efficacy (13), other (8)).	record information recorded. Participants randomised after baseline phase. Titration Drugs titrated upwards until either assigned dose or maximum tolerated dose was achieved. Topiramate: initial daily dose 25mg/d, titrated upwards in 25mg/d weekly increment Propranolol: initial daily dose 20mg/d, titrated upwards in 20mg/d weekly increment. Subjects continued receiving stable dose until end of maintenance period. A maximum of 2 dose level reductions were permitted for subjects who exerienced unacceptable tolerability problems .Not reported what happened in placeb group. Titration continued for 8 weeks then participants given 18 weeks treatment at target dose Rescue medications Permitted use of "acute rescue medication (i.e. aspirin, paracetamol, NSAIDs, ergot derivatives, triptans and opioids) for migraine attacks as needed".		**Group 4:** (baseline 5.3+2.52) -0.8+0.20 (n=143)	withdrawals due to adverse events **Notes:** All results reported using Intention to Treat population (ITT). Intention to treat population described as the randomised participants who had at least 1 post-baseline efficacy assessment. Results include data averaged over entire randomised treatment period including titration. Significantly more participants dropped out of the topiramate 200mg/d group, most of these due to adverse events.
			Number of subjects with >50% reduction in monthly migraine frequency (least mean square +SEM)	**Group 1:** 35/143 **Group 2:** 37/139 **Group 3:** 43/143 **Group 4:** 22/143	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & year: Diener et al, 2009[218] **Study design:** RCT **Comparison:** ARB vs placebo **Setting:** Headache clinic, Germany **Duration of follow-up:** 12 weeks 1 week screening period 4 week baseline period Randomisation 12 week double-blind	**Patient group:** Adults with migraine **Inclusion criteria:** Ability to provide written informed consent, age 18-65 years, history of migraine with or without aura according to IHS criteria at a rate of 3-7 documented attacks within the last 3 months. Start of migraine attacks at least 1 year prior to randomisation and before the age of 50 years. 3-7 migraine attacks with well-defined pain-free intervals of at least 24h between migraine attacks during the 4 week baseline period. **Exclusion criteria:** Premenopausal women who were not surgically sterile and/or nursing or pregnant; and/or of child-bearing potential and not practicing an acceptable means of birth control. Patients unable to distinguish interval headache from migraine headache Patient with a history of other types of headaches on>5 days/month. Previous failure on >1 prophylactic treatment. Current us or use of migraine prophylactics within last 6 weeks prior to signing the informed consent form Using >1 migraine prophylactic prior to randomisation. Hepatic and/or renal dysfunction. Bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, post-renal transplant or only 1 kidney	**Group 1 -** Telmisartan (Micardis; Boehringer Ingelheim) 80mg tablets **Group 2 -** Matching placebo 80mg **All patients** Screening period: 1 week Baseline period: 4 weeks-single blind treatment with placebo Treatment period: 12 weeks. Double-blind treatment with either telmisartan or placebo Recorded headache occurrence, type, intensity, autonomic symptoms, duration and acute medication use in a diary. Use of analgesic, ergotamine and triptan medication for rescue treatment of migraine attacks was allowed, and documents in the patient diary.	**Migraine days** (a calendar day with ≥1h of migraine symptoms, irrespective of intake of medication to treat a migraine attack)-efficacy analysis	**Baseline** (mean, SD) **Group1:** 6.18 (2.89) **Group 2:** 7.59 (3.66) **End of study** (mean, SD) **Group1:** 4.53 (3.41) (n=40) **Group 2:** 6.45 (4.47) (n=44) **Change from baseline** (Wilcoxin), mean, SD **Group 1:**-1.65 (3.46) (n=40) **Group 2:**-1.14 (3.78) (n=44) P value: 0.7388 % change from baseline (ANCOVA)*, mean (95% CI) Group 1:-38% (-49%, -24%) Group 2:-15% (-30%, 5%) p value: 0.0262 *adjusted for baseline and centre, data log-transformed	**Funding:** Unrestricted grant from Boehringer Ingelheim **Limitations:** Randomisation unclear Allocation concealment unclear Difference in number of migraine days at baseline between the 2 groups was close to being significant (p=0.09) Inadequate sample size (pilot study) **Additional outcomes:** Change from baseline in headache hours Change from baseline in triptan use Change from baseline in use of analgesics Blood pressure at baseline and end of the study Adverse events during the 12 week treatment period Previous use of prophylactic medication:
			Responder rate (≥50% reduction in migraine days during treatment period compared with baseline) - efficacy analysis	**Group1:** 16/40 (40%) **Group 2:** 11/44 (25%)	

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treatment period	Clinically relevant hypokalaemia or hyperkalaemia, uncorrected volume depletion, uncorrected sodium depletion. Hereditary fructose intolerance. Biliary obstructive disorders, cholestasis or moderate to severe hepatic insufficiency Previously experienced symptoms characteristic of angio-oedema during treatment with ACE inhibitors or angiotensin II receptor antagonists History or suspicion of drug or alcohol dependency. Chronic administration of any medications known to affect blood pressure (except medication allowed by the protocol). History of stroke within the past 6 months, MI, cardiac surgery, PTCA or unstable angina within the past 3 months, any other serious disorders. **All patients** **N:** 95 (randomised), 90 (completed study), 84 (efficacy analysis) **Age (mean):** 40.7 (SD 12.3) Range: 19-65 **M/F:** 13/71 (15.5%/84.5%) **BMI:** 23.4 (SD 3.5) **Drop outs:** 5 **Group 1 (Telmisartan)** **N:** 48 (randomised), 46 (completed study), 40 (efficacy analysis) **Age, mean (SD):** 39.8 (11.7)				patients who previously failed on more than one prophylactic treatment were excluded. **Notes:** 1:1 randomisation Efficacy analysis used. Described as patients who had an evaluable baseline period, were randomised, received at least 1 dose of study medication and had an evaluable final period. After unblinding it was apparent that the baseline value for the number of migraine days was different between treatment groups, and that reductions in migraine days were not consistent across centres. Therefore, a post-hoc analysis of covariance (ANCOVA) was performed that adjusted for baseline differences and centre effects. To account for the skewed distribution of migraine days, this

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 8/32 **Migraine days, mean (SD):** 6.2 (2.9) **Headache hours, mean (SD):** 58.2 (50.4) **Drop outs:** 2 **Group 2 (Placebo)** **N:** 47 (randomised), 44 (completed study), 44 (efficacy analysis) **Age, mean (SD):** 41.6 (12.9) **M/F:** 5/39 **Migraine days, mean (SD):**7.6 (3.7) **Headache hours, mean (SD):** 74.4 (64.2) **Drop outs**: 3				analysis was based on log-transformed data. Consequently, reductions from baseline are presented as % changes.

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

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Di Trapani et al, 2000[196] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** NR **Duration of follow-up:** 12 weeks	**Patient group:** Adults with migraine with or without aura **Inclusion criteria:** Migraine with or without aura (IHS classification); between 4 and 7 mild, moderate or severe attacks per months during 1 year at least; 18 to 65 years of age. **Exclusion criteria:** Other headaches but migraine; cardiac, hepatic and renal disease; use of migraine preventive medication in the last 3 months; pregnancy or risk of pregnancy. **All participants** **N:** 63 (enrolled, randomised & analysed) **Presence of aura;** 32 without, 31 with **Drop outs:** 0 **Group 1** **N:** 35 **Presence of aura:** 18 without, 17 with **Age (mean):** NR **Drop outs:** 0 **Group 2** **N:** 28 **Presence of aura:** 14 without, 14 with **Age (mean):** NR **Drop outs:** 0	**Group 1 -** Gabapentin 1200mg/d **Group 2 -** Placebo **Baseline phase** Eligible participants entered into a 1 month screening phase during which they recorded headache activity in a headache diary. **Treatment Phase** 4 week titration phase followed by 8 week treatment. During titration participants received 400mg/d gabapentin days 1 to 3, 800mg/d days 4 to 6, and 1200mg/d from 7th day. **Acute treatment** Nothing reported in paper about the use of acute medication during the study.	**Migraine frequency** Mean +SD monthly frequency during treatment	**Group 1:** (baseline 5.11.+0.67) 2.81.+1.12 (n=35)* **Placebo:** (baseline 5.41.+0.56) 4.70.+0.82 (n=28)	**Funding:** NR **Limitations:** Unclear randomisation and allocation concealment. Not stated if patients were randomised before or after screening phase. Not reported how a migraine attack is defined i.e. how long one attack lasted. **Additional outcomes:** None **Notes:** * results presented for gabapentin arm by participants with aura and those without. NCGC calculated mean and standard deviations for total.
			Migraine intensity Mean +SD monthly intensity during treatment (mild =1, moderate =2, severe =3).	**Group 1:** (baseline 2.35.+0.53) 1.39.+0.54 (n=35)* **Placebo:** (baseline 2.50.+0.50) 2.01.+0.61 (n=28)	

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

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Frietag et al, 2002[290] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** NR **Duration of follow-up:** 12 weeks	**Patient group:** Aged >12 with Migraine with and without aura **Inclusion criteria:** Migraine with and without aura according to IHS criteria; average of >2 migraine headaches per month during the 3 months before screening; initial onset of migraine >6 months before screening; aged >12 years; women of childbearing potential required to practice contraception throughout study. **Exclusion criteria:** >15 headache days per month; women who were lactating or pregnant; had ever experienced cluster headaches; previously received an adequate course of treatment with divalproex sodium or valproate for migraine headaches; had a CNS neoplasm or infection, demyelinating disease, degenerative neurologic disease, or progressive CNS disease; had failed more > 2 adequate trials of prophylactic anti-migraine medication within 5 half lives of that medication before entering the baseline phase. **All participants** **N:** 262 recruited, 239 randomised (ITT=237) **Drop outs:** 37 **Group 1** **N:** 122	**Group 1 -** Extended release Divalproex sodium (Depakote) 500mg/d or 1000mg/d **Group 2 -** Placebo Washout and baseline phase Eligible participants entered into a single blind 4 week baseline phase during which they recorded headache activity in a headache diary. Subjects who completed the baseline phase compliant in using headache diary and had at least 2 migraine attacks (separated by a headache-free interval of at least 24 hours) were randomised on a 1:1 ratio at each centre for 12 weeks. Treatment Phase 2 week titration phase followed by 10 week treatment. During 1st week of titration participants received 500mg dvalproex (or placebo). After week 1 of titration participants received 1000mg/d divalproex (or placebo). During 2nd week	**Migraine frequency** Change in mean migraine headache rate per 4 weeks during treatment phase	**Baseline Group 1:** 4.4+1.62 (n=119) **Change Group 1:** -1.2 (n=119) **Baseline Placebo:** 4.2+1.94 (n=115) **Change Placebo:** -0.6 (n=115) Standard deviations not reported 95% CI of treatment difference (0.2 to 1.2), p=0.006	**Funding:** Abbot Laboratories **Limitations:** Study does not report standard deviations for results relating to mean change in headache rate and days. **Additional outcomes:** Migraine headache rate and days for last 4 weeks of treatment; baseline rescue medications used; specific adverse events. **Notes:** 1 week termination phase followed the 12 week treatment phase. The efficacy data set was an
			Migraine days Change in mean headache days per 4 weeks during treatment phase	**Baseline Group 1:** 6.3+2.83 (n=119) **Change Group 1:** -1.7 (n=119) **Baseline Placebo:** 5.8+2.85 (n=115) **Placebo:** -0.7 (n=115) SD not reported 95% CI of treatment difference (0.2 to 2.0), p=0.009	
			Incidence of serious adverse events	**Group 1:** 2/122 **Placebo:** 4/115	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 19.6 +12.24 **Maximum severity of headache:** excruciating (19), severe (84), moderate (12) **Mean +SD no. migraine headaches within 3 months before screening:** 13.7 +6.8 **Failed adequate trials of migraine prophylaxis medication regimens:** no adequate trials (95), 0 trials (10), 1 trial (12), 2 trials (5) **Drop outs:** 21 withdrawn (adverse events (10), ineffectiveness (2), loss to follow up (1), non-compliance (3), other (5) **Group 2** **N:** 115 **Age (mean):** 20.8 +12.29 **Maximum severity of headache:** excruciating (24), severe (88), moderate (10) **Mean +SD no. migraine headaches within 3 months before screening:** 13.1 +6.8 **Failed adequate trials of migraine prophylaxis medication regimens:** no adequate trials (85), 0 trials (5), 1 trial (18), 2 trials (7) **Drop outs:** 14 withdrawn (adverse events (10), ineffectiveness (1), loss to follow up (1), non-compliance (1), other (1)	the investigator had the option or reducing the subjects dose to 500mg/d for the remaining period if deemed necessary because of intolerance. Acute treatment Treatment with symptomatic medications was allowed on as-needed basis for treatment of individual headaches during the study.			intention-to-treat data set that included all data from randomised subjects who received the study drug and provided at least 1 headache evaluation during the experimental phase.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Gelmers et al, 1989[311] **Study design**: RCT **Comparison:** Calcium channel blocker vs placebo **Setting:** 11 neurology departments with a special interest in headache in 9 European countries **Duration of follow-up:** 12 weeks 4 week run-in	**Patient group:** Patients with migraine without aura **Inclusion criteria:** Age 18-60. Fulfilled criteria for common migraine according to the classification of the National Institute of Health: repeated idiopathic attacks of headache lasting between 3 hours and 3 days with pain free intervals between attacks. The headache attacks were associated with nausea and at least one of the following criteria: unilateral pain location, pulsating pain quality, photophobia or phonophobia. For patients fulfilling these criteria it was further required that the number of migraine days per month should be 2-8 documented not only by history, but also during the run-in phase of 4 weeks. No more than one classic migraine attack during the last 6 months. **Exclusion criteria:** Cluster headache >6 days a month with interval headaches of the tension-type and other recurrent headaches. Use of other drugs with prophylactic migraine activity e.g. beta blockers, amine-antagonists. Intake of psychotropic drugs and hormones unless patients stayed on a fixed dose throughout the trial. Contraindications to calcium-antagonists suck as orthostatic hypotension and cardiac arrhythmia. Females in the fertile age who did not use appropriate preventative measures Patients who were non-complying. Other severe chronic organic disease. Severe mental disease	**Group 1** Nimodipine 40mg t.i.d. **Group 2** placebo Identically looking, tasting and smelling to nimodipine. **All patients** Completed a 4 week run-in period following which patients were excluded if they had not had the required number of migraine days or if there were other reasons for exclusion. Throughout the run-in phase and the trial itself, patients kept a headache diary recording duration and severity of migraine and other headache, nausea, vomiting and other symptoms.	**Migraine days** (per 4 weeks) efficacy analysis 161 patients	**Group1:** 2.48 **Group 2:** 2.49 **p value:** not sig	**Funding:** Not reported **Limitations:** Randomisation unclear Allocation concealment unclear ITT analysis includes 12 patients who had been included despite violation of the protocol in the run-in phase. Baseline difference in migraine index was statistically significant between the 2 groups (P≤0.03). In the group valid for analysis of efficacy the difference between migraine days, but not migraine index was significant (P≤0.02) at baseline. Statistically significant difference in body weight (8kg) between groups. **Additional outcomes:** Migraine index at run-in, 1-4 weeks, 5-8 weeks and 9-12 weeks. Life table analysis of the time taken to reach the same number of migraine days as observed during the run-in period. **Previous use of prophylactic medication:**
			Migraine days (per 4 weeks) ITT analysis 192 patients	**Group1:** 3.04 **Group 2:** 2.70 **p value:** not sig	
			Adverse events (% reporting serious)	None reported	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
12 week double-blind period	Previous prophylactic migraine treatment had to be withdrawn at least 4 weeks before the trial, and if patients had had 2 or more previous prophylactic treatments without effect, they were excluded. **All patients** **N:** 192 (randomised) **Drop outs:** 19 **Group 1** **N:** 94 (randomised) **Age (mean):** 38.0 **M/F:** 17/77 **Migraine days/4weeks:**4.5 **Median duration of migraine (years):**16 **Migraine index (days/4weeks x severity):** 9.27 **Drop outs**: 12 **Group 2** **N:** 98 (randomised) **Age (mean):** **M/F:** 25/73 **Migraine days/4weeks:**4.2 **Median duration of migraine (years):**17 **Migraine index (days/4weeks x severity):**8.79 **Drop outs:** 7				Previous prophylactic migraine treatment had to be withdrawn at least 4 weeks before the trial, and if patients had had 2 or more previous prophylactic treatments without effect, they were excluded. **Notes:** Stratified randomisation (matched for sex, age: 10 year intervals and number of migraine days: 2-4 and 5-8 days per month) ITT and efficacy analysis

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Gelmers et al, 1989[312] **Study design:** RCT **Comparison:** Calcium channel blocker vs placebo **Setting:** 11 neurology departments with a special interest in headache in 9 European countries **Duration of follow-up:** 12 weeks 4 week run-	**Patient group:** Adults with migraine with aura **Inclusion criteria:** Age 18-60. Fulfilled criteria for classic migraine according to the classification of the National Institute of Health: repeated idiopathic attacks of headache lasting between 3 hours and 3 days with pain free intervals between attacks. The headache attacks are preceded by or accompanied by an aura consisting of one or more of the following symptoms: zig zag lines, scotoma, hemisemsory symptoms, speech disturbance, pareisis, ataxia. At least 2 attacks must be associated with an aura during the last 6 months. Number of migraine days per month should be 2-8 documented not only by history but also during the run-in phase of 4 weeks. No more than 1 attack during the last 6 months. **Exclusion criteria:** Cluster headache. >6 days a month with interval headaches of the tension-type and other recurrent headaches. Use of other drugs with prophylactic migraine activity e.g. beta blockers, amine-antagonists. Intake of psychotropic drugs and hormones unless patients stayed on a fixed dose throughout the trial. Contraindications to calcium-antagonists suck as orthostatic hypotension and cardiac arrhythmia. Females in the fertile age who did not use appropriate preventative measures. Patients who were non-complying. Other severe chronic organic disease. Severe mental disease. Previous prophylactic migraine treatment had to be withdrawn at least 4	**Group 1 -** Nimodipine 40mg t.i.d. **Group 2 -** Placebo Identically looking, tasting and smelling to nimodipine. **All patients** Completed a 4 week run-in period following which patients were excluded if they had not had the required number of migraine days or if there were other reasons for exclusion. Throughout the run-in phase and the trial itself, patients kept a headache diary recording duration and severity of migraine and other headache, nausea, vomiting and other symptoms.	**Migraine days** (per 4 weeks) at end of test period- 89 patients (ITT analysis) **Migraine days** (per 4 weeks) at 9-12 weeks- 72 patients (efficacy analysis) **Adverse events**	**Group1:** 1.6 (n=43) **Group 2:** 0.9 (n=46) **p value:** NR **Group1:** 1.61 (n=33) **Group 2:** 0.87 (n=39) **p value**: NR None reported	**Funding:** Not reported **Limitations:** Randomisation unclear. Allocation concealment unclear. Study too small to obtain sufficient power. **Additional outcomes:** Migraine index at run-in, 1-4 weeks, 5-8 weeks and 9-12 weeks. Life table analysis of the time taken to reach the same number of migraine days as observed during the run-in period. Significant difference in body weight in the groups valid for analysis of efficacy. **Previous use of prophylactic medication:** Previous prophylactic migraine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
in 12 week double-blind period	weeks before the trial, and if patients had had 2 or more previous prophylactic treatments without effect, they were excluded. **All patients** **N:** 89 **Drop outs:** 17 **Group 1 (nimodipine)** **N:** 43 (randomised), 33 (valid) **Age (mean):** 33.2 **M/F**: 9/34 **Migraine days/4weeks:**3.4 **Duration of migraine (years):**15 **Drop outs:** 3 **Group 2 (placebo)** **N:** 46 (randomised), 39 (valid) **Age (mean):** 34.8 **M/F:** 10/36 **Migraine days/4weeks:**3.1 **Duration of migraine (years):**10 **Drop outs:** 4				treatment had to be withdrawn at least 4 weeks before the trial, and if patients had had 2 or more previous prophylactic treatments without effect, they were excluded. **Notes**: Stratified randomisation (matched for sex, age: 10 year intervals and number of migraine days: 2-4 and 5-8 days per month) ITT and efficacy analysis

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Holroyd et al, 2010[384] **Study design:** RCT **Comparison:** Beta-blocker vs placebo **Setting**: 2 outpatient sites in USA **Duration of follow-up:** 12 months 5 week run-in (optimised acute treatment) 3 month dose-adjusting phase 12 month evaluation	**Patient group:** Adults with migraines associated with disability uncontrolled on optimised acute treatment. **Inclusion criteria:** Age 18-65 years Diagnosis of migraine with or without aura according to the international classification of headache disorders criteria at 2 separate evaluations during the evaluation clinic visit Diary confirmed criteria for severity of migraine during the optimised acute treatment run-in of at least 3 migraines with disability per 30 days. **Exclusion criteria:** Diagnosis of probable medication overuse headache according to the international classification of headache disorders criteria: A pain disorder other than migraine as the primary presenting problem , 20 or more days with headache a month, Contraindication or sensitivity to any study drug, Current use of migraine preventative drugs (with participant's preference or welfare	**Group 1 -** B-blocker (doses ranged from 40 mg to 180 mg) Treatment was started with 1 capsule (60mg long acting propranolol hydrochloride) and increased to 3 capsules (180mg) at week 12 as tolerated. Participants who did not tolerate at least 2 capsules (120mg) of long acting propranolol hydrochloride and, in the judgement of the treating neurologist were unimproved, were switched with blindness maintained to nadolol. Participants initially received a single 40mg capsule of nadolol. The dose was increased at the next visit to 2 capsules (80mg) as tolerated. At week 12, the dose was stabilised at the highest tolerated level. In the evaluation phase, an increase to 4 capsules of long acting propranolol hydrochloride (240mg) or 3 capsules of nadolol was permitted (120mg). **Group 2 -** placebo Treatment was started with 1 capsule (60mg placebo) and increased to 3 capsules (180mg) at week 12 as tolerated. Participants who did not tolerate at least 2 capsules (120mg) placebo and, in the judgement of the treating neurologist were unimproved, were switched with blindness	**Migraine frequency** (Number of migraines per 30 days (with at least a 24 hour pain free period between distinct migraines): mean change) **Migraine days** (per 30 days) **Migraine specific quality of life scores** (migraine-specific quality of life MSQL version 2.1, a 14 item self reported measure with established	**Month 10** **Group1:** -2.1 (-1.9 to -2.2) (n=35) **Group 2:** -2.1 (-1.9 to -2.2) (n=40) **p value:** NR **Month 16** **Group1:** -2.5 (-2.2 to -2.8) (n=25) **Group 2:** -2.5 (-2.3 to -2.6) (n=30) **p value:** NR **Month 10** **Group1:** -3.9 (-3.5 to -4.2) (n=35) **Group 2:** -3.3 (-3.0 to -3.6) (n=40) **p value:** NR **Month 16** **Group1**: -4.5 (-4.0 to -5.1) (n=25) **Group 2:** -3.9 (-3.5 to -4.3) (n=30) **p value:** NR **Month 10** **Group1:** -7.1 (-6.6 to -7.7) (n=35) **Group 2:** -7.1 (-6.3 to -7.8) (n=40) **p value:** NR **Month 16**	**Funding:** National Institutes of Health provided primary support for the trial Merck Pharmaceuticals and GlaxoSmithKline Pharmaceuticals donated triptans **Limitations:** 2 different beta blockers were used: at end of study 87% were taking propranolol and 13% were taking nadolol. Missing data unclear. Definition of 'optimised acute treatment' unclear. **Additional outcomes:** Resting heart rate at baseline, month 5, 10 and 16 **Previous use of prophylactic medication:** Uncontrolled on optimised acute treatment of a 5-HT

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	contraindicating withdrawal), Current psychological treatment, Psychiatric disorder needing immediate or priority treatment, Inability to read and understand the study materials, Current or planned breast feeding/pregnancy/ unwillingness to use an established contraceptive method. **All patients** **N:** 232 (randomised) **Age (mean):** 38.2 (SD 10.2) **Mean migraine days/ 30 days:** 8.5 (SD 3.6) **Group 1** (optimised acute treatment plus Beta blocker) **N:** 53 (randomised), 52 (began treatment), 42 (evaluated at 5 months), 35 (evaluated at 10 months), 25 (evaluated at 16 months) **Age (mean):** 37.7 (SD 10.1) **Female :** 45 (85%) **Mean (SD) migraines/30 days:** 5.2 (1.9) **Mean (SD)migraine days/ 30 days:** 8.6 (3.3) **Mean (SD) migraine specific QoL** score:40.3 (13.4)	maintained to nadolol placebo. Participants initially received a single 40mg capsule of matched placebo. The dose was increased at the next visit to 2 capsules (80mg) as tolerated. At week 12, the dose was stabilised at the highest tolerated level. In the evaluation phase, an increase to 4 capsules of matched placebo (240mg) or 3 capsules of matched nadolol placebo (120mg) Group 3 - Behavioural migraine management plus B blocker (results not reported in this table) Group 4 - Behavioural migraine management plus placebo (results not reported in this table) **All patients** 5 week run-in during which all participants received optimised acute treatment. 4 monthly visits to the clinic and 3 telephone contacts during the 3 month treatment/ dose adjusting phase (months 1-4). During the 12 month (months 5-16) evaluation phase, clinic visits were scheduled at months 5,7, 10, 13 and 16 The acute treatment protocol emphasised treatment with a 5HT	psychometric properties) range 14-84, with higher scores reflecting greater improvement in quality of life. **Responder rate** (≥50% reduction in migraines) at month 10 **Adverse events** (% reporting serious)	**Group1:** -8.5 (-7.6 to -9.4) (n=25) **Group 2:** -8.8 (-8.1 to -9.5) (n=30) **p value:** NR **Group1:** 18/35 (34%) **Group 2:** 22/40 (40%) **p value:** Not sig None reported	agonist or triptan. NSAID (ibuprofen) and anti-emetic (metoclopramide) agents could be added as needed. Rescue drugs e.g. steroids could be prescribed. Notes: Computer generated randomisation sequence; supplied in sealed opaque envelopes by statistician unconnected with study. Randomisation stratified by sex and by site. Results analysed as an available case analysis.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 28 **Group 2** (optimised acute treatment plus placebo) **N:** 55 (randomised), 53 (began treatment), 44 (evaluated at 5 months), 40 (evaluated at 10 months), 30 (evaluated at 16 months) **Age (mean):** 39.5.1 (SD 10.2) **Female :** 45 (82%) **Mean (SD) migraines/ 30 days:** 5.5 (1.9) **Mean (SD) migraine days/ 30 days:** 8.4 (3.5) **Mean (SD) migraine specific QoL score:** 40.3 (13.4) **Drop outs:** 25	agonist or triptan. NSAIDs and anti-emetic agents could be added as needed. Rescue drugs such as steroids could also be prescribed. Patients recorded headache symptoms in a handheld electronic diary for 16 months of the trial.			

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

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Klapper, on behalf of the Divalproex Sodium in Migraine Prophylaxis Study Group, 1997[440] **Study design:** RCT **Comparison:** Anti-epileptic vs placebo **Setting:** NR **Duration of follow-up:** 12 weeks	**Patient group**: Aged over 16 with migraine with or without aura **Inclusion criteria:** Migraine with or without aura (IHS classification) for at least 6 months; averaged >2 migraine attacks per month over last 3 months; >16 years; previously untreated for migraine or, in investigators opinion, had previously failed no more than 2 'adequate' trials (e.g. at least 1 month of treatment at full therapeutic dose) of prophylactic therapy. Patients already receiving prophylactic treatment required to discontinue these medications and complete a washout period of length equivalent to at least 5 half-lives of the medication prior to enrolment. **Exclusion criteria:** Other headache types >15 days per month; migraines always un-associated with headache; cluster headaches; pregnant women; women of child bearing potential not practicing effective birth control; previously treated with valproate; significant medical or psychiatric disorder, particularly one requiring medication that could have confounded data interpretation; **All participants** **N:** 211 enrolled, 176 randomised, 171 included in ITT analysis. **Drop outs:** 39 (ineffectiveness (4),	**Group 1 -** Divalproex (DVPX Depakote) 1500mg/d **Group 2 -** Divalproex (DVPX Depakote) 1000mg/d **Group 3 -** Divalproex (DVPX Depakote) 500mg/d **Group 4 -** Placebo Washout and baseline phase: Eligible participants entered into a single blind 4 week baseline phase during which they recorded headache activity in a headache diary and took placebo medication. Subjects who completed the baseline phase compliant in using headache diary and had at least 2 migraine attacks were randomised on a 1:1:1:1 ratio at each centre for 12 weeks. Treatment Phase and treatment: 4 week titration phase followed by 8 week treatment. During 1st week of titration participants received 250mg/d divalproex	**Migraine frequency** Change in mean monthly migraine frequency during treatment phase after adjustment for baseline differences	**Group 1:** (baseline 4.7) -1.7 (n=44) **Group 2:** (baseline 4.7) -2.0 (n=40) **Group 3:** (baseline 4.5) -1.7 (n=45) **Placebo:** (baseline 6.1) -0.5 (n=42) **p value:** <0.05 compared to placebo SD not reported	**Funding:** Abbott Laboratories **Limitations:** Baseline 4 migraine attack characteristics are higher in the placebo arm than other arms. Randomisation and allocation concealment not reported. **Additional outcomes**: No. of patients achieving >50% reduction in mean no. migraine attacks with nausea, vomiting, photophobia and phonophobia; no. of patients achieving >50% reduction in mean no. non-migraine attacks; specific adverse events.
			Responder rate No. of participants with >50% reduction in migraine attacks during treatment phase	**Groups 1,2 & 3:** 57*/129 (44%) **Placebo:** 9*/42 (21%) **p value:** p<0.05	
			Baseline mean monthly migraine attacks impairing usual activity	**Group 1:** 5.9 (n=44) **Group 2:** 5.0 (n=40) **Group 3:** 5.8 (n=45) **Placebo:** 6.5 (n=42) Standard deviations not reported	
			No. of participants achieving >50% reduction in mean monthly migraine attacks impairing usual activity during treatment phase	**Group 1:** 24*/44 (55%) **Group 2:** 15*/40 (38%) **Group 3:** 25*/45 (56%) **Placebo:** 11*/42 (26%)	
			Baseline mean no. monthly migraine	**Group 1:** 6.5 (n=44) **Group 2:** 6.0 (n=40)	

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
	intolerance (27), personal reasons (5), non-compliance (2), lost to follow up (1)). **Group 1** **N:** 44 (ITT = 44) **Age (mean):** 40.7 **Drop outs:** 13 (ineffectiveness (0), intolerance (11), personal reasons (2), non-compliance (0), lost to follow up (0)). **Group 2** **N:** 43 (ITT = 40) **Age (mean):** 41.5 **Drop outs:** 10 (ineffectiveness (0), intolerance (6), personal reasons (2), non-compliance (2), lost to follow up (0)). **Group 3** **N:** 45 (ITT = 45) **Age (mean):** 40.8 **Drop outs:** 6 (ineffectiveness (0), intolerance (6), personal reasons (0), non-compliance (0), lost to follow up (0)). **Group 4** **N:** 44 (ITT = 42) **Age (mean):** 40.2 **Drop outs**: 8 (ineffectiveness (4), intolerance (2), personal reasons (1), non-compliance (0), lost to follow up (1)).	(or placebo). Doses titrated upwards at 250mg every 4 days (every 8 days for 500mg) until the assigned dose achieved. Doses then remained fixed for study period. Acute treatment Treatment with symptomatic medications was allowed on as-needed basis for treatment of individual headaches during the study, but was to average fewer than 3d/week. Disallowed medications included beta-blockers, tricyclic antidepressants, calcium channel blockers, monoamine oxidase inhibitors, methysergide maleate, lithium carbonate, phenobarbital, phenytoin, carbamazepine, warfarin sodium, and any of the following on a daily basis: ergotamine preparations, NSAIDs, analgesics, benzodiazepines or cyproheptadine hydrochloride.	attacks requiring rescue medication	**Group 3**: 6.0 (n=45) **Placebo**: 7.1 (n=42) Standard deviations not reported	**Notes:** * values calculated by NCGC Efficacy analyses based on the intent to treat dataset of all randomised patients providing headache data during experimental phase.
			No. of participants achieving >50% reduction in mean no. monthly migraine attacks requiring rescue medication during treatment phase	**Group 1**: 19*/44 (43%) **Group 2**: 15*/40 (38%) **Group 3**: 19*/45 (43%) **Placebo**: 6*/42 (14%)	

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

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Lewis et al, 2009[490] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** Multicentre study (31 US and non-US sites) **Duration of follow-up:** 16 weeks	**Patient group:** Adolescents with Migraine **Inclusion criteria:** Aged between 12 and 17 years; history of migraine (IHS criteria for pediatric migraine) for > 6 months; average of 3 to 12 migraine episodes on no more than 14 headache days (migraine and nonmigraine) per month during 3 months before screening visit and during 4 week baseline period; participants who required preventive migraine treatment (in the opinion of investigators) or who had previously had an unsatisfactory response to preventive treatment; participants in > 5th percentile for body weight according to age; no clinically significant or relevant abnormalities in physical and neurologic examinations, laboratory analyses or electrocardiography at screening. **Exclusion criteria:** Participants taking topiramate at screening, previously failed to achieve efficacy for with topiramate for migraine prevention, or discontinued topiramate treatment because of adverse events; participants with mixed headaches or unable to distinguish migraines from other headaches; overuse of acute migraine medication; BMI >40kg/m2 or weighed >200lb; participants had taken flunarizine within the 4 months before study screening,	**Group 1 -** Topiramate 100mg/day Mean +SD daily dose actually taken = 73.6 +18.7mg/d (91% achieved target dose, 51% taking target dose at end of study) **Group 2 -** Topiramate 50mg/day Mean +SD daily dose actually taken = 40.9 +10.1mg/d (94% achieved target dose, 63% taking target dose at end of study) **Group 3 -** Placebo Pre-treatment phase Eligible participants entered into up to 1 week screening period, 4 week washout period of disallowed migraine-preventive medications and 4 week baseline. Participants randomised after pre-treatment. Titration 4 week period. Topiramate doses started at 25mg/d and gradually increased at investigators discretion until participants reached assigned dose or maximum tolerated dose. Dose maintained for 12 weeks. In event of tolerability problems	**Migraine frequency** Mean +SD frequency for last 12 weeks of randomised phase (i.e. excluding titration) per 28 days	**Group 1:** (baseline 4.3+1.59) end 1.3+1.23 (n=35) **Group 2:** (baseline 4.1+1.74) end 2.4+1.84 (n=35) **Placebo:** (baseline 4.1+1.48) end 2.4+1.93 (n=33)	**Funding:** National Institutes of Health, Ortho-McNeil Jansen Scientific Affairs **Limitations:** Unclear if investigators were blinded to treatment **Additional outcomes:** Median migraine frequency at baseline, for last 12 weeks of randomised phase and percentage reduction between these; mean migraine frequency for last 4 weeks of randomised phase; percentage change from baseline in mean migraine frequency at last 4 weeks of randomisation, treatment emergent adverse events; weight change, change in BMI (Body Mass Index)
			Percentage change in mean migraine frequency between baseline and last 12 weeks of randomised phase	**Group 1:** -70.1 +25.07% (n=35) **Group 2:** -34.1 +55.21% (n=35) **Placebo:** -42.3 +43.15% (n=33)	
			Migraine days Mean +SD monthly migraine days for last 12 weeks of randomised phase	**Group 1:** (baseline 6.9+3.02) end 2.0+2.86 (n=35) **Group 2:** (baseline 6.4+2.86) end3.6+3.00 (n=35) **Placebo:** (baseline 6.1+3.02) end 3.9+3.27 (n=33)	
			Percentage change in mean monthly migraine days between baseline and last	**Group 1:** -70.8 +28.27% (n=35) **Group 2:** -34.9 +59.84% (n=35) Placebo: -35.8 +52.16%	

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
	were taking nonstable doses of psychostimulant or used corticosteriods, local anaesthetics or botox for migraine, or had a history of using antipsychotics or centrally acting sympathomimetics in nonstable doses; baseline serum ammonia levels >2 times upper limit of normal; history of any condition that could have impaired reliable participation in the study. **All participants** **N:** 106 randomised, ITT = 103 (Not reported to which groups the 3 participants not in the ITT were assigned). 141 screened. **Drop outs:** 21 **Group 1** **N:** 35 **Age (mean):** 14.2+1.5 **Age stratification:** 12 to <15 years (19), 15 to <18 years (15), >18 (1) **Drop outs:** 5 (subject choice (1), adverse event (3), other (1)) **Group 2** **N:** 35 **Age (mean):** 14.2+1.6 **Age stratification:** 12 to <15 years (20), 15 to <18 years (15), >18 (0) **Drop outs:** 6 (loss to follow up (1),	investigators could recommend dose reduction or a pause of halt of further dose titration. At treatment all participants received 2 matching tablets at each dose (4 tablets per day). Tablets contained either 25mg topiramate or placebo. Rescue medications: Rescue medications permitted included non-prescription analgesics, NSAIDs, ergot derivatives, triptans and dihydroergotamine mesylate. Treatment could not exceed 14 days per month.	12 weeks of randomised phase	(n=33)	**Notes:** Migraine episode defined as all recurrences of migraine symptoms within 48 hours of onset. Migraine day defined as calendar day during which the subject experienced >1 migraine attack, with or without aura, or a calendar day during which a subject experienced aura only but received rescue medication within 30 minutes of aura onset. Participants stratified according to age at randomisation (12 to 14 and 15 to 17 years). All results reported using Intention to Treat population (ITT). Intention to treat population described as the randomised participants who had
			Responder rate Number of participants who had a >50% reduction in mean monthly migraine frequency during last 12 weeks of randomised phase	**Group 1:** 29*/35 (83%) **Group 2:** 16*/35 (46%) **Placebo:** 15*/33 (45%)	

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
	adverse event (3), other (2)) **Group 3** **N:** 33 **Age (mean):** 14.4+1.7 **Age stratification:** 12 to <15 years (17), 15 to <18 years (14), >18 (2) **Drop outs:** 7 (subject choice (1), adverse event (1), pregnancy (1), lack of efficacy (2), other (2)) 3 subjects reached 18 years of age between screening and randomisation.				at least 1 post-baseline efficacy assessment. Results include data averaged over entire randomised treatment period including titration. Results include data from the randomised period averaged over the 12 week period after titration. * figures calculated by NCGC

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

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Lipton et al, 2011[509] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** Multicentre study (87 sites) **Duration of follow-up:** 26 weeks	**Patient group:** People with migraine **Inclusion criteria**: History of migraine (ICHD-II) for at least 1 year prior to screening; at risk of progression of episodic migraine to chronic migraine based on a prior history of experiencing migraines at high monthly frequency defined as 9 to <15 days and total of <15 headache days over 28 days before screening visit; in good health; capable of taking oral medication; females had to be postmenopausal for at least 1 year, surgically sterile or otherwise incapable of pregnancy, or using an acceptable method of birth control. **Exclusion criteria:** Previously failed >2 'adequate' trials of medications from different drug classes used for migraine prophylaxis; used medication considered effective for migraine prevention in 6 weeks before baseline visit; previously stopped topiramate because of lack of efficacy or adverse event; onset of migraine after the age of 50; migraine aura without headache; cluster headache; basilar or hemiplegic migraine; had an equally or more painful condition than their headache at the time of screening; had used a combination of headache medications for >4 days/week on a regular basis during 3 months before	**Group 1 -** Topiramate 100mg (2 x 25mg tablets twice per day) Mean daily dose actually taken = 89.5+14.2 mg/d **Group 2 -** Placebo Mean daily dose actually taken = 90.5+14.9 mg/d All medications for migraine prevention stopped 6 weeks before baseline phase Washout and baseline phase Eligible participants entered into a screening/washout period up to 42 days. This followed by a 28 day prospective baseline phase. Participants permitted to take rescue medication during this time. Participants randomised after baseline phase. Titration Topiramate doses started at 25mg/d and increased by 25mg weekly (for a total of 6 weeks) until participants	Change in mean +SD no. headache days per 28 days after treatment	**Group 1:** (baseline 13.0+2.5) -6.6+3.8 (n=159) **Group 2:** (baseline 13.1+2.6) -5.3+3.6 (n=171) **p value:** 0.001	**Funding:** Ortho McNeil Janssen Scientific Affairs **Limitations:** Study reports "approximately 10% of subjects had baseline migraine rates <9 or >15 per month", but this was an exclusion criteria **Additional outcomes:** No. of participants reporting >15 headache days per 28 days; no. of participants reporting >15 headache during last 28 days; time to first reporting of >15 headache days per 28 days; change from baseline in 28 day frequency of nausea, phonophobia and photophobia; MSQ scores for preventive function role, restrictive function role and emotional function; treatment emergent adverse events **Notes:**
			Migraine days Change in mean +SD no. migraine days per 28 days after treatment	**Group 1:** (baseline 11.6+2.0) -6.6+3.5 (n=159) **Group 2:** (baseline 11.8+2.2) -5.3+3.6 (n=171) **p value:** 0.001	
			Use of acute medication Change in mean +SD number of days of rescue medication use per 28 days after treatment	**Group 1:** (baseline 8.6+3.2) -4.8+3.5 (n=159) **Group 2:** (baseline 8.6+3.5) -3.8+3.7 (n=171) **p value:** 0.001	
			Responder rate Number of subjects with >50% reduction in headache days and migraine days	States statistically significantly different between groups but does not give values nor in favour of which intervention. **p value:** <0.001	
			Migraine specific QoL Change in mean +SD Migraine Disability Assessment score	**Group 1:** -29.7+33.05 (n=159) **Group 2:** -22.6+36.89 (n=171)	

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
	baseline phase; progressive neurological disorder other than migraine; malignancy or history of malignancy within past 5 years (except for basal cell carcinoma that was treated with local excision and was no longer present); significant medical condition of neurological, cardiovascular, hepatic or renal disease; nephrolithiasis; any unstable medical condition that may have impaired a subject's reliable participation in the study or necessitate the use of medications not permitted in study; renal or liver function tests at least twice the upper limit for normal (ULN) range or abnormal screening laboratory tests exceeding any of the following limits: alanine transaminase or aspartate transaminase >2x ULN, total white blood cell count <2300/mm^3 or 2x ULN, platelet count <80,000/mm^3, serum creatinine >2xULN; any history of suicide attempt or suicidal ideation or major psychotic disorder; history of drug or alcohol abuse within the past 2 years; positive urine drug screen for amphetamines, cocaine metabolite, marijuana metabolite, methadone, methaqualone, phencyclidine, propoxyphne or alcohol. **All participants** **N:** 385 randomised, ITT = 346, 330 evaluable for efficacy, 361 evaluable for safety **Drop outs:** 155	reached assigned dose or maximum tolerated dose, whichever was less. Participants then received that amount for 12 weeks. Rescue medications permitted during course of study	(MIDAS) **Incidence of serious adverse events** No. of participants (serious adverse events not described but study reports World Health Organisation Adverse Reaction Terminology used to code adverse events)	**p value:** 0.001 **Group 1:** 3/176 **Group 2:** 5/185	The efficacy population for this study was defined as randomised subjects who have received at least 1 dose of study drug, completed at least 28 days of the double blind phase, and had at least 1 post-dose efficacy assessment. The ITT analysis set was defined as randomised subjects who have received at least 1 dose of study drug and had at least 1 post-dose efficacy assessment. Results include data averaged over entire randomised treatment period including titration. The evaluable for safety population was defined as randomised subjects who took at least 1 dose of study drug and had at least 1 safety assessment post-dosing.

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 188 (ITT = 177, Efficacy evaluation (EE) = 159, safety evaluation = 176) **Age (mean +SD):** 39.6+10.6 **Age (mean +SD) at migraine onset:** 19.8 +10.0) **Drop outs:** 69 (lost to follow up (25), Limiting adverse event (21), Subject choice (11), Lack of efficacy (6), Significant protocol violation (2), other (4)) **Group 2** **N:** 197 (ITT = 175, Efficacy evaluation (EE) = 171, safety evaluation = 185) **Age (mean +SD):** 40.9+11.2 **Age (mean +SD) at migraine onset:** 20.8 +10.8 **Drop outs:** 86 (lost to follow up (29), Limiting adverse event (18), Subject choice (22), Lack of efficacy (8), Significant protocol violation (5), other (4))				

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

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Mathew et al, 1995[541] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** NR **Duration of follow-up:** 12 weeks	**Patient group:** Aged 16-75 with migraine **Inclusion criteria:** Migraine (IHS criteria) for >6 months; 2 or more migraine episodes per month for at least 3 months prior to screening; aged 16 to 75; not received prophylaxis treatment previously or had failed no more than 2 adequate trials of established prophylactic antimigraine regimens. **Exclusion criteria:** Only migraine episodes un-associated with headache; chronic daily headache or tension-type headaches occurring >15 days per month; cluster headaches, history of any significant medical or psychiatric disorder (particularly one that would confound data interpretation or required medication whose known effects include migraine prophylaxis); history of poor compliance with previous medication regimens; history of previous valproate use; women of child bearing potential. **All participants**	**Group 1 -** Extended release Divalproex sodium (Depakote) 500mg/d or 1000mg/d **Group 2 -** Placebo Washout and baseline phase Eligible participants entered into a single blind 4 week baseline phase during which they recorded headache activity in a headache diary and took placebo medication. Subjects who completed the baseline phase compliant in using headache diary and had at least 2 migraine attacks were randomised on a 2:1 ratio at each centre for 12 weeks. Treatment Phase: 4 week titration phase followed by 8 week treatment. During 1st week of titration participants received 250mg/d divalproex (or placebo). Doses titrated upwards at 250mg every other day (or 250mg every 3rd day for patients weighing <60kg) with the goal of achieving a trough plasma valproate sodium concentration of approximately 70 to 120mg/l.	**Migraine frequency** Mean migraine rate per 4 weeks during treatment phase	**Group 1:** (4 wk baseline 6.0) 3.5 (n=69) **Placebo:** (4 wk baseline 6.4) 5.7 (n=36) **SD:** NR p value: 0.001	**Funding:** Abbot Laboratories **Limitations:** Randomisation and allocation concealment not reported, standard deviations not reported for results. **Additional outcomes:** Frequency of migraine with nausea, vomiting, aura, photophobia, phonphobia; specific adverse events. **Previous medication:** Patients either had no previous prophylaxis or failed no more than 2 adequate trials **Notes**: Description of efficacy analyses is not given in the study.
			Migraine days Mean number per 4 weeks during treatment phase	**Group 1:** (4 wk baseline 6.9) 3.9 (n=69) **Placebo:** (4 wk baseline 7.2) 6.2 (n=36) **SD**: NR p value: <0.01	
			Responder rate No. achieving >50% reduction in 4 week migraine frequency from baseline	**Group 1:** 33/69 (48%) **Placebo:** 5/36 (14%) **p value**: <0.001	
			Mean duration of episodes during treatment phase	**Group 1:** (baseline 13.7) 11.3 (n=69) **Placebo:** (baseline 10.9) 9.5 (n=36) **SD**: NR	
			Migraine intensity Mean severity at peak intensity during treatment phase (0 = no headache, 1 = mild, 2=	**Group 1:** (baseline 2.1) 2.0 (n=69) **Placebo:** (baseline 2.2) 2.2 (n=36) **SD**: NR	

Study Details	Participants	Interventions	Outcome measures	Effect size	Comments
	N: 107 randomised, (117 enrolled) **Group 1** **N:** 70 randomised (efficacy analysis 69) **Age (mean):** 47 **Drop outs:** 12 (intolerance to study medication (9), loss to follow up (2), ineffective treatment (1). **Group 2** **N:** 37 randomised (efficacy analysis 36) **Age (mean):** 43 **Drop outs:** 5 (intolerance to study medication (2), intercurrent illness (1), non-compliance (1), personal reasons (1).	Acute treatment: Treatment with symptomatic medications was allowed on as-needed basis for treatment of individual headaches during the study, but was to average fewer than 3d/week. Disallowed medications included beta-blockers, tricyclic antidepressants, calcium channel blockers, monoamine oxidase inhibitors, methysergide maleate, lithium carbonate, phenobarbital, phenytoin, carbamazepine, warfarin sodium, and any of the following on a daily basis: ergotamine preparations, NSAIDs, analgesics, benzodiazepines or cyproheptadine hydrochloride.	moderate, 3 = severe, 4 = excruciating) Mean severity related to functional ability during treatment phase (0 = no headache, 1 = normal activity allowed, 2= disturbance of normal activity but no interruption or bed rest necessary, 3 = discontinuation of normal activity with bed rest required, 4 = emergency department visit or hospitalisation)	**Group 1:** (baseline 2.0) 1.9 (n=69) **Placebo:** (baseline 2.0) 2.1 (n=36) **SD**: NR	

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Mei et al, 2004[551] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** Headache clinic, Italy **Duration of follow-up:** 16 weeks	**Patient group:** People with migraine with and without aura for more than one year **Inclusion criteria:** Diagnosis of migraine with and without aura according to 1988 IHS criteria. Frequency of crises ranging from 2 to 6 per month. **Exclusion criteria:** Those with renal pathologies. Women taking oral contraceptives. Women who were potentially fertile and sexually active and did not use any form of contraception. Those who presented episodes indistinguishable from migraine without aura in the intercritical period. Those who had commenced any form of prophylactic therapy in the 2 months preceding the trial. Subjects on continuing medication for other pathologies were included and did not modify the dosages during the study. **All patients** **N:** 115 **Drop outs:** NR **Group 1** **N:** 58 (randomised), 35 (completed) **Age (mean):** 39.74±12.02 **Drop outs:** 23	**Group 1 -** Topiramate 25mg/day initially Increased by 25mg weekly until patients reached the dose of 100mg/day; patients then continued on that dose for 12 weeks (maintenance period); at the end, the daily dose was decreased by 25mg weekly **Group 2 -** Placebo All patients: In the month preceding the trail the selected subjects noted the number and intensity of the crises, the number of days of disability and the quantity of symptomatic drugs taken in a diary. Following randomisation, patients noted the number, intensity, duration of the crisis, signs or symptoms attributable to side effects of the drug and quantity of symptomatic drugs prescribed (NSAIDs or triptans) in a diary.	**Mean migraine frequency** (comparison of baseline period to the last 4 weeks of the study i.e. 12th to 16th weeks)	**Group1:** 2.60 **Group 2:** 4.57 **p value:** <0.001 (for TPM) **p value:** 0.10 (for placebo)	**Funding:** Not reported **Limitations:** Allocation concealment unclear Information on treatment schedule with TPM unclear; no information given for placebo. High drop out rate in both groups **Additional outcomes:** Mean cumulative migraine rate at baseline, 4, 8, 12 and 16 weeks Number of days of disability (subject absent from work/ unable to do all non-work activities) at baseline, 4,8,12 and 16 weeks. **Previous use of prophylactic medication:** Not reported
			Responder rate (reduction of ≥50% in migraine frequency) (comparison of baseline period to the last 4 weeks of the study i.e. 12th to 16th weeks)	**Group1:** 63% **Group 2:** 21% **p value:** <0.01 (for topiramate) **p value:** NR (for placebo)	
			Use of acute pharmacological treatment (comparison of baseline period to the last 4 weeks of the study i.e. 12th to 16th weeks)	**Group1:** **Baseline:** 6.17 ±1.80 **Week 16:** 2.57 ±0.80 **Group 2:** not stated **p value:<**0.001	
			Incidence of adverse events (% reporting serious)	None reported; 17 (29%) of randomised patients to topiramate group did not complete the study due to adverse events	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	M:F (%): 46:54 **Migraine with aura, n (%):** 8 (23) **Migraine without aura, n (%):** 27 (77) **Mean baseline frequency of crisis mean ±SD:** 5.26±1.29 **Monthly average days of disability, mean ±SD:** 6.83±0.923 **Mean monthly quantity of symptomatic drugs, mean ±SD**:6.17±1.8 **Group 2** **N:** 57 (randomised), 37 (completed) **Age (mean):** 38.7±11.04 **Drop outs:** 20 **M:F (%):**46:54 **Migraine with aura, n (%):**6 (16) **Migraine without aura, n (%):**31 (84) **Mean baseline frequency of crisis, mean ±SD:** 5.76±0.98 **Monthly average days of disability, mean ±SD:** 6.95±0.941 **Mean monthly quantity of symptomatic drugs, mean ±SD:** 6.49±1.29				**Notes:** Randomisation: ratio1/1. balanced blocks of 2 using a computer- generated random number scheme

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Pradalier et al, 1989[638] **Study design:** RCT **Comparison:** Beta blocker vs placebo **Setting:** Multicentre, France **Duration of follow-up:** 12 weeks 4 week run in 12 week treatment	**Patient group:** People with migraine with or without aura for more than one year **Inclusion criteria:** Suffering from migraine for at least 2 years with or without aura according to 1988 IHS classification. Age 18-65 years. Duration of symptoms prior to admission of at least 2 years. History of 2-8 crises per month. No prophylactic treatment taken during the 2 weeks preceding the start of the study. **Exclusion criteria**: History of congestive heart failure, asthma, a heart block, a bradycardia of <50 beats/min, a Raynaud phenomenon, high blood pressure. Resistant to 2 previously well-followed prophylactic treatments **All patients** **N:** 74 (entered study), 55 (entered treatment period), 41 (completed study) **Drop outs:** 14 **Group 1 (Long acting propranolol)** **N:** 40 (entered study), 31 (entered treatment period), 22 (completed study) **Age (mean):** 37.1±1.7 **Sex:** 31F, 9M **Drop outs:** 9 **Frequency of migraine (per week):** 1.66±0.23 **Former treatment with propranolol:** 10 **Previous prophylactic treatment:** 32	**Group 1 -** Long-acting propranolol, oral capsule (160mg) once daily at lunch time, for 12 weeks **Group 2 -** placebo, oral capsule once daily at lunch time, for 12 weeks **All patients** Completed a 4 week placebo run-in period. Could take their usual medication to alleviate migraine attacks	**Number of crises per month** (mean±SD) Crisis not defined	**Day 0** **Group1:** 6.11±0.93 **Group 2:** 6.00±1.37 **Day 42 (6 weeks)** **Group1:** 5.89±1.20 **Group 2:** 7.37±1.20 **Day 84 (12 weeks)** **Group1:** 3.15±0.77 **Group 2:** 6.41±1.70	**Funding:** Not reported **Limitations:** Randomisation method and timing unclear Allocation concealment unclear Unclear missing data Crisis not defined **Additional outcomes:** Blood pressure at day -28, 0, 42 and 84 Heart rate at day -28, 0, 42 and 84 Tolerability rated by the patient at day 0, 42 and 84 **Previous use of prophylactic medication:** Resistant to 2 previously well-followed prophylactic treatments **Notes:** Reported that the analysis was based on ITT principle but it is unclear that this was the case. Multivariate variance
			Adverse events (% serious)	None reported	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 (placebo) **N:** 34 (entered study), 24(entered treatment period), 19 (completed study) **Age (mean):** 37.7±1.8 **Sex:** 25F, 9 M **Drop outs:** 5 **Frequency of migraine (per week):** 1.40±0.20 **Former treatment with propranolol:** 7 **Previous prophylactic treatment:** 23				analysis used (ANOVA) to assess efficacy.

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

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Silberstein et al, 2004 MIGR-001 Study[728] **Study design:** RCT **Comparison:** Anitconvulsant vs placebo **Setting:** Multicentre study (49 US outpatient treatment centres) **Duration of follow-up:** 26 weeks	**Patient group:** Aged >12 with migraine **Inclusion criteria:** Age 12 to 65; 3 to 12 migraines during prospective 28 day baseline period; women had to be postmenopausal, surgically incapable of childbearing or practicing a medically accepted method of birth control for 1 month or longer before study enrolment. **Exclusion criteria:** Headaches other than migraine, episodic tension or sinus headaches; failure of >2 previous adequately dosed migraine preventive medications; onset after age of 50; overused acute migraine treatments (>8 treatment days per month of ergots or triptans); used beta-blockers, tricyclic antidepressants, anti-epileptics, calcium channel blockers, mono-amine oxidase inhibitors, daily NSAIDs, high-dose magnesium supplements (600mg/d), high dose riboflavin (100mg/d), corticosteroids, local anaesthetics, botulinum toxin or herbal remedies during study; participants with nephrolithiasis or those who participated in a previous topiramate study, used topiramate for 2 weeks or longer, or used an experimental drug or device within 30 days of screening. **All participants** **N:** 487 randomised, ITT = 469, (658 screened) **Drop outs:** 222 **Group 1** **N:** 117 (ITT=112) **Age (mean):** 40.5+11.4	**Group 1 -** Topiramate 200mg/d Mean daily dose actually taken = 116.2 +46.9mg/d (58.0% achieved target dose) **Group 2 -** Topiramate 100mg/d Mean daily dose actually taken = 78.3 +21.2mg/d (87.2% achieved target dose) **Group 3 -** Topiramate 50mg/d Mean daily dose actually taken = 44.7 +6.4mg/d (96.9% achieved target dose) **Group 4 -** Placebo Mean daily dose actually taken = 143.3 +43.4mg/d (based on algorithm used for 200mg/d topiramate group) 85.1% achieved target dose Washout and baseline phase Eligible participants entered into washout period up to 14 days. This followed by 28 day prospective baseline phase. Participants permitted to take rescue medication during this time. Participants randomised after	**Migraine frequency** Mean +SD monthly frequency during treatment phase	**Group 1:** (baseline 5.6+2.6) 3.3+2.9 **Group 2:** (baseline 5.4+2.2) 3.3+2.9 **Group 3:** (baseline 5.4+2.4) 4.1+3.6 **Placebo:** (baseline 5.6+2.3) 4.6+3.0 **p value**: NR	**Funding:** Johnson and Johnson Pharmaceuticals **Limitations:** Only 54% of participants completed the treatment regimen. **Additional outcomes:** Specific adverse events **Notes:** * calculated by NCGC All results reported using Intention to Treat population (ITT). ITT population described as the randomised participants who had at least 1 post-baseline efficacy assessment. Results include data averaged over entire randomised treatment period including titration.
			Responder rate Number of participants with >50% reduction in migraine during treatment phase	**Group 1:** 59*/112 (52.3%) **Group 2:** 68*/125 (54.0%) **Group 3:** 42*/117 (35.9%) **Placebo:** 26*/115 (22.6%) **p values compared to placebo:** Group 1 p<0.001, Group 2 p<0.001, Group 3 p=0.04	
			Migraine days Mean +SD monthly migraine days during treatment phase	**Group 1:** (baseline 6.6+3.1) 3.9+3.4 **Group 2:** (baseline 6.4+2.7) 3.7+3.3 **Group 3:** (baseline 6.4+2.7) 4.8+4.0 **Placebo:** (baseline 6.6+2.6) 5.3+3.6	
			Use of acute	Group 1: (baseline	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 72 (5 no post baseline efficacy data; 67 withdrew because: participant choice (8), lost to follow up (6), adverse events (38), lack of efficacy (8), other (7)). **Group 2** **N:** 128 (ITT=125) **Age (mean):** 40.6+11.0 **Drop outs:** 45 (3 no post baseline efficacy data; 42 withdrew because: participant choice (6), lost to follow up (2), adverse events (24), lack of efficacy (6), other (4)). **Group 3** **N:** 125 (ITT=117) **Age (mean):** 40.2+11.5 **Drop outs:** 57 (8 no post baseline efficacy data; 49 withdrew because: participant choice (10), lost to follow up (4), adverse events (21), lack of efficacy (10), other (4)). **Group 4** **N:** 117 (ITT=115) **Age (mean):** 40.4+11.5 **Drop outs:** 48 (2 no post baseline efficacy data; 46 withdrew because: participant choice (3), lost to follow up (5), adverse events (11), lack of efficacy (21), other (6)).	baseline phase. Titration: Topiramate doses started at 25mg/d and increased by 25mg weekly (for a total of 8 weeks) until participants reached assigned dose or maximum tolerated dose, whichever was less. Participants then received that amount for 18 weeks in 2 divided daily doses. Rescue medications permitted included aspirin acetaminophen, NSAIDs, ergot derivatives, triptans and opioids.	**pharmacological treatment** Mean +SD number of day requiring rescue medication during treatment phase	6.1+2.6) 4.0+2.8 Group 2: (baseline 5.9+2.5) 4.0+3.4 Group 3: (baseline 5.8+2.5) 4.5+3.1 Placebo: (baseline 6.1+3.0) 5.2+3.3	

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

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Silberstein et al, 2006[725,726] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** Out-patients Duration of follow-up: 20 weeks	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18 and 65 years; history of migraine with or without aura (IHS classification) for at least 12 months before screening; 3 to 8 migraines per month (28 days) but <15 headache days per month for 3 months before screening up to end of baseline period; **Exclusion criteria:** Previously failed to respond to topiramate; had taken preventive medication within 2 weeks of start of the baseline period; diagnosis of cluster headache, basilar, ophthalmoplegic, hemiplegic or transformed migraine; migraine aura exclusively without headache; failure to respond to >2 'adequately' dosed migraine preventive medications; migraine onset after age of 50; overuse of migraine treatment (e.g. triptan use on >8 days per month); injected corticosteriods, local anaesthetics or botulinum toxin within 60 days before screening; pregnant or lactating women (women of child bearing age were required to be using an approved birth control method or to abstain from sexual intercourse); serum alanine or aspartate aminotransferase levels >2 times the upper limit of the normal range; active liver disease. **All participants**	**Group 1 -** Topiramate 200mg/d Mean daily dose actually taken = 161.3 mg/d (61.3% achieved target dose) **Group 2 -** Placebo Mean daily dose actually taken = 185.6 mg/d (86.4% achieved target dose) Washout and baseline phase Eligible participants entered into a screening/washout period up to 4 weeks. This followed by 4 week prospective baseline phase during which participants kept a daily headache record. Participants permitted to take rescue medication during this time. Participants randomised after baseline phase. Titration: Topiramate doses started at 25mg/d and increased by 25mg weekly (for a total of 8 weeks) until participants reached assigned dose or maximum tolerated dose, whichever was less. Participants then received that amount for 12 weeks.	**Migraine days** Change in least mean square migraine days per 28 days during treatment phase **Responder rate** Number of participants who had a >50% reduction in mean monthly migraine frequency during treatment phase	**Group 1:** (baseline 4.8+1.5) -1.43 **Group 2: (**baseline 5.2+1.7) -1.04 SD not reported **Group 1:** 55/138 (39.9%) **Group 2:** 25/73 (34.2%) p value: NR	**Funding:** Ortho McNeil Neurologics **Limitations:** Unclear blinding and allocation concealment. **Additional outcomes:** Treatment emergent adverse events Number of patients with a >75% reduction in migraine frequency **Notes:** A migraine period defined as any occurrence that started, ended or recurred within 24 hours. Migraine that recurred within the same 24 period was considered to be part of the same episode All results reported using ITT population. ITT population described as the randomised participants who

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	N: 213 randomised, ITT = 211 **Drop outs:** 58 **Group 1** **N:** 140 (ITT = 138) **Age (mean):** 39.9+11.8 **Drop outs:** 45 (2 didn't provide post baseline efficacy data; 43 withdrew because: participant choice (8), lost to follow up (7), adverse events (21), lack of efficacy (4), protocol violation (2), other (1)). **Group 2** **N:** 73 (ITT = 73) **Age (mean):** 41.7+9.4 **Drop outs:** 13 withdrew because: participant choice (1), lost to follow up (0), adverse events (4), lack of efficacy (2), protocol violation (2), other (4)).	Rescue medications permitted during study			received at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment. Results include data averaged over entire randomised treatment period including titration.

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

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Silberstein et al, 2007[227,727,730] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** Mutlicentre study (46 US clinical centres) **Duration of follow-up:** 26 weeks (56 days pre-treatment phase, 16 weeks treatment phase, 2 weeks 'taper/exit period'.	**Patient group:** Chronic migraine **Inclusion criteria:** Diagnosis of chronic migraine according to; >15 headache days per 28 days (defined as a calendar day during which they experienced head pain for >30 minutes; experienced migraine with or without aura (IHS criteria) or migrainous headache on at least half their headache days; migrainous headache† was moderate to severe with at least 1 following migraine features: unilateral pain or pain worse on 1 side of the head, pulsatile pain, photophobia and/or phonophobia, nausea and/or vomiting, pain made worse by physical activity; Migraine Disability Assessment (MIDAS) score of at least 11 at visit 1. **Exclusion criteria:** Previously failed >2 adequate trials of migraine preventive medications (adequate defined as >3 months duration at the recommended dose); previously failed adequate trial of topiramate therapy due to lack of efficacy or adverse events; history of cluster headache or basilar, ophthalmoplegic or hemiplegic migraines; migraine onset after age of 50; overuse of acute migraine medication (defined as use in excess of 4 days per week during prospective	**Group 1 -** Topiramate 100mg/d Mean +SD dose used during study period 74.6+17.7mg/d (72.5% achieved target dose) **Group 2 -** Placebo Mean +SD dose used during study period 88.2+16.7mg/d (80.4% achieved target dose) Washout and baseline phase Eligible participants entered into washout period up to 28 days. This followed by 28 day prospective baseline phase during which participants maintained a daily headache record. Participants permitted to take rescue medication during this time. Participants randomised after baseline phase. Titration for both treatments: 4 week titration period followed by 12 week maintenance period. Titration period: 25mg 1/day for 7 days, followed by weekly increases of 25mg until either 100mg/day or max tolerated dose reached. Starting in week 2 doses given twice per day. During maintenance period a	**Migraine days** Change in mean +SD migraine/migrainous† days per 28 days during treatment phase	**Group 1:** (baseline 17.1+5.4) -6.4+5.8 (n=153) **Group 2:** (baseline 17.0+5.0) -4.7+6.1 (n=153) **p value:** 0.010	**Funding:** Ortho-McNeil Neurologics **Limitations:** Unclear allocation concealment. Only 55% of participants completed the treatment regimen (similar for each group). **Additional outcomes:** Number of patients with >25% and >75% reduction in migraine days. Change in monthly headache-free days; occurrence of associated symptoms of photophobia, phonophobia and nausea; absolute change in Headache Index, change in worst daily headache severity; unilateral pain, pulsatile pain and pain worsened because of physical activity; Physician's and Subject's Global Impression of Change (PGIC and SGIC); Migraine-Specific Quality of Life Questionnaire (MSQ) version 2.1 by domain (restrictive role function, preventive role function & emotional function, grouped
			Change in mean +SD migraine days per 28 days during treatment phase	**Group 1:** (baseline 15.2+6.4) -5.6+6.0 (n=153) **Group 2:** (baseline 15.1+5.8) -4.1+6.1 (n=153) **p value:** 0.032	
			Responder rate Number of participants who had a >50% reduction in mean migraine/migrainous† days during treatment phase	**Group 1:** 57*/153 (37.3%) **Group 2:** 44*/153 (28.8%) **p value:** NR	
			Number of participants who had a >50% reduction in mean migraine days during treatment phase	**Group 1:** 59*/153 (38.8%) **Group 2**: 47*/153 (30.9%) **p value:** NR	
			Use of acute medication Change in mean +SD number of	**Group 1:** (baseline 11.9+7.2) 4.4+5.8 (n=153) **Group 2:**	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	baseline period); history of hepatic disorder or nephrolithiasis; progressive neurologic disorder other than migraine; pregnant or nursing. **All participants** **N:** 328 randomised, ITT = 306, (686 screened) **Drop outs:** 146 **Group 1** **N:** 165 (ITT population = 153) **Age (mean):** 37.8+12.38 (n=153) **Duration of chronic migraine:** 9.3+10.5 years **Drop outs:** 73 (21 lack of efficacy, 13 subject choice, 5 protocol violation, 18 limiting adverse event, 15 lost to follow up, 1 'other'. **Group 2** **N:** 163 (ITT population = 153) **Age (mean):** 38.6+11.80 (n=153) **Duration of chronic migraine:** 9.1+10.6 years **Drop outs:** 73 (30 lack of efficacy, 10 subject choice, 6 protocol violation, 10 limiting adverse event, 16 lost to follow up, 1 'other'.	stable topiramate dose of at least 50mg/day was required. All subjects exiting the study (completers or those who discontinued) a dose taper period of up to 2 weeks was recommended. Concomitant headache medications: All preventative migraine treatments discontinued at least 14 to 28 days prior to prospective baseline period for the duration of the study. Rescue medications: Use of acute headache medication such as analgesics, NSAIDs, triptans, opioids and ergot derivatives permitted but could not exceed 4 days per week during maintenance period. Specific acute medications recorded in daily headache record along with migraine episode information. As much as possible subjects were to use same acute medications throughout the study as those they had prior to enrolment.	days per month requiring headache medication for all headache types during treatment phase	(baseline 11.4+6.6) 3.4+5.3 (n=153) **p value:** 0.127	as one); adverse events (treatment related, treatment emergent and specific adverse events). **Notes:** * calculated by NCGC † see inclusion criteria for definition of 'migrainous' headache. All results reported using ITT population. Described as the randomised participants who received at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment. Results include data averaged over entire randomised treatment period including titration. Previous preventive medications used or years used not reported.
			MIDAS Change in mean +SD MIDAS total scores from baseline during treatment phase	**Group 1:** -31.4+53.8 (n=153) **Group 2:** -21.0+52.2 (n=153) **p value:** 0.123	
			Number of deaths or serious adverse events	**Group 1:** 0/160 **Group 2:** 0/161	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Silberstein et al, 2008[723] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** 23 centres in the USA **Duration of follow-up:** 15 weeks Baseline- 4 weeks Randomisation Titration- 6 weeks Maintenance- 8 weeks Down-	**Patient group:** People with migraine **Inclusion criteria:** Age 16-65 years Clinical diagnosis of migraine headache at least 1 year before study entry, according to 1988 IHS criteria. Patients experiencing 3-9 migraine attacks during the 4 week single-blind baseline phase before 50 years of age. Serum sodium levels ≥135mEq/L at visit 1. Able to read, write and understand English. Capable of satisfying the requirements of the protocol. Willing and able to give informed consent/assent according to legal requirements. Females without childbearing potential/practicing approved contraceptive methods/negative pregnancy test. **Exclusion criteria**: ≥14 headache days with each headache lasting >4 hours (of either migraine or non-migraine type) during the last 28 days of the single-blind phase. Required symptomatic (acute) therapy more than 3 days per 7 consecutive day period for a non-migraine headache during the last 28 days of the single-blind baseline phase. Missed more than 20% of their expected doses of placebo during the last 28 days of the single-blind baseline phase. Missed 3 or more consecutive migraine diary entries during the last 28 days of the single-blind baseline phase. Previously	**Group 1 -** Oxcarbazepine: initiated at 150mg/day and increased by 150mg/day every 5 days to a maximum tolerated dose of 1200mg/day. At the investigator's discretion (based on poor tolerability) the dose could then be tapered downwards if necessary. Following step-down, the patient could be maintained at that dose level for the remainder of the titration phase, or the dose could be titrated up so the patient could reach his/her optimal dose. No further dose increases were allowed after the end of the 6 week titration period. **Group 2 -** placebo **All patients** 4 week single-blind baseline phase: patients were administered one placebo tablet (150mg matched size) in the morning and one placebo tablet in the evening. 6 week titration phase: oxcarbazepine was initiated at 150mg/day and increased by	**Migraine frequency** No. of migraine attacks, LS mean (SE) during entire double-blind phase	**Group 1**:-1.10 (0.209) **Group 2**:-1.16 (0.209) **95% CI**:-0.472, 0.593 **p value:** 0.8220	**Funding:** Novartis Pharmaceuticals Corporation **Limitations:** The interactive voice response system used to record patients' migraine characteristics was not validated between personal responses and interviews with study personnel prior to randomisation. **Additional outcomes:** Last 28 days of double-blind phase: Number of migraine attacks, Responder rate, Number of migraine days, Use of acute pharmacological treatment, Peak severity of migraine attacks, Acute therapy administered. CGI (clinical global impressions) score. PGI (patient global
			Responder rate Patients with ≥50% reduction in no. of migraines, n (%)during entire double-blind phase	**Group 1:** 23 (27.1) **Group 2:** 20(23.5) **95% CI:** 0.605, 2.568 **p value:** 0.5573	
			Migraine days No. of migraine days during entire double-blind phase	**Group 1**: -1.65 (0.330) **Group 2:** -2.02 (0.331) **95% CI**: -0.473, 1.213 **p value:** 0.3876	
			Migraine intensity Peak severity of migraine attacks, LS mean (SE) during entire double-blind phase	**Group 1:** 0.10 (0.058) **Group 2:** 0.04 (0.058) **95% CI:** -0.085, 0.213 **p value:** 0.3957	
			Use of acute pharmacological treatment Acute migraine therapy administered, LS mean (SE) during entire double-blind	**Group 1:** -0.98 (0.306) **Group 2:** -1.53 (0.306) **95% CI**:-0.232, 1.329 **p value:** 0.1670	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
titration- 1 week	failed more than 3 standard courses of a commonly effective preventative migraine treatment or had taken antidepressants (except SSRIs), beta-blockers, verapamil, diuretics, other anti-epileptics, magnesium, herbal supplements, or >50mg/day of vitamin B2 within 1 month of study entry. **All patients** **N:** 170 (randomised) **Group 1 (oxcarbazepine)** **N:** 85 **Age (mean, range):**40.6, 17-63 **M/F:** 13/72 **Average severity of migraine headache, n (%):** Moderate: 42 (49.4) Severe: 43 (50.6) **Drop outs:** 32 (29 discontinued intervention, 3 lost to follow up) **Group 2 (placebo)** **N:** 85 **Age (mean, range):** 40.3, 17-68 **M/F:** 13/72	150mg/day every 5 days to a maximum tolerated dose of 1200 mg/day. At the investigator's discretion, based on poor tolerability, the dose could then be tapered downwards, if necessary. Following step-down, the patient could be maintained at that dose level for the remainder of the titration phase, or the dose could be titrated up so the patient could reach his or her optimal dose. No further dose increases were allowed after the end of the 6 week titration period. Upon completion of the 8 week maintenance period, or at premature discontinuation, patients were gradually withdrawn from study medication in a 1 week down-titration phase. Patients were instructed to make daily telephone calls to the interactive voice response system, used to collect information from each patient	phase		impressions) score. Previous use of prophylactic medication: Those who had previously failed more than 3 standard courses of a commonly effective preventative migraine treatment were excluded **Notes:** Randomisation: performed by a contracted outside clinical research organisation using a validated system that automates the random assignment of treatment groups to randomisation numbers. Study drug packaged and labelled according to a medication code generated before the
			Serious adverse events	**Group1:** 1/85 (1.2%)patient mistakenly took a double dose and developed acute vestibulopathy; did not discontinue trial **Group 2:** 2/85 (2.4%) ankle fracture - did not discontinue trial; major depression with psychotic symptoms- not suspected to be related to study treatment- discontinued trial. **p value:** NR	
			Change in MIDAS scale, LS mean (SE) during entire double-blind phase	**Group1**: -1.16 (0.173) **Group 2:** -0.64 (0.165) **95% CI: -**0.87, -0.15 **p value:** 0.0055	
			SF-36 physical health, LS mean (SE)	**Group1:** 5.00 (1.732) **Group 2:** 3.05 (1.773) **95% CI: -**2.55, 6.44 **p value:** 0.3931	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Average severity of migraine headache, n (%): Moderate: 41(48.2) Severe: 44 (51.8) **Drop outs:**18 (16 discontinued intervention, 2 lost to follow up)	through a set of prerecorded questions. Concomitant medications were permitted during the double-blind phase. The most common were: multivitamins, SSRIs and NSAIDs. 94% used rescue medication.	**SF-36 mental health** LS mean (SE)	**Group1:** 1.17 (1.660) **Group 2:** 2.71 (1.694) **95% CI:**-5.85, 2.76 **p value:** 0.4790	trial. Each bottle had a 2 part tear off; study medication was concealed and only revealed in case of an emergency. ITT analysis - described as all randomised patients who received at least one dose of double-blind study medication.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, LS=least squares, SSRIs=Selective serotonin reuptake inhibitors

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Author & Year: Steiner et al, 1997[757] **Study design:** RCT **Comparison:** Antiepileptic vs placebo **Setting:** NR **Duration of follow-up:** 3 months	**Patient group:** People with migraine **Inclusion criteria:** Recognisable attacks of migraine for at least 2 years; between 2 & 8 attacks per month in each of the 3 months prior to screening; IHS diagnostic criteria. **Exclusion criteria:** Other troublesome headaches; other causes of chronic or recurrent pain; cardiac, hepatic or renal disease; overt depression whether treated or not; other prophylactic medication in the last 2 months (or during trial); pregnancy or risk of pregnancy; change within the last 6 months (or during trial) in use of oral contraceptives; inability or unwillingness to cooperate; entry into more than 2 clinical trials ever in the past. **All participants** **N:** 77 randomised, (110 screened) **Drop outs:** 24 (adverse events (11), ineffective treatment (4), withdrew consent (8), protocol violation (1) **Group 1** **N**: 37 **Age (mean):** 35.9	**Group 1 -** Lamotrigine Started on full dose 200mg/d (n=18) or titrated: 25mg/d weeks 1 & 2, 50mg/d weeks 3 & 4, 200mg/d thereafter (n=19) **Group 2 -** Placebo Baseline phase: Study started with a 1 month patient-blind placebo run in period at the end of which the entry criteria were required to be met a 2nd time. The intention of this was to remove placebo responders and non-compliers as far as possible prior to randomisation. Treatment phase: Participants randomised for 3 months treatment after baseline period. Rescue medication: Codamol recommended for acute treatment but other medications allowed. Ergotamine discouraged in patients were suffering frequent attacks. All recognised prophylactics were excluded from 2 months before entry.	**Migraine frequency** Mean migraine headache rate per 28 days during treatment phase	**Group 1:** (baseline 3.6) 3.0 (n=37) **Placebo:** (baseline 4.4) 3.1 (n=40) SDs not reported	**Funding:** NR **Limitations:** Unclear randomisation and allocation concealment, mean baseline migraine frequency per month higher in placebo group. **Additional outcomes:** Headache frequency in last 4 week period; mean analgesic consumption during last 4 week period; specific adverse events. **Notes:** Study states the clinical worthwhile change in headache frequency calculated a priori was a fall >1.5 attacks per month. Neither group achieved this. All randomised patients were included in the efficacy and safety analyses.
			Migraine days Mean migraine headache days per 28 days during treatment phase	**Group 1:** 4.4 (n=37) **Placebo:** 6.9 (n=40) SDs not reported	
			Migraine intensity Mean total severity scores (and index of frequency and severity) per 28 days during treatment phase	**Group 1:** 9.6 (n=37) **Placebo:** 13.1 (n=40) SDs not reported	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 14 **Group 2** **N:** 40 **Age (mean):** 38.4 **Drop outs:** 10				

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Van De Ven et al, 1997[815] **Study design:** RCT **Comparison:** Beta blocker vs placebo **Setting:** 14 centres in France, the Netherlands, Belgium and Spain **Duration of follow-up:** 12 weeks	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-75 years. Migraine with or without aura. Migraine history of at least 2 years duration. Developed at least 3 documented migraine attacks during 28 day run-in period. Not less than 3 and not more than 10 migraine attacks during the run-in period. **Exclusion criteria:** People who were already using drugs for the prevention of migraine or who were being treated with cardiovascular drugs. Contraindications for beta-blocker use or hypersensitivity to these agents. **All patients** **N:** 226 **Age (mean):** 38.7 (range 14-68) **Migraine with aura:** 23% **Migraine without aura:** 77% **Mean attack frequency:** 5.5±2.8 **Drop outs:** 31 **Group 1 (bisoprolol 5 mg)** **N:** 74 **Age (mean):** 38.3 **M/F**: 16/58 **Frequency of migraine attacks per month at run-in:** 4.4±1.6	**Group 1** Bisoprolol 5 mg, one tablet every morning **Group 2** Bisoprolol 10mg, one tablet every morning **Group 3** Placebo, one tablet every morning **All patients** Not allowed to use any other drugs for migraine prophylaxis, but allowed to use their usual acute medication for relief of pain and vomiting during each attack. Seen at 4 weeks intervals at the outpatient clinic Kept a diagnostic headache diary recording all periods of headache during the entire study period	**Migraine frequency** (attacks per month, endpoint) **Serious adverse events**	**Group1:** 2.7±1.7 **Group 2:**2.6±1.9 **Group 3**:3.2±1.8 Bisoprolol 5mg v placebo: p=<0.05 Bisoprolol 10mg v placebo: p=<0.05 None reported	**Funding:** Merck KgaA, Darmstadt, Germany **Limitations:** Randomisation method and timing unclear Allocation concealment unclear **Additional outcomes**: Frequency of migraine attacks per month in the last 2 years, at 1-4 weeks, at 5-8 weeks and at 9-12 weeks Headache severity (no results given, but stated to be not significant) Duration of attack Changes to heart rate and blood pressure **Previous use of prophylactic medication:** Not reported **Notes:** ITT analysis Attacks were rated

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mean duration of attacks (h): 20.6±18.8 **Drop outs:** 11 **Group 2 (bisoprolol 10 mg)** **N:** 77 **Age (mean):** 38.9 **M/F:** 13/64 **Frequency of migraine attacks per month at run-in:** 4.2±1.9 **Mean duration of attacks (hours):** 25.8±21.5 **Drop outs:** 9 **Group 3 (placebo)** **N:** 75 **Age (mean):** 38.8 **M/F:** 11/64 **Frequency of migraine attacks per month at run-in:** 4.0±1.8 **Mean duration of attacks (hours):** 23.4±17.5 **Drop outs:** 11				moderate to severe by almost all patients; in 7 patients with aura the attacks were rated as mild.

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