National Institute for Health and Care Excellence

Final

Addendum to Clinical Guideline 150, Headaches in over 12s: diagnosis and management

Clinical Guideline Addendum 150.1

Methods, evidence and recommendations

November 2015

Final version

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1Summary section

1.1 Update information

The NICE guideline on headaches (NICE clinical guideline CG150) was reviewed in 2013 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence relating to pharmacological treatment for the prevention of migraine. The full report can be found here: https://www.nice.org.uk/guidance/cg150/resources/headaches-surveillance-review-document2.

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Recommendations in this addendum fall into 3 categories:

[new 2015] if the evidence has been reviewed and the recommendation has been added or updated, or

[2015] if the evidence has been reviewed but no change has been made to the recommended action, or

[2012, amended 2015] if the evidence has not been reviewed since the original guideline, but the recommendation has been edited for consistency with the new recommendations, without changing the meaning. Recommendations

1. **Offer topiramate or propranolol[a] for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Advise women and girls of childbearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception if needed. [2015]**

2. **Consider amitriptyline[b] for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. [new 2015]**

3. **Do not offer gabapentin for the prophylactic treatment of migraine. [new 2015]**

4. **For people who are already having treatment with another form of prophylaxis and whose migraine is well controlled, continue the current treatment as required. [2012, amended 2015]**

1.2 Patient-centred care

This guideline offers best practice advice on the care of young people (aged 12 to 18) and adults with migraine.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the person is under 16, their family or carers should also be given information and support to help the child or young person make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

[a] At the time of publication (November 2015), topiramate did not have a UK marketing authorisation for use in children and young people for this indication. Propranolol did not have a UK marketing authorisation for use in children under 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[b] At the time of publication (November 2015), amitriptyline did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with migraine and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1.3 Methods

The scoping phase of this update (including development of the review protocol) was conducted based on the process and methods described in the guidelines manual 2012. Where there are deviations from the process and methods, these are clearly stated in the interim process and methods guide for updates pilot programme 2013. The development and validation phases of this update followed the guidelines manual 2014. For details specific to the evidence review, see Section 2.3.1.

2 Evidence review and recommendations

2.1 Introduction

Migraine is a common type of primary headache (meaning a headache not caused by an underlying disease or abnormality). Around 15% of the population are affected (Steiner et al. 2003). Acute treatment is given at the time of attacks, but preventative treatment may also be considered. The aim of the review was to evaluate the effectiveness of preventative pharmacological treatment for migraine.

The NICE technology appraisal programme has published guidance on Botox (Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. TA260). This treatment option has therefore not been included in the current review.

2.2 Review question

In people with chronic or episodic migraine (with or without aura), what is the clinical evidence and cost-effectiveness of prophylactic pharmacological treatment with:

- ACE (angiotensin converting enzyme) inhibitors and angiotensin II receptor antagonists
- Antidepressants (SNRIs, SSRIs, tricyclics)
- Centrally acting alpha-adrenergic-receptor agonists
- Beta blockers
- Calcium channel blockers
- Antiepileptics
- Other serotonergic modulators
- NMDA receptor antagonists

2.3 Clinical evidence review

2.3.1 Methods

A systematic review of the literature was conducted, as specified in the review protocol in Appendix C. The protocol was developed in consultation with the topic expert members, and then reviewed by the core Committee members, before the review was carried out. The following outcomes were considered critical for decision making: change in migraine/headache days, 50% responder (defined as the number of participants with a 50% reduction in migraine/headache frequency) and change in migraine/headache severity. The following outcomes were considered important for decision making: change in migraine/headache frequency, quality of life, change in acute medication use and serious adverse events. The outcomes ‘change in migraine/headache days’, ‘50% responder’, ‘change in migraine/headache severity’, ‘change in migraine frequency’ and ‘change in acute medication use’ were all reported per 28 days or per month.

A systematic search was conducted (see appendix D). The titles and abstracts were screened and full-text version of articles that were identified as potentially relevant were obtained and reviewed against the criteria specified in the review protocol (appendix C).

Many of the outcomes for the review were change measures from baseline (for example, change in migraine/headache days). Some studies did not report this measure directly, but instead reported the measure at baseline and at follow up for each group. In these situations the reviewer calculated the mean change from baseline and imputed the standard deviation for this measure using the following equation:

$$SD(change) = \sqrt{SD(baseline)^2 + SD(followup)^2 - (2 \times \rho \times SD(baseline) \times SD(followup)}$$

Where SD is the standard deviation and ρ is the correlation between baseline and follow up measurements across participants. This correlation can be estimated from studies that report both baseline and follow-up measurements as well as change scores. However, such studies were not available for all outcomes in this review, and so a conservative value of 0.5 was used, as is recommended when reliable correlation coefficients for the outcomes and populations of interest are not available (Follman et al., 1992; Fu et al., 2013).

When more than one study assessed an outcome for a given comparison, data were combined using meta-analyses. For the outcome 'change in migraine/headache days' a hierarchical Bayesian network meta-analysis was used to compare multiple treatments in a single internally consistent model which allowed indirect comparisons to be made between treatments that had not been directly compared in trials. Details of the methods used in this analysis, and the results are given in Appendix J. For other outcomes (and for studies reporting change in migraine/headache days that were not included in the network meta-analysis), pair-wise meta-analyses were conducted. The Mantel-Haenszel and inverse variance methods were used for dichotomous and continuous outcomes, respectively. A random effects model was chosen because the treatment effects were unlikely to be identical across studies due to differences in baseline migraine frequency and age. The I^2, chi^2 and tau^2 statistics were calculated to assess heterogeneity. Forest plots showing the outcome of these meta-analyses are shown in appendix I. For the outcome 'quality of life' the Committee agreed to use the migraine disability assessment scale (MIDAS) or paediatric version (pedMIDAS) when more than one quality of life measure was reported by the same study. Overall quality of life measures were combined in meta-analyses when reported. Sub scales are reported in full in the evidence tables.

For some medicines, different studies used different doses, or a single study reported results from several groups who were given different doses of the same medicine. Data from groups with different doses was combined, provided that the doses fell within the British National Formulary (BNF) recommended range for migraine prophylaxis. If no BNF recommended range was available, a range agreed by the topic experts was used. The original intention was to perform subgroup analyses for doses within, below and above the recommended range. However, this was not possible because the only studies that included doses below or above the recommended range were studies that reported data from more than one group with different doses. In these cases, for the pair-wise analyses data from groups outside the recommended range were excluded (and groups with doses within the recommended range were combined) because including several groups from a single trial in the same analysis would lead to a unit of analysis error. Note that for the network meta-analysis combination of the data across groups was not required as the correlation in multi-arm trials can be correctly accounted for the in the model.

Subgroup analysis was conducted for the subgroups identified in the review protocol when data was available. The presence of a significant subgroup effect was assessed by examining the statistical significance of a test for subgroup differences. A p value of less that 0.05 was taken as possible evidence for a significant subgroup effect.

For the pair-wise analyses, the quality of evidence for each outcome for each comparison was appraised using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (for full GRADE profiles, see appendix H). When there was possible evidence for a statistically significant subgroup effect, GRADE profiles were created for the overall effect and for subgroups separately. All included studies were randomised controlled trials. Typical reasons for downgrading the evidence for risk of bias included lack of or unclear blinding (of clinicians or outcome assessors; open label trials were excluded from the review) or large dropout rates, particularly when this was not accounted for in the analysis. Inconsistency (the variability in

the results from different trials) was only assessed when data were combined in a meta-analysis. The degree of heterogeneity was assessed, and 95% confidence intervals were examined to determine whether serious inconsistency was present, using the methods described by the GRADE working group. Indirectness was assessed by noting whether the evidence directly applied to the review question; no cases of serious indirectness were noted. Imprecision was assessed by determining whether 95% confidence intervals incorporated clinically important harm, no effect and clinically important benefit. If all three were incorporated in the confidence interval, imprecision was judged very serious. If two of the three were incorporated, imprecision was considered serious.

The same minimally important differences were used as those that were agreed by the guideline development group for the original NICE guideline on headaches. For quality of life measurement scales with published minimally important differences, these were used. For the outcome 'change in migraine/headache days' a minimally importance difference of 0.5 days was agreed by consensus by the previous group. For the remaining outcomes the GRADE default minimally important differences were used (0.75 and 1.25 for dichotomous outcomes, and -0.5 and 0.5 standardised mean differences for continuous outcomes). Other factors such as publication bias were also considered, but none gave rise to serious uncertainty.

For the network meta-analysis, a modified version of the approach recommended by the GRADE working group was used. Details are given in Appendix J.

2.3.2 Results

The systematic search identified 6714 articles. Three hundred and four articles were identified as potentially relevant based on their title and abstract and full-text versions were obtained. Of these, 227 were excluded as they did not meet the criteria, 33 met the inclusion criteria but either did not report any of the outcomes specified in the review protocol or did not report sufficient details to be included in the analysis. Seven articles reported the same study as another included article. Thirty seven studies met the criteria and were included.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

Details of the included studies are given in evidence tables in appendix G. Table 1 shows the number of studies included for each comparison, and Table 2 shows a summary of the included studies.

Table 1: Number of included studies reporting any of the outcomes specified in the review protocol for each comparison. Blank cells indicate comparisons for which no studies were included.

	Placebo	Telmisartan	Amitriptyline	Trazodone	Gabapentin	Levetiracetam	Divalproex Sodium	Sodium Valproate	Topiramate	Bisoprolol	Metoprolol	Nadolol	Nebivolol	Propranolol	Propranolol /nadolol	Cinnarizine	Nimodipine
Telmisartan	1																
Amitriptyline																	
Trazodone	1																
Gabapentin	2																
Levetiracetam	1																
Divalproex Sodium	4																
Sodium Valproate																	
Topiramate	11		1					2									
Bisoprolol	1																
Metoprolol																	
Nadolol	1																
Nebivolol											1						
Propranolol	4							1	1								
Propranolol /nadolol	1																
Cinnarizine							1	1	1								
Nimodipine	2																

Table 2: Summary of included studies

Study id	Population	Intervention & comparator	Location and setting	Outcomes reported
Afshari 2012	Adults with 4-10 migraines per month	Topiramate vs Sodium Valproate	Iran, hospital neurology clinic	Change in migraine/headache severity, Change in migraine/headache frequency, Change in acute

Study id	Population	Intervention & comparator	Location and setting	Outcomes reported
				medication use
Ashrafi 2014	Children and young people (aged 4 to 17) with 1 or more migraine per month	Cinnarizine vs Sodium valproate	Iran, Outpatient setting	50% responder, Change in migraine/headache severity, Change in migraine/headache frequency
Apostol 2008	Young people (aged 12 to17) with 4 to 11 migraines per month	Divalproex sodium vs Placebo	USA, Setting not specified	Change in migraine/headache days, 50% responder, Change in migraine/headache frequency
Battistella 1990	Children and young people with at least one migraine per month	Nimodipine vs Placebo	Italy, University research setting	Change in migraine/headache frequency
Battistella 1993	Children and young people with at least 3 migraines per month	Trazodone vs Placebo	Italy, University research setting	Change in migraine/headache frequency
Bavrasad 2010	Adults (aged 20 to 50) with 1 to 6 migraines per month.	Topiramate vs Sodium Valproate	Iran, University research setting	Change in migraine/headache severity, Change in migraine/headache frequency
Bidabadi 2010	Children and young people (aged 5 to 15) with migraine.	Propranolol vs Sodium valproate	Iran, Outpatient setting	50% responder, Change in migraine/headache frequency
Bostani 2013	Adults (aged 18 to 65) with 4 to 10 migraines per month.	Cinnarizine vs Sodium valproate	Iran, Neurology clinic	50% responder, Change in migraine/headache severity, Change in migraine/headache frequency, Quality of life, Change in acute medication use
Brandes 2004	Young people and adults (aged 12 to 65) with 3 to 12 migraines per month.	Topiramate vs Placebo	USA, multiple clinical centres	Change in migraine/headache days, 50% responder, Change in migraine/headache intensity, Change in migraine/headache frequency, Quality of life, Change in acute medication use
Diener 1996	Adults (aged 18 to 60) with 2 to 10 migraines per month.	Propranolol vs Placebo	Unclear (multicentre)	50% responder
Diener 2004	Young people and adults (aged 12 to 65) with 3 to 12 migraines per month.	Topiramate vs Propranolol vs Placebo	International multicentre, tertiary care headache centres	Change in migraine/headache days, 50% responder, Change in migraine/headache frequency, Change in acute medication use

Study id	Population	Intervention & comparator	Location and setting	Outcomes reported
Diener 2007	Adults with chronic migraine (at least15 migraines per month)	Topiramate vs Placebo	USA, Neurology departments (multicentre)	Change in migraine/headache days, Quality of life, Change in acute medication use, Serious adverse events
Diener 2009	Adults (aged 18 to 65) with 3 to 7 migraines per month.	Telmisartan vs Placebo	Germany, Headache clinic	Change in migraine days, Change in acute medication use
Dodick 2009	Adults (aged over 18) with 3 to 12 migraines per month.	Topiramate vs Amitriptyline	USA, Outpatient setting (multicentre)	Change in migraine/headache days, Change in migraine/headache frequency, Quality of life
Feuerstein 1990	Adults with at least 8 migraines per month.	Gabapentin vs Placebo	Austria and Germany, Outpatient/research centre setting (multicentre)	Change in migraine/headache frequency
Freitag 1984	Adults with migraine.	Nadolol vs Placebo	USA, setting not reported	50% responder
Freitag 2002	Young people and adults (aged 12+) with at least 2 migraines per month.	Sodium valproate vs placebo	Not reported	Serious adverse events
Holroyd 2010	Adults (aged 18 to 65) with at least 3 migraines per month.	Propranolol/nadolol vs Placebo	USA, Outpatient setting	Change in migraine/headache days, 50% responder, Change in migraine/headache frequency, Quality of life
Klapper 1997	Adults (aged 16+) with at least 3 migraines per month.	Divalproex sodium vs Placebo	Not reported	50% responder
Lakshmi 2007	Children and young people (aged 8 to 14) with at least 2 migraines per month.	Topiramate vs Placebo	India outpatient setting	50% responder, Change in migraine/headache frequency, Quality of life
Lewis 2009	Young people (aged 12 to 17) with 3 to 12 migraines per month.	Topiramate vs Placebo	International, multicentre	Change in migraine/headache days, 50% responder, Change in migraine/headache frequency
Lipton 2011	Adults with between 9 and 14 migraine days per month.	Topiramate vs Placebo	International, multicentre	Change in migraine/headache days, Quality of life, Change in use of acute medication, Serious adverse events
Mansoureh	Adults (aged 16 to 60)	Cinnarizine vs	Iran, Neurology department	50% responder

Study id	Population	Intervention & comparator	Location and setting	Outcomes reported
2008	with 3 to 10 migraines per month.	Divalproex sodium		
Mathew 1995	Adults with at least 2 migraines per month.	Divalproex sodium vs Placebo	USA, headache/neurology clinics (multicentre)	50% responder, Change in migraine/headache frequency
Mei 2004	Adults with 2 to 6 migraines per month.	Topiramate vs Placebo	Italy, headache clinic	50% responder
Nadelmann 1986	Adults (aged 18 to 60) with at least 4 migraines per month.	Propranolol vs Placebo	USA, setting not reported	Change in use of acute medication
Pradalier 1989	Adults (aged 18 to 65) with 2 to 8 migraines per month.	Propranolol vs Placebo	France, multicentre	Change in migraine/headache frequency
Schellenberg 2007	Adults (aged 18 to 65) with at least 2 migraines per month.	Metoprolol vs Nebivolol	Germany, Outpatient setting	50% responder rate, Change in migraine/headache frequency, Quality of life
Silberstein 2004	Young people and adults (aged 12 to 65) with 3 to 12 migraines per month.	Topiramate vs Placebo	USA, Outpatient setting (multicentre)	Change in migraine/headache days, 50% responder, Change in migraine/headache frequency, Quality of life, Change in use of acute medication.
Silberstein 2006	Adults (aged 18 to 65) with 3 to 8 migraines per month.	Topiramate vs Placebo	USA outpatient setting	50% responder, Serious adverse events.
Silberstein 2007	Adults with chronic migraine (at least 15 headache days per month, at least half of which were migrainous).	Topiramate vs Placebo	USA, Multicentre	Change in migraine/headache days, change in migraine/headache severity, Quality of life, Change in use of acute medication, Serious adverse events.
Silberstein 2013	Adults (aged 18+ with at least 3 migraines per month.	Gabapentin vs Placebo	USA/Canada, Multicentre	Change in migraine/headache days, Change in migraine/headache severity, Change in migraine/headache frequency, Change in acute medication use.
Stewart 1980	Adults (aged 18 to 65) with 2 to 10 migraines per month.	Nimodipine vs Placebo	Canada, setting not reported	Change in migraine/headache frequency

Study id	Population	Intervention & comparator	Location and setting	Outcomes reported
Van de Ven 1997	Adults (aged 18 to 75) with 3 to 10 migraines per month.	Bisoprolol vs Placebo	International, Multicentre	Change in migraine/headache frequency
Verma 2013	Adults with at least 4 migraines per month.	Levetiracetam vs Placebo	India, Outpatient neurology department	50% responder, Change in migraine/headache severity, Change in migraine/headache frequency, Change in use of acute medication
Winner 2008	Children and young people (aged 6 to15) with 3 to 10 migraine days per month.	Topiramate vs Placebo	US, Outpatient setting (multicentre)	Change in migraine/headache days, 50% responder

2.4 Health economic evidence review

2.4.1 Methods

Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits rather than the total implementation cost.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline update was sought. The health economist:

- undertook a systematic review of the published economic literature; and
- adapted the original model developed for the previous version of the guideline.

Economic literature search

A systematic literature search was undertaken to identify health economic evidence within published literature relevant to the review question. The evidence was identified by conducting a broad search relating to prophylactic medicines for migraine in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA). The search also included Medline and Embase databases using the clinical review protocol and an economic filter. Studies published in languages other than English were not reviewed. The search was conducted on 20 January 2015. The health economic search strategy is detailed in Appendix K.

The health economist also sought out relevant studies identified by the surveillance review or Committee members.

Economic literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.
- Critically appraised relevant studies using the economic evaluations checklist as specified in *Developing NICE Guidelines: the manual 2014.*
- Extracted key information about the studies' methods and results into an economic evidence profile (Table 5) and full economic evidence tables (appendix N).

Inclusion and Exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that address the review question in the relevant population were considered potentially includable as economic evidence. Studies that only reported burden of disease or cost of illness were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly

applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix M). A flowchart summarising the number of studies included and excluded at each stage of the systematic review can be found in Appendix L.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

Economic evidence profile

The economic evidence profile summarises cost-effectiveness estimates. It shows an assessment of the applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from *Appendix H of Developing NICE Guidelines: the manual 2014*. It also shows the incremental cost, incremental effect and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty. Table 3 explains the information contained in the economic evidence profile.

Table 3: Explanation of fields used in the economic evidence profile

Item	Description
Study	This field is used to reference the study and provide basic details on the included interventions and country of origin.
Applicability	Applicability refers to the relevance of the study to specific review questions and the NICE reference case. Attributes considered include population, interventions, healthcare system, perspective, health effects and discounting. The applicability of the study is rated as: • Directly applicable – the study meets all applicability criteria or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	This field provides an assessment of the methodological quality of the study. Attributes assessed include the relevance of the model's structure to the review question, timeframe, outcomes, costs, parameter sources, incremental analysis, uncertainty analysis and conflicts of interest. The methodological quality of the evaluation is rated as having: • Minor limitations – the study meets all quality criteria or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	This field contains particular issues that should be considered when interpreting the study, such as model structure and timeframe.
Incremental cost	The difference between the mean cost associated with one strategy and the mean cost of a comparator strategy.
Incremental effect	The difference between the mean health effect associated with the intervention and the mean health effect associated with the comparator. This is usually represented by quality-adjusted life years (QALYs) in accordance

Item	Description
	with the NICE reference case.
Incremental cost effectiveness ratio (ICER)	The incremental cost divided by the incremental effect which results in the cost per quality-adjusted life year gained (or lost). Negative ICERs are not reported as they could represent very different conclusions: either a decrease in cost with an increase in health effects; or an increase in cost with a decrease in health effects. For this reason, the word 'dominates' is used to represent an intervention that is associated with decreased costs and increased health effects compared to the comparator, and the word 'dominated' is used to represent an intervention that is associated with an increase in costs and decreased health effects.
Uncertainty	A summary of the extent of uncertainty about the ICER. This can include the results of deterministic or probabilistic sensitivity analysis or stochastic analyses or trial data.

Undertaking de novo health economic modelling

As well as reviewing the published economic literature for each review question, an adaption of an existing economic analysis was undertaken by the health economist.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.
- The Committee was involved in the design of the model, selection of inputs and interpretation of results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available, Committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was quality assured by another health economist within NICE's Centre for Clinical Practice.

Full methods and results for the cost-effectiveness analysis conducted for this guideline update are described in appendix O. There are many differences between the modelling conducted for this update and the original model conducted in 2012. Please refer to the discussion section of appendix O.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues

regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*.

2.4.2 Results of the economic literature review

1464 articles were retrieved by the database search. 1441 of these were excluded based on title and abstract. 23 full papers were subsequently examined. 21 of these were excluded as they did not meet the inclusion criteria. Two studies from the published literature were included in the systematic review along with the 2012 NCGC model developed for CG150 and the results of the modelling conducted for this update. Four studies have been summarised in the economic evidence profile. Table 5 contains a summary of the main results of each study included in the economic literature review and de novo modelling conducted for this update. Full economic evidence tables with additional detail for each of these studies is available in appendix N.

The economic search strategy is provided in appendix K. The flowchart summarising the systematic review process is available in appendix L. The list of excluded full articles can be found in appendix M.

2.4.3 De novo economic modelling

The model developed in 2012 for CG150 was adapted for this update. Please refer to appendix O for the full details of this analysis.

2.4.4 Unit cost of prophylactic medicines

Table 4 provides the cost of a 6 month course of treatment of most of the prophylactic medicines considered in this update.

Table 4: Unit cost of prophylactic medicines

Treatment	Calculations	6 month cost (£)	Source
Compared in 2015 economic model			
Amitriptyline 50 mg/day	7 packs of 28 x 50 mg tablets at £1.19 per pack	8.33	Drug Tariff April 2015
Topiramate 100 mg/day (after a few days at 25mg/day)	1 pack of 60 x 25 mg tablets at £2.39 per pack plus 3 packs of 60 x 100 mg tablets at £3.13 per pack	11.78	Drug Tariff April 2015
Propranolol 160 mg/day	4 packs of 56 x 160 mg tablets at £5.34 per pack	21.36	Drug Tariff April 2015
Potentially effective in pairwise analysis			
Levetiracetam	3 packs of 60 x 1 g tablets at £8.38 per pack	25.14	Drug Tariff April 2015
Divalproex sodium 1000 mg/day (valproic acid and sodium valproate, Depakote)	4 packs of 90 x 500 mg tablets at £29.15 per pack	116.60	Drug Tariff April 2015
Sodium valproate 400 mg/day	4 packs of 100 x 200 mg tablets at £4.49 per pack	17.96	Drug Tariff April 2015
Sodium valproate 600 mg/day	6 packs of 100 x 200 mg tablets at £4.49 per pack	26.94	Drug Tariff April 2015
Sodium valproate 500 mg/day	2 packs of 100 x 500 mg tablets at £8.56 per pack	17.20	Drug Tariff April 2015
Included in the network meta-analysis but excluded from the economic model because the NMA found they were ineffective			

Gabapentin 1800 mg/day	6 packs of 100 x 600 mg tablets at £10.17 per pack	61.02	Drug Tariff April 2015
Nadolol 80 mg/day	7 packs of 28 x 80 mg tablets at £5 per pack	35.00	Drug Tariff April 2015
Telmisartan	7 packs of 28 x 80 mg tablets at £1.98 per pack	13.86	Drug Tariff April 2015

Table 5 contains a summary of the main results of each study included in the economic literature review and de novo modelling conducted for this update. Full economic evidence tables with additional detail for each of these studies is available in appendix N.

Table 5: Economic evidence profile

Study	Applicability	Limitations	Comments	Incremental cost	Incremental effect	Incremental cost-effectiveness ratio	Uncertainty
Brown et al. 2006 Topiramate vs. no prophylaxis United Kingdom	Partially applicable [1,2,3,4]	Potentially serious limitations [5,6]	Decision tree	£220	0.0384 QALYs	£7,209 per QALY	• All one-way sensitivity analyses results in ICERs below £20,000 per QALY • No probabilistic sensitivity analysis
Yu et al. 2010 Amitriptyline 75 mg/day Topiramate 100 mg/day Topiramate 200 mg/day Timolol 20 mg/day Divalproex sodium 1000 mg/day Propranolol 160 mg/day No prophylaxis United States	Partially applicable [7,8]	Potentially serious limitations [9,10,11]	Markov model	Compared with no treatment (£, 2015) [12] • Topiramate 200: 1399 • Amitriptyline: 1418 • Topiramate 100: 1453 • Timolol: 1528 • Divalproex sodium: 1631 • No prophylaxis: 1896 • Propranolol: 1985	Compared with no treatment (QALYs) • Topiramate: 0.456 • Amitriptyline: 0.453 • Topiramate 100: 0.440 • Timolol: 0.488 • Divalproex sodium: 0.461 • No prophylaxis: 0.411 • Propranolol: 0.476	Topiramate 200 vs. no treatment: £3,067/QALY [13] Timolol vs. topiramate 200: £4,058/QALY Dominated by topiramate 200: • Amitriptyline • Topiramate 100 • No prophylaxis Dominated by timolol: • Propranolol • Divalproex sodium	In a scenario where each treatment resulted in the lowest percentage education in monthly frequency, highest rate of adverse events and a greater disutility associated with adverse events, amitriptyline and topiramate 100 resulted in lower QALYs at a lower cost compared to no prophylaxis and topiramate 200, timolol and divalproex sodium dominated no prophylaxis and propranolol had an ICER of US$4695 (2009) compared to no prophylaxis. Probabilistic sensitivity analysis: all prophylaxis options >90% likelihood of being cost effective compared to no prophylaxis at all cost-effectiveness thresholds up to US$100,000
NCGC 2012 Acupuncture	Directly applicable	Minor limitations [14]	Bayesian network meta-analysis	Compared with no prophylaxis: • Propranolol: £90	Compared with no prophylaxis (QALYs): • Propranolol:	Expected incremental net monetary benefit at a cost-effectiveness	Probability the treatment is most cost-effective: • No prophylaxis: 2.2%

Study	Applicability	Limitations	Comments	Incremental cost	Incremental effect	Incremental cost-effectiveness ratio	Uncertainty
Telmisartan Propranolol Topiramate United Kingdom				• Topiramate: £112 • Telmisartan: £194 • Acupuncture: £228	0.594 • Topiramate: 1.065 • Telmisartan: 0.510 Acupuncture: 0.583	threshold of £20,000/QALY: • No prophylaxis: £0 • Propranolol: £53.63 • Topiramate: £139.90 • Telmisartan: -£66.53 • Acupuncture: -£75.21	• Propranolol: 25.5% • Topiramate: 45.2% • Telmisartan: 20.7% • Acupuncture: 6.4%
NICE 2015 [15] No prophylaxis Amitriptyline Topiramate Propranolol United Kingdom	Directly applicable	Minor limitations [16,17]	Bayesian network meta-analysis	Compared with no prophylaxis: • Amitriptyline: £6.52 • Topiramate: £7.40 • Propranolol: £19.08	Compared with no prophylaxis: • Amitriptyline: 0.01688 • Topiramate: 0.01853 • Propranolol: 0.02118	Amitriptyline vs. no prophylaxis: £386 per QALY Topiramate vs. amitriptyline: £538 per QALY Propranolol vs. topiramate: £4,359 per QALY Incremental net monetary benefits (£20,000 per QALY threshold): • Amitriptyline: £331 • Topiramate: £363 • Propranolol: £405	Probability that treatment is the most cost effective: Amitriptyline: 31% Topiramate: 22% Propranolol: 47%

Acronyms: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

1. *The utilities were based on the SF-36 quality of life measure. The NICE reference case specifies the EQ-5D as the preferred quality of life measurement tool.*
2. *The cost of topiramate is now substantially lower than the cost used in this analysis (£1.60 per month in 2015 compared with £34 per month used by Brown et al. in 2006).This would not change the main conclusions of the study because it would only make topiramate even more cost effective.*
3. *The cost of triptan is now substantially reduced compared with what was used in this analysis. For example, sumatriptan costs £0.28 per tablet compared with £4.57 per tablet used in the 2006 analysis. The specific triptan medicine used for this analysis was not specified.*
4. *The main factor limiting the applicability of this analysis is that it compared only one antiepileptic medicine against no prophylaxis. The cost effectiveness of all effective prophylactic medicines is required for the present decision-making context.*
5. *No utility decrement or cost consequences were included for side effects of topiramate treatment despite the paper noting a 25% discontinuation rate due to adverse events and 40% discontinuation rate in total.*
6. *The study was funded by Johnson & Johnson.*

7. *Utilities derived from the Health Utilities Index Mark 3 (HUI3) measure*
8. *Analysis conducted for compliant population. This may not be generalisable to the clinical practice.*
9. *Cost of triptan derived from an average of all available triptans resulting in a cost of US$22.26 (2009). This contrasts with the cost of £0.28 per dose for sumatriptan in 2015 (subsequently used for the economic modelling for the present update). The higher cost of triptan would have had the effect of decreasing the relative cost effectiveness of no prophylaxis and increasing the relative cost effectiveness of prophylactic medicines than they would have been with a lower cost for triptan, other things being equal.*
10. *Probabilistic sensitivity analysis used triangular and uniform distributions.*
11. *No cost was applied to adverse events.*
12. *2009 US$ have been converted to 2015 UK£. These are direct costs only.*
13. *Incremental analysis was conducted by the guideline update author to derive incremental cost-effectiveness ratios rather than average cost-effectiveness ratios.*
14. *Adverse events not included*
15. *Full details of the methods and results of this analysis can be found in appendix O.*
16. *6 month timeframe*
17. *Other resource use outside of the cost of medicines not included*

2.5 Evidence statements

The results of the network and pair-wise meta-analyses can be found in Appendices J and I, respectively. Full GRADE profiles can be found in Appendix H.

2.5.1 Clinical evidence statements

Change in migraine days per month– network meta-analysis (episodic migraine)

Eleven trials on 3002 participants with episodic migraine reported the outcome 'change in migraine days' and were combined in a network meta-analysis (NMA). Overall, the evidence from the NMA was low quality and there was considerable uncertainty associated with the treatment rankings.

There was evidence of a clinically important benefit of topiramate [MD=-1.03 days (95%CrI -1.53 to -0.58)] and of a benefit of less certain clinical importance of propranolol [MD=-1.19 days (95%CrI -2.20 to -0.21)] compared with placebo. Amitriptyline was ranked highly among the treatment options, but the treatment effect compared with placebo was associated with a high degree of uncertainty [MD=-0.93 days (95%CrI -2.27 to 0.38)].

Gabapentin, telmisartan, divalproex sodium, and propranolol/nadolol (a treatment plan that started with propranolol and switched to nadolol if propranolol was not tolerated or was ineffective) did not rank highly overall and there was no evidence of clinically important benefits compared with placebo.

Change in migraine days per month– pairwise analysis (chronic migraine)

Two trials on 359 participants with chronic migraine compared topiramate with placebo on the outcome 'change in migraine days' and were combined in a pairwise meta-analysis, which provided low-quality evidence favouring topiramate over placebo [MD=-2.27 days (95%CI -4.2 to -0.35)].

Other outcomes – pairwise meta-analysis (episodic and chronic migraine)

Evidence from pairwise comparisons across a range of outcomes was broadly consistent with evidence from the NMA.

Overall, moderate to low quality evidence from pairwise comparisons favoured topiramate (11 trials, 2529 participants) and propranolol (5 trials, 619 participants) over placebo, with no evidence of a difference in effectiveness between episodic and chronic migraine, or between ages.

There was moderate quality evidence from 2 trials (514 participants) suggesting no clinically important difference between gabapentin and placebo, and moderate quality evidence from 1 trial (84 participants) suggesting no clinically important difference between telmisartan and placebo.

Four trials (778 participants) compared divalproex sodium with placebo. Evidence suggested a clinically important benefit from divalproex sodium for people over 18, but not for people under 18. However, because there was only 1 trial that included people under 18, it was difficult to be certain that this effect was due to age rather than some other difference between trials. When the age groups were considered separately, the quality of evidence for divalproex sodium compared with placebo was high to low. However, if considered as a single group the quality was low to very low because of inconsistency between studies.

There were no trials comparing amitriptyline with placebo, but 1 trial (331 participants) compared topiramate with amitriptyline and provided moderate quality evidence showing no clinically important difference in effectiveness.

Some additional treatments were included in the pairwise analyses that were not included in the NMA. There was moderate quality evidence from 1 small trial (52 participants) favouring levetiracetam over placebo. Three studies compared cinnarizine with other treatments, although there was no evidence comparing cinnarizine with placebo. Overall evidence from 2 studies (229 participants) favoured divalproex sodium/sodium valproate over cinnarizine, but low to very-low quality evidence from 1 study (40 participants) in children and young people favoured cinnarizine over topiramate.

No comparisons involved trade-offs between harms and benefits across outcomes. Evidence on serious adverse events was generally very-low quality and inconclusive because of the small numbers of events in all trial arms.

There was no clear evidence for benefit for trazodone, nimodipine, bisoprolol, metoprolol, nebivolol or nadolol as evidence for these comparisons was generally low to very-low quality and only a small number of outcomes were reported.

2.5.2 Health economic evidence statement

An economic analysis undertaken for the update found that propranolol was the optimal treatment for the prophylaxis of migraine and had the highest probability of being the most cost effective prophylactic medicine. Amitriptyline and topiramate also had incremental cost effectiveness ratios that were well below the cost-effectiveness threshold. There was a high degree of uncertainty surrounding the results of the model. This analysis is directly applicable with minor limitations.

A 2006 analysis found that topiramate was cost effective compared with no prophylaxis. This study was partially applicable with potentially serious limitations. A 2010 analysis found that topiramate and timolol were cost effective compared with no treatment, amitriptyline, propranolol and divalproex sodium. This study was partially applicable with potentially serious limitations. The 2012 NCGC model for CG150 found that topiramate was the most cost effectiveness treatment compared with propranolol, no prophylaxis, telmisartan and acupuncture. Propranolol was the only other treatment to result in a positive incremental net monetary benefit compared with no prophylaxis. Telmisartan and acupuncture resulted in negative incremental net monetary benefits. This analysis was directly applicable with minor limitations.The costs of prophylactic and acute medicines for migraine have decreased since studies prior to 2015 were conducted.

2.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee valued the outcome ‘change in migraine/headache days’ highly because it incorporates both migraine frequency and duration, and so was considered a good estimate of the effectiveness of prophylactic medication because either a reduction in the frequency or duration of migraine is a valuable outcome for patients. The outcome ‘change in migraine/headache days’ was therefore prioritised for network meta-analysis and formed the basis of the economic model. 50% responder was considered important as a 50% reduction in migraine frequency is considered an adequate response to prophylactic medication clinically. Migraine severity was valued highly because the severity of migraine was considered to be an important outcome for patients, which is not captured by measures of frequency or duration; a prophylactic medication could be considered useful even if it had no effect on migraine frequency, but reduced the severity of attacks. Quality of life was valued less highly as the

	Committee discussions
	Committee considered that this outcome was difficult to accurately measure and would be reflected in the 3 critical outcomes. Likewise, change in migraine/headache frequency and change in acute medication use were valued less highly because they were considered likely to be reflected in the critical outcomes.
Quality of evidence	The network meta-analysis for the outcome 'change in migraine days' was overall low in quality; many of the trials had large dropout rates and the effect estimates for many of the interventions were associated with high degrees of uncertainty. In particular, the 95% credible intervals (which, like confidence intervals for traditional analysis give an estimate of the precision of an effect) for the mean difference in change in migraine days between amitriptyline and placebo were wide and encompassed 0. The consistency between direct and indirect evidence could not be assessed because there were no loops in the network (other than one formed by a single 3-arm trial). However, the effect estimates for the network meta-analysis and pair-wise analyses were broadly consistent. All trials that formed the network meta-analysis were double blind, which strengthened the certainty in the evidence, and the network meta-analysis allowed coherent comparison between multiple treatments. Evidence from pair-wise analysis was of variable quality, ranging from high to very low. Drop-out rates were often high, and analysis was not always based on the intention to treat principle, leading to serious risk of bias. Much of the evidence was collected in secondary care settings outside of the UK, and there was no evidence from UK primary care settings. The Committee noted that the majority of patients with migraine would be cared for in a primary care setting, and so considered the applicability of the evidence to this setting. The Committee concluded that although there may be some differences in criteria for the initiation of prophylactic treatment across healthcare systems, the patients in the trials were likely to be broadly similar to those typically encountered in UK practice (although the Committee did not review evidence for this), and so the evidence was generalisable. Evidence on serious adverse events was of very low quality across comparisons, largely due to the small number of serious adverse events in all study groups leading to high degrees of uncertainty in the effect estimates.
Trade-off between benefits and harms	The review did not identify evidence of a harmful effect for any of the medicines identified. However, the evidence on serious adverse events was often absent or of very low quality. The Committee noted that side effects were likely to occur for all of the medicines identified, and that the side effect profile differed for each medicine. This, as well as the patient's co-morbidities and pregnancy potential should be taken into account when offering prophylactic treatment. Overall, the Committee considered that evidence supported the use of topiramate and propranolol as effective treatments for the prevention of migraine across a range of outcomes, and so these medicines should be offered for the prophylaxis of migraine. The Committee also judged that overall, evidence also favoured amitriptyline as a possible treatment, although the evidence was less certain. There was a single trial comparing topiramate and amitriptyline which was included in the network and pairwise analyses. Evidence from the pairwise analysis suggested that topiramate and amitriptyline had similar effectiveness, and indirect evidence suggested that amitriptyline was favoured over placebo, but with wide credible intervals that included 0. The Committee also noted that amitriptyline does not have a current marketing authorisation for migraine prophylaxis, whereas topiramate and propranolol do. The Committee therefore that the balance of evidence favoured amitriptyline less strongly that topiramate and

	Committee discussions
	propranolol and warranted a weaker recommendation. The topic expert members noted that topiramate, propranolol and amitriptyline had been successfully used in clinical practice for many years. They noted that the choice of medication may depend on individual patient preference and comorbidities, and the acceptability of side effects. In contrast to the evidence review for the original guideline, the current review identified evidence that gabapentin was not more effective than placebo in the prevention of migraine. The previous guideline considered a study by Di Trapani (2000) which was not included in the current review because the treatment period at the final dose was less than the 12 weeks specified in the review protocol (see the list of excluded studies in Appendix F). Two studies comparing gabapentin were included in the current review: 1 was a research report originally produced in 1990, but that only entered the public domain subsequent to the publication of the previous guideline (Feuerstein 1990), and the second was a study reported subsequent to the previous guideline (Silberstein 2013). The previous NICE guideline on headaches recommended that gabapentin was considered for migraine prophylaxis if topiramate and propranolol were ineffective or unsuitable, and this has been implemented in clinical practice. The committee therefore believed that in the light of the new evidence for the ineffectiveness of gabapentin, a specific recommendation stating that gabapentin should not be used for migraine prophylaxis should be made. The Committee considered that the evidence for levetiracetam and divalproex sodium/sodium valproate was not sufficiently strong to support a positive recommendation for these medicines. There was some evidence favouring levetiracetam, but this was from a single small study, and the outcome 'change in migraine/headache days' was not reported, so the medicine could not be included in the network meta-analysis. There was also possible evidence favouring divalproex sodium in adults (but not young people). However, it was not clear whether the evidence for a difference in effectiveness across age groups was robust, and if the data from both age groups was combined in a single analysis the evidence for a beneficial effect of divalproex sodium was much less robust, with 95% confidence intervals crossing the line of no effect. Evidence for other medicines included in the review was either absent, of low or very low quality or only included a small number of outcomes. The Committee therefore agreed that no recommendations could be made for these medicines (angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, antidepressants except amitriptyline, centrally-acting alpha adrenergic receptor agonists, calcium channel blockers, betablockers except propranolol, antiepileptics except topiramate, other serotonergic modulators and NMDA receptor antagonists).
Trade-off between net health benefits and resource use	Two economic studies were identified in the literature review. The Committee also considered the model developed for CG150 in 2012 and an adaption of this model for the present update. The usefulness of previous economic studies prior to 2015 was limited because the costs of both prophylactic and acute treatments have decreased since they were conducted. The 2015 NICE model found that propranolol was the preferred prophylactic treatment and highest probability of being the most cost effective treatment. Propranolol was subsequently recommended as first-line prophylactic treatment for migraine. The Committee decided to include topiramate as first-line prophylactic treatment as well because it had a positive incremental net monetary benefit compared with no prophylaxis, the point estimates of incremental

	Committee discussions
	cost-effectiveness were close together and there was a wide degree of uncertainty around these results. In addition, both propranolol and topiramate were licensed for prophylaxis of migraine. The Committee did not include amitriptyline as first-line prophylaxis because the economic model showed that additional health benefits were available with topiramate and propranolol at an acceptable cost, it was not currently licensed for prophylaxis against migraine and the credible interval in the clinical network meta-analysis was wide. The Committee decided to include amitriptyline as a second-line prophylaxis option for people with migraine because there was a high degree of uncertainty around the results and the clinical review showed that amitriptyline was a potentially effective prophylactic medicine. The committee considered three sensitivity analyses in the economic modelling. The first was based on the higher cost of liquid forms of medicines for adolescents who find it difficult to take tablets. This sensitivity analysis resulted in ICERs for amitriptyline and propranolol compared with no prophylaxis that were well under the cost-effectiveness threshold. The second sensitivity analysis considered a lower disutility for migraine. This sensitivity analysis resulted in a reduction in cost effectiveness compared with the base case analysis due to the lower health benefits achieved with prophylactic medicines. However, all three prophylactic medicines, topiramate, amitriptyline and propranolol, were still highly cost effective under this scenario compared with no prophylaxis. The third sensitivity analysis attempted to incorporate adverse events into the analysis. This scenario resulted in incremental net monetary benefits that were similar to the base case analysis because, although there was a slight reduction in health benefits, there was also a reduction in cost because of the proportion of people who do not continue taking prophylactic medicine for the full 6 months.
Other considerations	The topic-expert committee members noted that many of the medicines (including topiramate, sodium valproate, gabapentin and levetiracetam) were associated with high teratogenicity which meant that they are contra-indicated in pregnancy. Consequently the Committee agreed that recommendation 1 (which was unchanged from the previous version of the guideline in 2012) should continue to include specific reference to advising women of childbearing age of the risk of fetal malformations and the effect of topiramate on the effectiveness of hormonal contraception.

2.7 Recommendations

1. Offer topiramate or propranolol[c] for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Advise women and girls of childbearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception if needed. [2015]

[c] At the time of publication (November 2015), topiramate did not have a UK marketing authorisation for use in children and young people for this indication. Propranolol did not have a UK marketing authorisation for use in children under 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

2. **Consider amitriptyline[d] for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. [new 2015]**

3. **Do not offer gabapentin for the prophylactic treatment of migraine. [new 2015]**

4. **For people who are already having treatment with another form of prophylaxis and whose migraine is well controlled, continue the current treatment as required. [2012, amended 2015]**

[d] At the time of publication (November 2015), amitriptyline did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

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4 Glossary and abbreviations

Please refer to the NICE glossary.

Appendices

Appendix A: Standing Committee members and NICE teams

A.1 Core members

Name	Role
Susan Bewley (Chair)	Professor of Complex Obstetrics, Kings College London
Gita Bhutani	Clinical Psychologist, Lancashire Care NHS Foundation Trust
Simon Corbett	Cardiologist, University Hospital Southampton NHS Foundation Trust
John Graham	Consultant Oncologist & Trust Cancer Lead Clinician, Taunton & Somerset Hospital
Peter Hoskin	Consultant in Clinical Oncology, Mount Vernon Hospital
Roberta James	Programme Lead, Scottish Intercollegiate Guidelines Network (SIGN)
Jo Josh	Lay member
Asma Khalil	Obstetrician, St George's Hospital University London
Manoj Mistry	Lay member
Amaka Offiah	Reader in Paediatric Musculoskeletal Imaging and Honorary Consultant Paediatric Radiologist, University of Sheffield
Mark Rodgers	Research Fellow, University of York
Nicholas Steel	Clinical Senior Lecturer in Primary Care, Norwich Medical School
Sietse Wieringa	General Practitioner, Barts & the London School of Medicine & Dentistry

A.2 Topic expert Committee members

Name	Role
Ishaq Abu-Arafeh	Consultant Paediatrician, Forth Valley Royal Hospital, Stirlingshire
Fayyaz Ahmed	Consultant Neurologist, Hull & East Yorkshire Hospitals NHS Trust
Kay Kennis	GPwSI, Bradford Primary Care Neurology Service
Susie Lagrata	Headache Specialist Nurse, The National Hospital for Neurology and Neurosurgery
Wendy Thomas	Lay member

A.3 NICE project team

Name	Role
Phil Alderson	Clinical Advisor
Emma Banks	Co-ordinator
Elizabeth Barrett	Information Specialist
Paul Crosland	Health Economist
Nicole Elliott	Associate Director
Kathryn Hopkins	Technical Analyst
Susannah Moon	Programme Manager
Rebecca Parsons	Project Manager
Charlotte Purves	Administrator
Toni Tan	Technical Advisor

A.4 Clinical guidelines update team

Name	Role
Martin Allaby	Clinical Advisor
Jessica Fielding	Public Involvement Advisor
Annette Mead	Senior Medical Editor
Bhash Naidoo	Technical Lead (Health Economics)
Louise Shires	Guideline Commissioning Manager
Sharon Summers-Ma	Guideline Lead
Judith Thornton	Technical Lead
Trudie Willingham	Guideline Co-ordinator

Appendix B: Declarations of interest

Member name	Interest declared	Type of interest	Decision
Susan Bewley	Self-employed academic and obstetric expert.	Personal financial interest	Declare and participate
Susan Bewley	100 hour per annum teaching contract with Kings College London.	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee for Teaching (BSc law and ethics tutor at KCL, occasional fees for lectures on obstetrics)	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee for Medico-legal reports (approx. 2/year) and Medical Defence Union cases committee and council	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee for external reviews for NHS organisations related to my obstetric expertise (serious incident and maternal mortality investigations, RCOG review)	Personal financial interest	Declare and participate
Susan Bewley	Received fee for Chairing NICE GDG	Personal financial interest	Declare and participate
Susan Bewley	Received royalties from edited books	Personal financial interest	Declare and participate
Susan Bewley	Expressed views in publications about obstetric matters, largely based on evidence.	Personal non-financial interest	Declare and participate
Susan Bewley	A trustee and committee member of Healthwatch (a charity devoted to evidence and “for treatments that work”) and a trustee of Sophia (a charity devoted to women with HIV and the UK arm of the Global Coalition for Women and AIDS).	Personal non-financial interest	Declare and participate
Susan Bewley	Member of the following editorial boards: Medical Law Review, International Journal of Childbirth, Journal Article Summary Service; Member All-Parliamentary Party Group on Maternity; Trustee of Maternity Action (a charity which aims to end inequality and improve the health and well-being of pregnant women, partners and young children), one of seven members of the Women’s Health and Equality Consortium which is a Strategic Partner of the Department of Health.	Personal non-financial interest	Declare and participate
Susan Bewley	Part-time on call sexual offences examiner (forensic medical examinations) working at the Haven Camberwell Sexual Assault Referral Centre (Kings College Hospital)	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee as Consultant for the World Health Organisation (five days approx), for their updated guideline on Reproductive and Sexual Health and Human Rights for Women living with HIV	Personal financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Susan Bewley	Received fee as Chair of NICE Fertility Evidence Update	Personal financial interest	Declare and participate
Susan Bewley	Received income/fee as External examiner obstetrics and gynaecology, University College Dublin	Personal financial interest	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for maternal mortality investigation	Personal financial interest	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for RCOG service review Independent Review panel	Personal financial interest	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for medicolegal criminal case	Personal financial interest	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for obstetric and managerial advice (overseas not- hospital) for-profit	Personal financial interest	Declare and participate
Susan Bewley	Received fee for attending NICE GRADE training development	Personal financial interest	Declare and participate
Susan Bewley	Received fee for appearances on BBC Radio 4 (inside health, in the ethics committee)	Personal financial interest	Declare and participate
Susan Bewley	Received fee for lecture at Royal Society of Medicine Retired Fellows Modern Reproduction: blood, guts, loss and King Midas	Personal financial interest	Declare and participate
Susan Bewley	Expenses paid to lecture at the National RCOG trainees annual conference	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the Royal Society of Medicine	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the GLADD Annual conference	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the FIL Annual conference	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the RCOG Review training	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the BPAS Annual Meeting Clinical Forum	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lecture at the WOW Festival	Personal financial interest	Declare and participate
Susan Bewley	Expenses only lectures relating to publicising NICE intrapartum guidelines	Personal non-financial interest	Declare and participate
Susan Bewley	Lecture fee, at ‘safe hands conference’ Bolton	Personal	Declare and

Member name	Interest declared	Type of interest	Decision
		financial interest	participate
Susan Bewley	Unpaid (but travel, hotel and subsistence) trip to two not-for-profit maternity hospitals in return for four days teaching/ expert advice, India	Personal financial interest	Declare and participate
Gita Bhutani	Chair of Psychological Professions Network North West	Personal non-financial interest	Declare and participate
Gita Bhutani	Member of British Psychological Society; Division of Clinical Psychology; Faculty of Leadership and Management Committee Member	Personal non-financial interest	Declare and participate
Gita Bhuitani	Project lead on BPS Division of Clinical Psychology project on 'Comprehensively representing the complexity of psychological services'	Personal non-financial interest	Declare and participate
Gita Bhutani	Analytical support in partnership with Liverpool University on Liverpool Health Partners project on Patient Quality and Safety	Personal non-financial interest	Declare and participate
Gita Bhutani	Joint project lead on Health Education North West funded project on Schwartz Rounds	Personal, non-financial, non-specific	Declare and participate
Simon Corbett	Network Service Adviser for the British Cardiovascular Society. This role incorporates the regional specialty adviser role for the Royal College of Physicians.	Personal non-financial interest	Declare and participate
Simon Corbett	Director for Clinical Effectiveness for employer (University Hospital Southampton NHS Foundation Trust). Part of this role involves the dissemination and implementation of NICE guidance in the Trust.	Personal non-financial interest	Declare and participate
Simon Corbett	Independent cardiologist on the Trial Steering Committee of the randomised controlled AVATAR trial, a randomised trial of medical therapy vs ablation in patients with atrial fibrillation. The study is sponsored by Imperial College London and is part funded by Medtronic. Travel expenses are paid by Imperial.	Personal non-financial interest	Declare and participate
Gail Fortes Mayer	None		Declare and participate
John Graham	Director of National Collaborating Centre for Cancer – this post is funded through a contract with NICE to produce NICE's clinical guidelines.	Non-personal financial interest	Declare and participate
John Graham	Principal investigator for On-going clinical trials in prostate cancer: 1) With Custirsen funded by OncoGenex Technologies Inc and Teva Pharmaceutical Industries Ltd. 2) Orteronel Affinity Trial funded by Millenium Pharmaceuticals Inc 3) Principal investigator for a study of radium-223 in prostate cancer that is funded by Bayer	Non-personal financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
	Pharmaceuticals		
John Graham	Principal investigator for 8 On-going clinical trials in breast and prostate cancer run via the National Cancer Research Network (not pharmaceutical industry funded)	Non-personal financial interest	Declare and participate
John Graham	Member of the trial management groups for 2 prostate cancer trials: RT01 and CHHIP. Both are closed to recruitment but continuing to report trial results.	Personal non-financial interest	Declare and participate
John Graham	Consultancy work for NICE International on a project with the Philippines Department of Health to produce clinical guidelines on breast cancer. Travel expenses paid	Personal non-financial interest	Declare and participate
John Graham	Council member of the South-West England Clinical Senate	Personal non-financial non specific	Declare and participate
Peter Hoskin	Investigator in research studies sponsored by various companies with payment for expenses to NHS Trust and department which fund research staff. Recent studies have been on behalf of Millenium, Astellas, Ipsen and Amgen.	Non-personal financial interest	Declare and participate
Peter Hoskin	Fellow of the Royal College of Radiologists and member of Faculty Board, Specialist Training Board and Chair of Exam Board.	Personal non-financial interest	Declare and participate
Peter Hoskin	Consultant to the IAEA; Undertake by invitation lectures and working group meetings for which expenses may be paid.	Personal financial interest	Declare and participate
Peter Hoskin	Department reimbursed for studies on alpharadin by Astellas.	Non-personal financial interest	Declare and participate
Peter Hoskin	Department reimbursed for studies on MDV 3100 by Medivation. and Astellas	Non-personal financial interest	Declare and participate
Peter Hoskin	Department receives grants from Astellas for trials in prostate cancer.	Non-personal financial interest	Declare and participate
Peter Hoskin	Department receives grants from Bayer for trials in prostate cancer.	Non-personal financial interest	Declare and participate
Peter Hoskin	Department received grants from Millennium for trials in prostate cancer.	Non-personal financial interest	Declare and participate
Peter Hoskin	Trustee for funding research within the unit/department. Funded by Donations/Legacies.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the Steering Group for National Cancer Intelligence Network (NCIN)	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the faculty board of the Royal College of Radiologists.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the specialist training committee for the Royal College of Radiologists.	Personal non-financial	Declare and participate

Member name	Interest declared	Type of interest	Decision
		interest	
Peter Hoskin	Editorial board member for the Journal of Contemporary Brachytherapy.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the East of England senate.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member of the NICE standing committee for rapid updates / and non-Hodgkin's lymphoma GDG.	Personal non-financial interest	Declare and participate
Peter Hoskin	Member European Society for Radiotherapy and Oncology (ESTRO) Board	Personal non-financial interest	Declare and participate
Peter Hoskin	Member HTA Clinical Evaluation and Trials Board	Personal non-financial interest	Declare and participate
Peter Hoskin	Clinical Editor, radiotherapy and Oncology	Personal non-financial interest	Declare and participate
Roberta James	Programme Lead at Scottish Intercollegiate Guidelines Network	Personal financial interest	Declare and participate
Roberta James	Member of Guideline Implementability Research and Application network	Personal non-financial interest	Declare and participate
Roberta James	Expert group member of Project on a Framework for Rating Evidence in Public Health	Personal non-financial interest	Declare and participate
Asma Khalil	Member of the National Clinical Reference Group for Fetal Medicine	Personal non-financial	Declare and participate
Asma Khalil	Co-chair of the "Improving Outcomes" working group, South West London Maternity Network	Personal non-financial	Declare and participate
Asma Khalil	Associate Editor for the journal Biomedical Central Pregnancy and Childbirth	Personal non-financial	Declare and participate
Asma Khalil	Member of the Maternal and Fetal Medicine National Clinical Study Group	Personal non-financial	Declare and participate
Asma Khalil	Assistant Convenor for the MRCOG Part1 course, RCOG	Personal non-financial	Declare and participate
Asma Khalil	Principal Investigator at St George's Hospital for several NIHR funded studies, e.g. Non-invasive Prenatal Testing	Personal non-financial	Declare and participate
Asma Khalil	Chief Investigator for Cardiovascular changes in Pregnancy study and Quantitative fetal fibronectin, Cervical length and ActimPartus® for the prediction of Preterm birth in Symptomatic women (QFCAPS)	Personal non-financial	Declare and participate
Asma Khalil	Collaboration with commercial companies, such as USCOM®, Roche Diagnostics®, Alere Diagnostics® and proact medical Ltd® (research equipment and/or consumables)	Personal non-financial	Declare and participate
Asma Khalil	Reviewer for the National Maternal Near-miss Surveillance Programme	Personal non-financial	Declare and participate

Member name	Interest declared	Type of interest	Decision
Manoj Mistry	Public member of Pennine Care NHS FT in the capacity as a carer	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI representative for the Health Research Authority, London	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI representative for the Health Quality Improvement Partnership, London	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI representative for the Primary Care Research in Manchester Engagement Resource group at the University of Manchester.	Personal non-financial interest	Declare and participate
Manoj Mistry	Carer representative on NICE Guideline Development Group: 'Transition between inpatient hospital settings and community or care home settings for adults with social care needs.'	Personal non-financial interest	Declare and participate
Manoj Mistry	Lay representative for the MSc Clinical Bioinformatics at the University of Manchester	Personal non-financial interest	Declare and participate
Manoj Mistry	Lay Educational Visitor with the Health and Care Professions Council, London	Personal non-financial interest	Declare and participate
Manoj Mistry	Lay representative at the Clinical Research Facility (collaboration between Central Manchester University Hospital NHS FT/University of Manchester)	Personal non-financial interest	Declare and participate
Manoj Mistry	Public Representative Interviewer at the Medical School, Lancaster University	Personal non-financial interest	Declare and participate
Manoj Mistry	Public Member of NIHRs 'Research for Patient Benefit Programme Committee' (North West region)	Personal non-financial interest	Declare and participate
Manoj Mistry	Member of the Patient Panel at NIHRs 'The Collaboration for Leadership in Applied Health Research and Care' Greater Manchester	Personal non-financial interest	Declare and participate
Manoj Mistry	Member of the Patient and Public Involvement Group, Liverpool Clinical Trials Unit, University of Liverpool	Personal non-financial interest	Declare and participate
Manoj Mistry	PPI panel assisting research into Information Systems: Dashboard: Monitoring and Managing from Ward to Board at the University of Leeds	Personal non-specific non-financial	Declare and participate
Manoj Mistry	Member of the Study Steering Committee for the research project: ''Comprehensive Longitudinal Assessment of Salford Integrated Care (CLASSIC): a study of the implementation and effectiveness of a new model of care for long term conditions ''(University of Manchester/ Salford Royal).	Non-specific non-personal	Declare and participate
Amaka Offiah	Provision of expert advice to Her Majesty's Courts in cases of suspected child abuse.	Personal financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Amaka Offiah	Recipient of honoraria and expenses for lectures and guidelines development from BioMarin.	Personal financial interest	Declare and participate
Amaka Offiah	Chairperson Skeletal Dysplasia Group for Teaching and Research	Personal non-financial interest	Declare and participate
Amaka Offiah	Chairperson Child Abuse Taskforce of the European Society of Paediatric Radiology.	Personal non-financial interest	Declare and participate
Amaka Offiah	Member Joint RCR/RCPCH NAI Working Party for Guideline Update - Imaging in Suspected Non-Accidental Injury.	Personal non-financial interest	Declare and participate
Amaka Offiah	Member of the Royal College of Radiology Academic Committee.	Personal non-financial interest	Declare and participate
Amaka Offiah	Committee member of the International Consortium for Vertebral Anomalies and Scoliosis.	Personal non-financial interest	Declare and participate
Amaka Offiah	Member of South Yorkshire (Sheffield) Research Ethics Committee.	Personal non-financial interest	Declare and participate
Amaka Offiah	Medical Academic Staff Committee Representative of the Yorkshire Regional Council of the BMA	Personal non-financial interest	Declare and participate
Amaka Offiah	Partner Governor of the Sheffield Children's NHS Foundation Trust (representing the University of Sheffield)	Personal non-financial interest	Declare and participate
Amaka Offiah	Editorial Committee Member of the journal Paediatric Radiology	Personal non-financial interest	Declare and participate
Amaka Offiah	Recipient of research funding from NIHR, ARUK, The Sheffield Children's Charity, Skeletal Dysplasia Group for Teaching and Research	Non-personal financial interest	Declare and participate
Amaka Offiah	Member of the Sheffield Children's Hospital Research and Innovations Committee	Personal non-financial	Declare and participate
Mark Rodgers	Associate editor of the journal Systematic Reviews that publishes research on health and social care.	Personal non-financial non-specific interest	Declare and participate
Mark Rodgers	Research fellow in health services research; has provided independent academic reviews of clinical effectiveness and diagnostic accuracy evidence for funders including NIHR and NICE.	Non-personal non-financial non-specific interest	Declare and participate
Mark Rodgers	Employee of the Centre for Reviews and Dissemination (University of York) which provides Evidence Review Group reports and Technology Assessment Reports as part of the NICE technology appraisals process.	Non-personal financial non-specific	Declare and participate
Nicholas Steel	Work as the principal investigator on a National Institute of Health Research funded project on: 'Are NICE clinical guidelines for primary care based on evidence from primary	Non-personal financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
	care?'		
Nicholas Steel	National Institute for Health Research Health Services & Delivery Research Programme Healthcare Delivery Research Panel member	Personal non-financial interest	Declare and participate
Nicholas Steel	NIHR Regional Advisory Committee for the Research for Patient Benefit Programme East of England region	Personal non-financial interest	Declare and participate
Nicholas Steel	Norfolk & Suffolk Primary & Community Care Research Steering Group	Personal non-financial interest	Declare and participate
Nicholas Steel	Advisory Committee on Clinical Excellence Awards East of England	Personal non-financial interest	Declare and participate
Nicholas Steel	'Implementation Science' Editorial Board member	Personal non-financial interest	Declare and participate
Nicholas Steel	'Quality in Primary Care' Editorial Board member	Personal non-financial interest	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Examiner	Personal non-financial interest	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Development Committee	Personal non-financial interest	Declare and participate
Nicholas Steel	Honorary Public Health Academic Consultant, Public Health England	Personal non-financial interest	Declare and participate
Nicholas Steel	Publication in press: Steel N, Abdelhamid A, Stokes T, Edwards H, Fleetcroft R, Howe A, Qureshi N. Publications cited in national clinical guidelines for primary care were of uncertain relevance: literature review. In Press Journal of Clinical Epidemiology	Personal non-financial interest	Declare and participate
Sietse Wieringa	At the Centre for Primary care & Public Health at Barts & The London School of Medicine & Dentistry/Queen Mary University I am working on a literature review of 'mindlines' (related to communities of practice) and a qualitative study of a large group of GPs on a virtual social network sharing medical knowledge. I was funded for this via an NIHR In practice fellowship.	Personal financial interest	Declare and participate
Sietse Wieringa	I co-own a small social enterprise called ZorgIdee that develops ideas to help GPs to collaborate. There are no current funders.	Personal financial interest	Declare and participate
Sietse Wieringa	Board member of the Platform of Medical Leadership in the Netherlands, via which I am involved in a mixed methods study for the development of a medical leadership competency framework. The study group receives funds from KNMG (Royal Dutch College of Medicine) and SBOH which receives its funds from the Dutch Ministry of Health.	Non-personal financial interest	Declare and participate

Member name	Interest declared	Type of interest	Decision
Sietse Wieringa	Member of Generation Next, a think tank and network of young GPs. It's indirectly funded by the Ministry of Health.	Personal non-financial interest	Declare and participate
Sietse Wieringa	Member of NHG (Dutch GP Society), which produces guidelines and I worked for this organisation in the past.	Personal non-financial interest	Declare and participate
Topic expert	**Interest declared**	**Type of interest**	**Decision**
Ishaq Abu-Arafeh	Paediatric Advisory Migraine Board (ad-hoc committee for AMGEN). Honorarium and expenses paid. Drug in question is still being investigated and does not impact on the update	Personal specific financial	Declare and participate
Ishaq Abu-Arafeh	Editor and co-author of Childhood Headache, Mac Keith Press. Part of clinics in developmental medicine and nominal royalties paid	Personal specific financial	Declare and participate
Ishaq Abu-Arafeh	Chairman, Child and Adolescent Standing Committee, International Headache Society	Personal specific non-financial	Declare and participate
Ishaq Abu-Arafeh	Member of the Childhood Headache Teaching Course, British Paediatric Neurology Association Steering Group	Personal specific non-financial	Declare and participate
Fayyaz Ahmed	Treasurer: North of England Neurological Association	Personal non-financial interest	Declare and participate
Fayyaz Ahmed	Trustee: Migraine International Trust	Personal non-financial interest	Declare and participate
Fayyaz Ahmed	Chairman: Headache (UK)	Personal non-financial interest	Declare and participate
Fayyaz Ahmed	Speciality Advisory Committee (SAC): Association of British Neurologists	Personal non-financial interest	Declare and participate
Fayyaz Ahmed	Director: European Headache and Migraine Trust International Council	Personal non-financial interest	Declare and participate
Fayyaz Ahmed	Association of British Neurologists: Specialty Advisor for headache and facial pain	Personal non-financial interest	Declare and participate
Fayyaz Ahmed	Advisor: National Institute for Health Research	Personal non-financial interest	Declare and participate
Fayyaz Ahmed	PACES Examiner (UK and international)	Personal non-financial interest	Declare and participate
Kay Kennis	None		Declare and participate
Susie Lagrata	Training doctors to perform Botox injections on behalf of Allergen, paid directly to the Trust's headache fund	Non personal financial interest	Declare and participate
Wendy Thomas	Chief Executive of The Migraine Trust which	Non-personal	Declare and

Member name	Interest declared	Type of interest	Decision
	as a patient/research charity receives unrestricted educational/research grants from time to time from pharma and device companies. In the last year grants have been received from Allergan (for advocacy and research), Electrocore (support for patient group), Eneura (support for patient group) and Curelator (donation for involving patients in a trial).	financial interest	participate

Appendix C: Review protocol

	Details
Review Question	In people with chronic or episodic migraine (with or without aura), what is the clinical evidence and cost-effectiveness of prophylactic pharmacological treatment with: • ACE (angiotensin converting enzyme) inhibitors and angiotensin II receptor antagonists • Antidepressants (SNRIs, SSRIs, tricyclics) • Centrally acting alpha-adrenergic-receptor agonists • Beta blockers • Calcium channel blockers • Antiepileptics • Other serotonergic modulators • NMDA receptor antagonists
Objectives	The NICE guideline on headaches was reviewed by the NICE surveillance team, and new evidence on pharmacological treatment for migraine prophylaxis was identified. The aim is to review current evidence on pharmacological prophylactic treatment for migraine.
Type of Review	Intervention
Language	English (original English version or existing English translation)
Study Design	Randomised controlled trials, Systematic reviews of randomised controlled trials
Status	Published papers (full text only)
Population	People aged 12 or over with migraine (with or without aura) The following groups will be analysed as separate subgroups if data is available: • Chronic migraine, episodic migraine • Age: 12-18, 18 or over • Pregnant women • Medication overuse headache
Intervention	• ACE inhibitors and angiotensin II receptor antagonists (including candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan) • Antidepressants (SNRIs, SSRIs, tricyclics) (including paroxetine, citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, mirtazapine, venlafaxine, duloxetine, amitryptyline, imipramine, nortriptyline, desipramine, dosulepin) • Beta blockers (including propranolol, metoprolol, nadolol, timolol, atenolol) • Centrally acting alpha-adrenergic agonists (including clonidine) • Calcium channel blockers (including nimodipine, ditiazem, verapamil, flunarazine) • Antiepileptics (including sodium valproate, valproic acid, topiramate, gabapentin) • Other serotonergic modulators (including: methysergide, pizotifen, ergotamine, cyproheptadine) • NMDA receptor antagonists: (including memantine)

	Details
Comparator	• Any of the above interventions • Placebo • Usual care
Outcomes	**Critical outcomes:** • - Change in patient-reported migraine days • - Responder rate (50% reduction in migraine frequency) • - Change in patient reported migraine intensity **Important outcomes:** • - Change in patient-reported migraine frequency • - Health-related quality of life (general e.g. SF-36, or Euro-QoL or headache specific e.g. MIDAS, HIT 6 or PedMIDAS for adolescents) reported as either a change score from baseline, or an absolute score following treatment. • - Change in use of acute pharmacological treatment • - Incidence of serious adverse events **Minimally important differences:** Published data identified by the previous Guideline development group: • Migraine-Specific Quality of Life Questionnaire (MSQ) o Role restrictive domain: 3.2 o Role preventive domain: 4.6 o Emotional functioning domain: 7.5 • Headache Impact Test (HIT-6): 2.3 Agreed by previous Guideline development group consensus: • Change in headache days from baseline: 0.5 days Other outcomes: • GRADE default value of a relative risk of 1.25 or 0.75 for dichotomous outcomes • GRADE default value of 0.5 standard deviations for continuous outcomes
Other criteria for inclusion / exclusion of studies	**Inclusion** -Trials must have a minimum treatment duration of 12 weeks or 3 months **Exclusion:** - Trials investigating prophylaxis specifically for menstrual migraine - Open-label trials
Review strategies	• -A network meta-analysis will be conducted for the outcomes 'change in migraine/headache days' . Pair-wise meta-analysis will be conducted for other outcomes. • - Doses will be categorised as below the recommended dose range, within the recommended range, or above the recommended range. These categories will be analysed separately. The recommended range will be that specified by the British National Formulary if available. If not available, the recommended range will be agreed by consensus by the topic expert committee members. • -The quality of evidence for each outcome will be assessed using the approach for intervention questions outlined by the GRADE working group. "

Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 6. The Embase search strategy is shown in Table 7. The same strategy was translated for the other databases listed.

Table 6: Clinical search summary

Databases	Date searched	Number retrieved
CDSR (Wiley)	16/01/2015	29
Database of Abstracts of Reviews of Effects – DARE (Wiley)	16/01/2015	22
HTA database (Wiley)	16/01/2015	3
CENTRAL (Wiley)	16/01/2015	1087
EBM Reviews (Ovid)		
MEDLINE (Ovid)	16/01/2015	2011
MEDLINE In-Process (Ovid)	16/01/2015	73
EMBASE (Ovid)	16/01/2015	5030

Table 7: Clinical search terms (Medline/Mip)

Line number/Search term/Number retrieved
1 exp migraine/ 45071
2 (migrain* or hemicran*).tw. 37566
3 "alice in wonderland syndrome".tw. 86
4 1 or 2 or 3 50524
5 exp dipeptidyl carboxypeptidase inhibitor/ 139610
6 exp angiotensin receptor antagonist/ 63389
7 ((angiotensin receptor adj4 block*) or arb or arbs).tw. 11882
8 ((ACE or angiotensin or kininase) adj4 (inhibitor* or enzyme* or antagonist*)).tw. 59589
9 *candesartan/ 1254
10 *eprosartan/ 293
11 *irbesartan/ 1107
12 *losartan/ 4387
13 *olmesartan/ 1118
14 *telmisartan/ 1709
15 (candesartan or eprosartan or epratenz or tevesten or teveten or tevetan or irbesartan or approvel or aprovel or "arbez lr" or avapro or ifirmasta or irban or irbetan or iretensa or irovel or irvell or karvera or sabervel or losartan or acetensa or angiobloq or angioten or avastar or azarten or convertal or cormac or co?aar* or insaar or lifezar or lozaar or losacar or losacor or lozaprex or oscaar or satoren or tensartan or tozaar or olmesartan or alteis or benevas or benicar or olmec or olmetec or votum or telmisartan or "kinzal mono" or kinzalmono or micardis or predxal or pritor* or semintra or tolura or actelsar).tw. 17874
16 exp antidepressant agent/ 325458
17 exp serotonin uptake inhibitor/ 148597
18 (antidepress* or anti depress* or thymoleptic* or thymoanaleptic* or neurothymoleptic* or psychoenergi?er* or thymolytic* SNRI* or SSRI*).tw. 76090
19 ((serotonin or 5-ht or 5 ht or hydroxytryptamine) adj4 (uptake or reuptake) adj4 inhibitor*).tw. 18387
20 *paroxetine/ 4203
21 (paroxetine or seroxat or paxil or aropax or aroxat or brisdelle or deroxat or dexorat or divarius or motivan or paroxet or paroxetine or paxan or paxtine or paxxet or pexeva or setine or tagonis).tw.

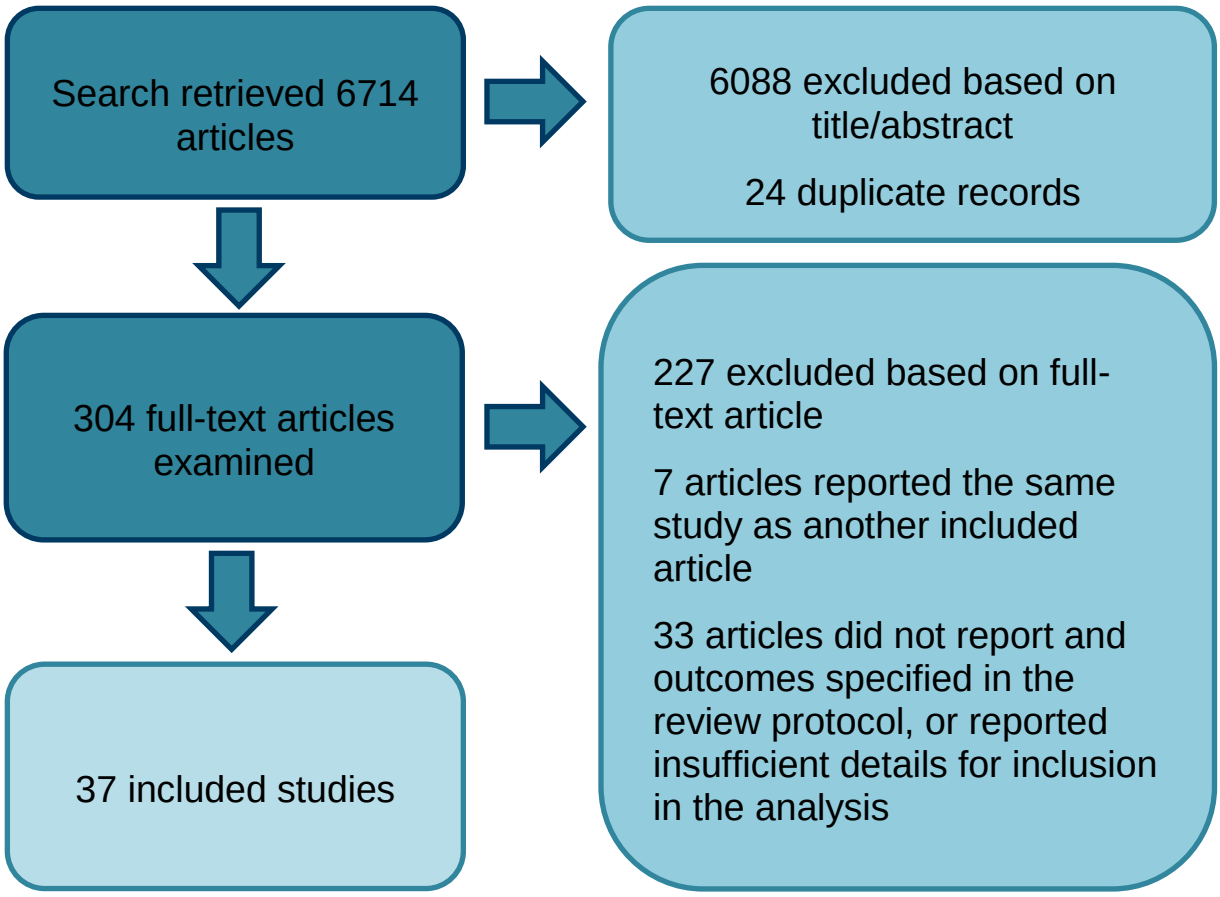
Line number/Search term/Number retrieved
8508
22 *citalopram/ 3357
23 (citalopram or cytalopram or celexa or cipram or citopram or elopram or futuril or humorap or kitapram or lupram or nitalapram or psiconor or recital or sepram or seralgan or serital or seropram or talam or zentius or cipramil).tw. 6686
24 *escitalopram/ 1479
25 (escitalopram or lexapro or cipralex or seroplex or sipralexa).tw. 3175
26 *fluoxetine/ 9258
27 (fluoxetin* or pro?ac or sarafem or actan or adofen or andep or ansilan or auroken or auscap or captaton or daforin or depren or deprexin or deprizac or deproxin or elizac or floxet or fluctin* or fludac or flufran or fluketin or flunil or flunirin or fluohexal or fluox or fluoxac or fluxeren or fluoxifar or fluoxil or fluronin or flusac or flutin* or fluxen or fluxet* or fontex or foxetin* or fropine or fuloren or lanclic or lorien or lovan or magrilan or margrilan or modipran or nopres or nuzac or oxedep or plinzene or pragmaten or prizma or proctin or prodep or prozamin or qualisac or rapiflux or rowexetina or salipax or sanzur or sarafem or selfemra or sinzac or zactin or zepax).tw. 16229
28 *fluvoxamine/ 2271
29 (fluvoxamin* or favarin or faverin or floxyfral or luvox or dumirox).tw. 3963
30 *sertraline/ 3197
31 (sertraline or lustral or sealdin or besitran or altruline or gladem or aremis or zolof* or dominum or doxime or fatral or fridep or lesefer or nudep or seltra or serad or sercerin or serlain or serlift or sertranex or sertranquil or sosser or tresleen or zosert or atruline).tw. 6750
32 *mirtazapine/ 1312
33 (mirtazapine or avanza or norset or remergil or remergon or remeron or zispin).tw. 2924
34 *venlafaxine/ 2559
35 (venlafaxine or efexor or effexor or trevilor or efectin or elafax or trewilor or vaxor or "venix-xr" or venla or venlax or viepax).tw. 5928
36 *amitriptyline/ 11920
37 (amitryptylin* or lentizol or endep or tryptizol or domical or amitrip or anapsique or amineurin or sarotex or dam?len or saroten or tryptine or larox?l or apo-amitriptyline or triptafen or elavil or novoprotect or syneudon or tryptanol or adepress or adepril or ambivalon or amilit or amiplin or amiprin or amitid or amitril or amyline or amytril or antalin or antitryptyline or alatrol* or anafron or enovil or etafon or euplit or lanton or lentizol or miketorin or pinsaun or proheptadien or qualtriptene or redomex or "sarboten retard 75" or saroten* or stelminal or sylvemid or teperin or terepin or trepiline or tridep or tripta or triptanol or triptizol or triptyl or triptyline or trynol or tryptizol or trytomer or uxen or vanatrip or amitryptylene or amitriptylinumhydrochloride or amitryptilline or amitryptine or damilene or damylene or elatrol or elatrolet or enafon or laroxal or laroxyl or sarotard or sarotex).tw. 3552
38 *imipramine/ 15070
39 (imipramin* or pryleugan or melipramin* or janimine or tofranil or norchlorimipramine or imidobenzyle or imizin* or berkomin or chrytemin or daypress or deprinol or depsol or ethipramine or fronil or "ia pram" or imavate or imidol or imipramide or norpramine or novopramine or pramine or presamine or primonil or psychoforin* or sermonil or serviapramine or talpramin or trofanil or venefon or antidep or antideprin or apo-imipramine or depsonil or imizin*).tw. 13425
40 *nortriptyline/ 4170
41 (nortriptylin* or nortrilen* or norfenazin or allegron or paxtibi or desmethylamtriptyline or desitriptyline or av?ntyl or pamelor or acetexa or altilev or ateben or martimil or noramitriptyline or noritren or norline or norpress or nortrix or nortryptilin* or nortyline or norventyl or ortrip or psychostyl or sens?val or vividyl).tw. 3765
42 *desipramine/ 8599
43 (desipramin* or pertofran* or demethylimipramine or petylyl or petrofan* or norpramin or desmethylimipramine or deprexan or "desmethyl imipram*" or despiramine or nebril or noripramin* or norpramin* or pentrofane or pertofrin* or sertofren or nortimil).tw. 8308
44 *dosulepin/ 674
45 (dosulepin* or dothiepin or prothiaden* or altapin or depresym or dothapax or idom or prepadine or prothiadiene or prothiadine or protiaden).tw. 731
46 *duloxetine/ 1585

Line number/Search term/Number retrieved
47 (duloxetine or cymbalta or ariclaim or duzela or xeristar or yentreve).tw. 3281
48 exp beta adrenergic receptor blocking agent/ 243938
49 ((beta adj4 (block* or antagonist* or adrenergic or sympathicolytic* or adrenolytic* or antiadrenergic*)) or (betasympatholytic* or "beta sympatholytic*")).tw. 87816
50 *propranolol/ 50014
51 (propanolol or ob?idan or dexpropanolol or inderal or propranolol or anaprilin* or avlocardyl or rexigen or obzid?n or betadren or dociton* or acifol or adrexan or alperol or anapryline or angilol or apsolol or arcablock or artensol or authus or becardin or bedranol or beprane or ber?olol or "beta neg" or betaneg or "beta tablinen*" or "beta-timelet" or "beta timelet" or betabloc or betadripresan or betaprol or betares or betaryl or blocard or blocaryl or cardinol or ciplar or corbeta or deralin or dibubinate or dideral or durabeton or duranol or efektolol or elbrol or emforal or farmadral or farprolol or frekven or frina or hemang?ol or hopranolol or ikopal or impral or inderalici or inderex or indicardin or indobloc or innopran or lederpronol or levopropranolol or napriline or noloten or obsin or oposim or phanerol or prandol or "prano puren" or pranopuren or prestoral or prolol or pronovan or propabloc or propal or propalong or propayerst or propercuten or prophylux or "propra ratiopharm" or propral or propanur or proprasylyt* or reducor or sagittol or stapranolol or sumial or tensiflex or waucoton or anaprilinium or inderal or inpanol or ipran).tw. 41324
52 *metoprolol/ 8807
53 (metoprolol or beloc* or betaloc* or betalok or belok or seloken or spesi?or or lopressor).tw. 9387
54 *nadolol/ 1836
55 (nadolol or solgol or corgard or "apo-nadol" or "apo-nadolol" or betadol or farmagard or nadic).tw. 1788
56 *timolol/ 5034
57 (timolol or timoptol or timacar or optimol or timoptic or blocadren or timol or apotimol or apotimolol or apotimop or betimol or timoptol or istatol or ofal or ofan or timolo or titol or "apo timol*" or "apo-timol*" or moducren or nyolol).tw. 5598
58 *atenolol/ 8850
59 (atenolol or tenormin* or ablok or adoll or alonet or altol or anolene or anolpin or anselol or arandin or asten or atarox or atcardil or atecard or atehexal or atelol or atenblock or atendol or atenet or ateni or atenil or ateno or atenogamma or atenol or atereal or aterol or atestad or atinol or atolmin or "b-vasc" or betablok or betacar or betarol or "betatop ge" or beten or bloket or blokium or blotex or cardioten or catenol or coratol or corotenol or durabeta or esatenolol or evitocor or farnormin or "felo-bits" or hypernol or internolol or "lo-ten" or loten or lotenal or martenol or mirobect or myocord or neotenol or nolol or normalol or norm?ten or nortelol or noten or oraday or ormidol or paesumex or plenacor or preloc or premorine or prenolol or prenormine or ranlol or rozamin or serten or stermin or temoret or tenblock or tenidon or tenoblock or tenocor or tenol or tenolin or tenolol or tenopress or tenoprin or tenostat or tensig or tensinor or ternolol or therabloc or tredol or velorin or vericordin or wesipin or hypoten).tw. 9391
60 exp alpha adrenergic receptor stimulating agent/ 200659
61 ((adrenergic or adrenoceptor or noradren*) adj4 (agonist* or agent* or stimulat*)).tw. 39527
62 (alpha adj4 (agonist* or sympathicomimetic*)).tw. 9605
63 *clonidine/ 17762
64 (clonidine or clofelin or klofelin or clopheline or clofenil or catapres* or klofenil or hemiton or clophazolin or isoglaucon or gemilon or dixarit or adesipress or arkamin or atensina or catasan or chlofazolin or clofelin* or clophelin* or clinidine or clomidine or clondine or clonicel or clonidin* or clonipresan or clonistada or clonnirit or daipres or dcai or dichlorophenylam or inomidazoline or duraclon or haemiton or hemiton or hypodine or jenloga or kapvay or melzin or normopres?n or paracefan or sulmidine or taitecin or "tenso timelets" or caprysin or chlofazolin* or chlophelin).tw. 18675
65 exp calcium channel blocking agent/ 186155
66 (calcium adj4 (block* or inhibit* or antagonist*)).tw. 52952
67 *nimodipine/ 3278
68 (nimodipin* or modus or nymalize or remontal or kenesil or brainal or admon or calnit or eugerial or grifonimod or kenzolol or nidip or nimodilat or nimotop or nisom or periplum or tropocer or vasoflex or vasotop).tw. 5656
69 *diltiazem/ 9527

Line number/Search term/Number retrieved
70 (diltiazem or dilacor or aldizem or cardil or tiazac or dilzem or cardizem or dilren* or acalix or adizem* or altiazem or anginyl or angiotrof?n or angiozem or angizem or angoral or anoheal or anzem or auscard or balcor or beatizem or "bi-tildiem" or bloclacin or britiazim or bruzem or calcicard or calnurs or cardcal or cardiazem or cardiben or cardiem or cardiosta or cardium or carex or cartia or cascor or cirilen or coras or cordizem or dazil or deltazen or diacor or diatal or diladel or dilatam* or dilcard* or dilem or dilfar or dilgard or diloc or dilso or "dilt-cd" or diltahexal or diltam or diltan or diltelan or diltia or diltiamax or diltiasyn or diltime or diltzac or diltzanton or dilzem or dilzene or dilzereal or dilzicardin or dinisor or dodexen or dyalac or entrydil or filazem or gadoserin or grifodilzem or hagen or helsibon or herbess?r or hesor or incoril or kaizem or lacerol or levodex or levozem or lytelsen or masdil or miocardie or "mono-tildiem* or monotildiem" or myonil or pazeadin or presoken or surazem or tazem or taztia or tiadil or tiamate or tilazem or tildiem or vasmulax or vasocardol or wentizem or "apo-diltiazem" or "apo diltiazem" or herben or tiazac or ziruvate or zandil or zemtrial or zildem).tw. 11848
71 *verapamil/ 20713
72 (verapamil or i?optin* or finoptin or lekoptin or dexverapamil or calan or falicard or cordilox or iproveratril or "aop-verap" or apoacor or arpamyl or azupamil or berkatens or calaptin or cardiagutt or cardibeltin or cardiolen or cardiover or caveril or cintsu or civicor or coraver or cordilat or corpamil or covera or dignover or dilacor?n or durasoptin or flamon or geangin or hexasoptin or ika?or or ikapress or "iso-card sr" or manidon or napamil or novapamyl or veramil or novopressan or phynoptin or quasar or ravamil or securon or univer or vasolan or vasomil or vasopten or verabeta or veracaps or veracor or verahaxal or veraloc or veramex or verapamil or verapin or verapress or veratad or verdilac or verelan or verexamil or veroptin or verpamil or vetrimil or vortac or zolvera).tw. 26772
73 *flunarizine/ 1995
74 (flunarizin* or sibelium or sibelum or flunagen or flunarin or flunarl or fluxarten).tw. 2138
75 exp anticonvulsive agent/ 298061
76 (antiepileptic* or anticonvuls* or antiepileptiform or (anti adj2 (convuls* or epileptic*))).tw. 55146
77 *valproic acid/14699
78 (((acid or acetate or sodium) adj4 (proylacetic or dipropyl* or propylpentanoate or proplyvalenrate or propyl)) or dipropylacetate).tw. 1987
79 (valproate adj4 (sodium or semisodium or calcium or magnesium)).tw.3864
80 (acid adj4 (valproic or propylisopylacetic or propylpentanoic)).tw. 8737
81 (depakin* or vupral or ergenyl or depakene or depakote or "sodium divalproex" or "alpha propylval" or apilepsin or atemperator or convulex or depacon or depalept or deprakine or diprosin or epil?m or epilex or everiden or goilim or labazene or leptilan* or myloproin or "myproic acid" or orfil or orfiril or orlept or petilin or propymal or stavzor or valcote or valeptol or valerin or valoin or valpakine or valparin or valporal or valprax or valpro or valprosid or valsup).tw. 3657
82 *topiramate/ 2882
83 (topiramate or top?max or epitomax or qudexy or trokendi).tw. 6090
84 *gabapentin/ 3214
85 (gabapentin or neurontin or fanatrex or gabarone or gralise or nupentin or neogab or dineurin or gabatin or gantin or kaptin or neurotonin).tw. 7593
86 exp serotonin receptor/ 32535
87 ((serotonin or serotonergic or serotoninergic) adj4 (modulat* or receptor*)).tw. 16961
88 ((5-ht or 5 ht or tryptamine or hydroxytryptamine) adj4 receptor*).tw. 14551
89 *methysergide/ 5057
90 (meth?sergid* or desernil or sandoz or dimethylergomertin or methylmethylgonovine or desril or deseril or sansert).tw. 12258
91 ((methyl adj4 (lysergic or sergid*)) or (methyllsergic adj4 butanolamide)).tw. 47
92 *pizotifen/ 821
93 (pizot?fen* or pizotylin* or sandom?gran or polomigran or litec).tw. 630
94 *ergotamine/ 2465
95 (ergotamin* or ergomar or ergo sanol or ergokranit or ergo-kranit or (ergo adj1 kranit) or gynergen or ergostat or cornutamine or ergodryl or “mono ergodryl” or “mono-ergodryl”).tw. 2186
96 *cyproheptadine/ 3868

Line number/Search term/Number retrieved
97 (cyproheptadine or peritol or antergan or dihexazin or periactin or viternum or lingraine or adekin or antisemin or cip?actin or ciproeptadine or ciproral or crypoheptadin* or cyheptine or cylat or cyprahept?dine or cyproatin or cyprogin or cyprohaptadin or cyproheptadiene or cyproheptadin* or cypromin or cyprono or cyprosian or cytadine or ennamax or glocyp or heptasan or ifrasal or "istam-far" or klavivitina or kulinet or nuran or periactinol or petina or pilian or pronicy or sinapdin or trimetabol or peritol).tw. 3270
98 exp n methyl dextro aspartic acid receptor blocking agent/ 59932
99 ((receptor* or antagonist* or block*) adj4 (nmda or n-methyl or n methyl or methylaspartate)).tw. 41203
100 *memantine/ 2062
101 (memantin* or axura or namenda or ebix* or akatinol or maruxa or nemdatine).tw. 3775
102 or/5-101 1281911
103 4 and 102 14243
104 exp Clinical Trials/ 126213
105 Randomization/ 64185
106 Placebo/ 262714
107 Double Blind Procedure/ 119352
108 Single Blind Procedure/ 19246
109 Crossover Procedure/ 41021
110 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. 1056459
111 (random$ adj3 allocat$).tw. 27603
112 placebo$.tw. 211539
113 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. 169785
114(crossover$ or (cross adj over$)).tw.73489
115 or/104-114 1424668
116 nonhuman/ not human/ 3515726
117 115 not 116 1366395
118 Systematic Review/ 83415
119 Meta Analysis/ 86024
120 Review/ 2036721
121 Review.pt. 2003724
122 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. 91108
123 (review$ or overview$).ti. 364055
124 (systematic$ adj5 (review$ or overview$)).tw. 83297
125 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. 6041
126 ((studies or trial$) adj2 (review$ or overview$)).tw. 33089
127 (integrat$ adj3 (research or review$ or literature)).tw. 7395
128 (pool$ adj2 (analy$ or data)).tw.21618
129 (handsearch$ or (hand adj3 search$)).tw. 6677
130 (manual$ adj3 search$).tw. 4277
131 or/118-130 2404682
132 nonhuman/ not human/ 3515726 Advanced
133 131 not 132 2278242
134 117 or 133 3365879
135 103 and 134 6205
136 limit 135 to embase 5832
139 limit 136 to english language 5030

Appendix E: Review flowchart



Appendix F: Excluded studies

Study	Reason for Exclusion
Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: A randomized, placebo-controlled, double-blind, 12-week pilot study (PII:S0149-2918(06)80160-8), Clinical Therapeutics, 28, 1482-, 2006	Correction (considered alongside original article).
Adam,E.I., Gore,S.M., Price,W.H., 19790425, Double blind trial of clonidine in the treatment of migraine in a general practice, Journal of the Royal College of General Practitioners, 28, 587-590, 1978	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Adwan,Z., Efficacy of cinnarizine and sodium valproate in migraine prophylaxis: A clinical trial, Journal of Headache and Pain , 11, S87-, 2010	Abstract only: no full text article available.
Agnoli,A., Bussone,G., Mailland,F., Manzoni,G.C., Martucci,N., Nappi,G., Dihydroergokryptine vs flunarizine in the basic treatment of migraine without aura, Cephalalgia, 11, 216-217, 1991	Intervention does not match review protocol (Dihydroergokryptine is a noradrenergic receptor agonist)
Agnoli,A., Bussone,G., Manzoni,G.C., Martucci,N., Nappi,G., Dihydroergokryptine (DEK) versus flunarizine (FLU) in common migraine. A multicentre double-blind study, Cephalalgia, 9, 373-375, 1989	Intervention does not match review protocol (Dihydroergokryptine is a noradrenergic receptor agonist)
al Deeb,S.M., Biary,N., Bahou,Y., al,Jaberi M., Khoja,W., 19921230, Flunarizine in migraine: a double-blind placebo-controlled study (in a Saudi population), Headache, 32, 461-462, 1992	Incorrect study design: no mention of random allocation to groups - presume not randomised.
Amelin,A.V., Skoromets,A.A., Korenko,L.A., Tumelevich,B.C., Gonchar,M.A., A comparative efficiency of amitriptyline, fluoxetine and maprotiline in prevention of migraine in attack-free period, Zhurnal nevrologii i psikhiatrii imeni S.S.Korsakova, 100, 20-23, 2000	Article not in English.
Andersson,P.G., Dahl,S., Hansen,J.H., Hansen,P.E., Hedman,C., Kristensen,T.N., de Fine,Olivarius B., 19840126, Prophylactic treatment of classical and non-classical migraine with metoprolol--a comparison with placebo, Cephalalgia, 3, 207-212, 1983	Treatment duration < 3 months.
Andersson,P.G., Petersen,E.N., 19820225, Propranolol and femoxetine, a HT-uptake inhibitor, in migraine prophylaxis. A double-blind crossover study, Acta Neurologica Scandinavica, 64, 280-288, 1981	Treatment duration (at target dose) < 12 weeks.
Anthony,M., beta-Blockers in migraine prophylaxis, Drugs, 15, 249-250, 1978	Abstract only: no full-text article available.
Anthony,M., Lance,J.W., Somerville,B., A comparative trial of prindolol, clonidine and carbamazepine in the interval therapy of migraine, Medical Journal of Australia, 1, 1343-1346, 1972	Incorrect study design: allocation to groups not randomised.
Arthur,G.P., Hornabrook,R.W., 19710415, The treatment of migraine with BC 105 (pizotifen): a double blind trial, New Zealand Medical Journal, 73, 5-9, 1971	Treatment duration < 3 months.
Ashrafi,M.R., Shabanian,R., Zamani,G.R., Mahfelati,F., 20070406, Sodium Valproate versus Propranolol in paediatric migraine prophylaxis, European Journal of Paediatric Neurology, 9, 333-338, 2005	Treatment duration (at target dose) <12 weeks.
Ashrafi,M.R., Togha,M., Rashidi,Ranjbar N., Assa,S.,	Abstract only - no full text article

Study	Reason for Exclusion
Efficacy and safety of cinnarizine compared with propranolol in the prophylaxis of childhood migraine headache, Developmental Medicine and Child Neurology, 54, 110-, 2012	available.
Azimova,Y.E., Tabeeva,G.R., 20070501, Prophylactic treatment of migraine with topamax: long-term results, Neuroscience & Behavioral Physiology, 37, 125-127, 2007	Not a randomised controlled trial (non-comparative)
BÃ¡nk,J., A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis, Headache, 34, 476-478, 1994	Incorrect study design: no mention of random allocation to groups - assume not randomised.
Bademosi,O., Osuntokun,B.O., 19780508, Pizotifen in the management of migraine, Practitioner, 220, 325-327, 1978	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Bartolini,M., Silvestrini,M., Taffi,R., Lanciotti,C., Luconi,R., Capecci,M., Provinciali,L., 20060302, Efficacy of topiramate and valproate in chronic migraine, Clinical Neuropharmacology, 28, 277-279, 2005	Open label study.
Battistella,P.A., Ruffilli,R., Moro,R., Fabiani,M., Bertoli,S., Antolini,A., Zacchello,F., 19900725, A placebo-controlled crossover trial of nimodipine in pediatric migraine, Headache, 30, 264-268, 1990	Incorrect study design: allocation to groups not randomised.
Behan,P.O., Prophylactic treatment for migraine - a comparison of pizotifen and clonidine, Cephalalgia, 5, 524-525, 1985	Treatment duration < 3 months.
Behan,P.O., Connelly,K., 19860813, Prophylaxis of migraine: a comparison between naproxen sodium and pizotifen, Headache, 26, 237-239, 1986	Treatment duration < 3 months.
Behan,P.O., Reid,M., 19800616, Propranolol in the treatment of migraine, Practitioner, 224, 201-203, 1980	Incorrect study design: allocation to groups was not randomised.
Berilgen,M.S., Bulut,S., Gonen,M., Tekatas,A., Dag,E., Mungen,B., 20051220, Comparison of the effects of amitriptyline and flunarizine on weight gain and serum leptin, C peptide and insulin levels when used as migraine preventive treatment, Cephalalgia, 25, 1048-1053, 2005	Open label trial.
Bernik,V., Maia,E., The use of propranolol on prophylaxis of migraine: A double-blind clinical trial comparing propranolol with an analgesic drug (acetaminophen) and placebo, Folha Medica, 77, 501-508, 1978	Treatment duration < 3 months.
Bono,G., Criscuoli,M., Martignoni,E., Salmon,S., Nappi,G., 19820326, Serotonin precursors in migraine prophylaxis, Advances in Neurology, 33, 357-363, 1982	Trial duration < 3 months.
Bordini, C.A., Arruda,M.A., Ciciarelli,M.C., Speciali,J.G., 19980910, Propranolol vs flunarizine vs flunarizine plus propranolol in migraine without aura prophylaxis. A double-blind trial, Arquivos de Neuro-Psiquiatria, 55, 536-541, 1997	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Borgesen,S.E., Nielsen,J.L., Moller,C.E., 19750127, Prophylactic treatment of migraine with propranolol. A clinical trial, Acta Neurologica Scandinavica, 50, 651-656, 1974	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Bulut,S., Berilgen,M.S., Baran,A., Tekatas,A., Atmaca,M., Mungen,B., 20050222, Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study, Clinical Neurology & Neurosurgery, 107, 44-48, 2004	Treatment duration (at target dose) < 12 weeks.

Study	Reason for Exclusion
Bussone,G., Baldini,S., D'Andrea,G., Cananzi,A., Frediani,F., Caresia,L., Ferro,Milone F., Boiardi,A., 19870608, Nimodipine versus flunarizine in common migraine: a controlled pilot trial, Headache, 27, 76-79, 1987	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Bussone,G., Diener,H.C., Pfeil,J., Schwalen,S., 20051219, Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomised controlled trials, International Journal of Clinical Practice, 59, 961-968, 2005	Pooled analysis of studies already included in review.
Cady,R.K., Mathew,N., Diener,H.C., Hu,P., Haas,M., Novak,G.P., Study Group, 20090430, Evaluation of carisbamate for the treatment of migraine in a randomized, double-blind trial, Headache, 49, 216-226, 2009	Exclusion post hoc by Committee (Carisbamate does not have marketing authorisation in UK for any indication).
Cangi,F., Boccuni,M., Zanotti,A., Mailland,F., Sicuteri,F., Dihydroergokryptine (DEK) in migraine prophilaxis in a double blind study vs methysergide, Cephalalgia, 9, 448-449, 1989	Interim report - treatment duration < 3 months at time of report.
Cano,A., Sanz,P., Fossas,P., Comparison between flunarizine, nicardipine and nimodipine in the preventive treatment of migraine, Neurologia, 12, 486-, 1997	Abstract only - no full-text article available.
Cano,A., Sanz,P., Palomeras,E., Fossas,P., Low doses of flunarizine in the prophylaxis treatment of migraine, Neurologia, 13, 480-, 1998	Abstract only - no full text article available. Abstract not in English.
Carpay,J., Luykx,J., Mason,M., Ferrari,M., A meta-analytic comparison of topiramate-related adverse drug reactions in epilepsy and migraine, Epilepsia, 50, 4-5, 2009	Abstract only: no full-text article available.
Carroll,J.D., Maclay,W.P., 19751011, Pizotifen (BC 105) in migraine prophylaxis, Current Medical Research & Opinion, 3, 68-71, 1975	Treatment duration < 3 months.
Carroll,J.D., Reidy,M., Savundra,P.A., Cleave,N., McAinsh,J., 19900806, Long-acting propranolol in the prophylaxis of migraine: a comparative study of two doses, Cephalalgia, 10, 101-105, 1990	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Centonze,V., Magrone,D., Vino,M., Caporaletti,P., Attolini,E., Campanale,G., Albano,O., Flunarizine in migraine prophylaxis: efficacy and tolerability of 5 mg and 10 mg dose levels, Cephalalgia, 10, 17-24, 1990	Treatment duration < 3 months.
Centonze,V., Tesauro,P., Trizio,T., Magrone,D., Vino,M., Macinagrossa,G., Campanozzi,F., Altomare,E., Attolini,E., Albano,O., 19850916, Efficacy and tolerability of flunarizine in the prophylaxis of migraine, Cephalalgia, 5, Suppl-8, 1985	Incorrect study design: non-comparative study
Chitsaz,A., Najafi,M.R., Zangeneh,F.A., Norouzi,R., Salari,M., Pizotifen in migraine prevention: A comparison with sodium valproate, Neurology Asia, 17, 319-324, 2012	Treatment duration (at target dose for pizotifen) < 3 months duration.
Chronicle,E., Mulleners,W., 20041130, Anticonvulsant drugs for migraine prophylaxis. , Cochrane Database of Systematic ReviewsCochrane Database Syst.Rev., CD003226-, 2004	Systematic review that does not match all aspects of review protocol (only includes anticonvulsants). Use for cross checking.
Curran,D.A., Lance,J.W., 19961201, Clinical trial of methysergide and other preparations in the management of migraine, Journal of Neurology, Neurosurgery & Psychiatry, 27, 463-469, 1964	Incorrect study type: non-comparative study.
Das,S.M., Ahuja,G.K., Narainaswamy,A.S., 19800327, Clonidine in prophylaxis of migraine, Acta Neurologica Scandinavica, 60, 214-217, 1979	Treatment duration < 3 months

Study	Reason for Exclusion
De Souza,R.F., Speciali,J.G., Martins,J., Al-Muharraqi,M.A., Flunarizine for the prevention of migraine, Cochrane Database of Systematic Reviews, -, 2009	Review protocol only (no results reported).
De,Benedittis G., Massei,R., 5-HT precursors in migraine prophylaxis: A double-blind cross-over study with L-5-hydroxytryptophan versus placebo, Clinical Journal of Pain, 2, 123-129, 1986	Treatment duration < 3 months.
de,Tommaso M., Marinazzo,D., Nitti,L., Pellicoro,M., Guido,M., Serpino,C., Stramaglia,S., 20071120, Effects of levetiracetam vs topiramate and placebo on visually evoked phase synchronization changes of alpha rhythm in migraine, Clinical Neurophysiology, 118, 2297-2304, 2007	Treatment duration < 3 months.
Deaton,T.L., Mauro,L.S., 20141113, Topiramate for migraine prophylaxis in pediatric patients. , Annals of Pharmacotherapy, 48, 638-643, 2014	Systematic review that does not match review protocol (population for review is children only).
Di Trapani, G., Mei,D., Marra,C., Mazza,S., Capuano,A., 20001026, Gabapentin in the prophylaxis of migraine: a double-blind randomized placebo-controlled study, Clinica Terapeutica, 151, 145-148, 2000	Treatment duration (at target dose) < 12 weeks. Also unclear whether reported measures of variability are standard deviations or standard errors.
Diamond,S., Freitag,F.G., A double blind trial of flunarizine in migraine prophylaxis, Headache Quarterly, 4, 169-172, 1993	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Diamond,S., Freitag,F.G., Diamond,M.L., Flunarizine in migraine therapy, Clinical Pharmacology and Therapeutics, 47, 165-, 1990	Abstract only - no full text article available.
Diamond,S., Kudrow,L., Stevens,J., Shapiro,D.B., Long-term study of propranolol in the treatment of migraine, Headache, 22, 268-271, 1982	Complex cross over design with optional crossovers - not possible to incorporate data into analysis.
Diamond,S., Medina,J.L., Controlled study of prophylaxis of migraine with propranolol, Clinical Pharmacology and Therapeutics, 17, 232-, 1975	Abstract only
Diamond,S., Schenbaum,H., Flunarizine, a calcium channel blocker, in the prophylactic treatment of migraine, Headache, 23, 39-42, 1983	Not a randomised controlled trial (described as a cross-over trial, but the order of treatments was not randomised).
Diener,H.C., Agosti,R., Allais,G., Bergmans,P., Bussone,G., Davies,B., Ertas,M., Lanteri-Minet,M., Reuter,U., Sanchez del,Rio M., Schoenen,J., Schwalen,S., van,Oene J., TOPMAT,M.I.G., 20080214, Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial.[Erratum appears in Lancet Neurol. 2008 Jan;7(1):25], Lancet Neurology, 6, 1054-1062, 2007	Study design assesses cessation vs continuation of prophylaxis, and is therefore not comparable to other studies in the review.
Diener,H.-C., Bussone,G., Van Oene,J.C., Lahaye,M., Schwalen,S., Goadsby,P.J., Erratum: Topiramate reduces headache days in chronic migraine: A randomized, double-blind, placebo-controlled study (Cephalalgia (2007) 27 (814-823)), Cephalalgia, 27, 962-, 2007	Erratum (considered alongside original study).
Diener,H.C., Matias-Guiu,J., Hartung,E., Pfaffenrath,V., Ludin,H.P., Nappi,G., De,Beukelaar F., 20020927, Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily.[Erratum appears in Cephalalgia. 2002 Jul;22(6):488], Cephalalgia, 22, 209-221, 2002	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.

Study	Reason for Exclusion
Dubenko,O.R., Sotnikov,D., The comparable effectiveness of different medication in migraine prevention, Cephalalgia, 31, 44-45, 2011	Abstract only: no full-text article available.
Edwards,K.R., Glantz,M.J., Norton,J.A., Cross,N., Prophylactic treatment of episodic migraine with topiramate: a double-blind, placebo-controlled trial in 30 patients, Cephalalgia, 20, 316-, 2000	Abstract only - no full text article available.
Edwards,K.R., Potter,D.L., Wu,S.C., Kamin,M., Hulihan,J., 20030819, Topiramate in the preventive treatment of episodic migraine: a combined analysis from pilot, double-blind, placebo-controlled trials, Cns Spectrums, 8, 428-432, 2003	Treatment period (at target dose) < 3 months.
EUCTR2009-013701-34-DE, Prophylactic treatment of vestibular migraine with metoprolol: a double-blind, placebo- controlled trial - PROVEMIG, EUCTR [accessed 11 July 2013], -, 2011	Trial protocol (no results reported).
Ford,L., Shi,Y., Shalayda,K., Manitpisitkul,P., Topiramate as migraine prophylaxis in pediatric patients: Results of an integrated analysis, Annals of NeurologyAnn.Neurol., 76, S217-S218, 2014	Abstract only - no full text article available.
Forssman,B., Lindblad,C.-J., Zbornikova,V., Atenolol for migraine prophylaxis, Acta Neurologica Scandinavica, 65, 75-76, 1982	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Forssman,B., Lindblad,C.J., Zbornikova,V., 19831028, Atenolol for migraine prophylaxis, Headache, 23, 188-190, 1983	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Fragoso,Y.D., 20030715, Low dose of sodium divalproate for the treatment of migraine, Medgenmed [Computer File]: Medscape General Medicine, 5, 32-, 2003	Incorrect study design: non-comparative study.
Freeland,K.N., Vandenberg,A.M.Y., Pharmacologic options for the management and prevention of migraines, Journal of Pharmacy Technology, 27, 222-228, 2011	Systematic review that does not meet the quality standards set out in NICE manual (only searches one database). Use for cross checking.
Freitag,F.G., Diamond,S., Diamond,M., A placebo controlled trial of flunarizine in migraine prophylaxis, Cephalalgia, 11, 157-158, 1991	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Freitag,F.G., Forde,G., Neto,W., Wang,D.Z., Schmitt,J., Wu,S.C., Hulihan,J., 20070925, Analysis of pooled data from two pivotal controlled trials on the efficacy of topiramate in the prevention of migraine, Journal of the American Osteopathic Association, 107, 251-258, 2007	Reanalysis of data from two trials that are already included in the review.
Frenken,C.W., Nuijten,S.T., 19840614, Flunarizine, a new preventive approach to migraine. A double-blind comparison with placebo, Clinical Neurology & Neurosurgery, 86, 17-20, 1984	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Garcia-Monco,J.C., Foncea,N., Bilbao,A., Ruiz,de Velasco,I, Gomez-Beldarrain,M., 20071012, Impact of preventive therapy with nadolol and topiramate on the quality of life of migraine patients, Cephalalgia, 27, 920-928, 2007	Incorrect study design: Allocation to groups was not randomised.
Gawel,M., Kreeft,J., Nelson,R., Simard,D., Flunarizine is comparable to propranolol in the prophylaxis of migraine with and without aura, Cephalalgia, 11, 156-, 1991	Insufficient details to assess whether meets inclusion criteria (treatment duration not reported).

Study	Reason for Exclusion
Gawel,M.J., Kreeft,J., Nelson,R.F., Simard,D., Arnott,W.S., 19921117, Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine, Canadian Journal of Neurological Sciences, 19, 340-345, 1992	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Ghose,K., Niven,B.E., Berry,D., A double-blind crossover comparison of the effects of vigabatrin with placebo in the prevention of migraine headache, Journal of Headache and Pain, 3, 79-85, 2002	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Gillies,D., Sills,M., Forsythe,I., 19860218, Pizotifen (Sanomigran) in childhood migraine. A double-blind controlled trial, European Neurology, 25, 32-35, 1986	Treatment duration (at target dose) < 12 weeks.
Gode,S., Celebisoy,N., Kirazli,T., Akyuz,A., Bilgen,C., Karapolat,H., Sirin,H., Gokcay,F., 20100818, Clinical assessment of topiramate therapy in patients with migrainous vertigo, Headache, 50, 77-84, 2010	Comparison does not match review protocol (compares two doses of topiramate).
Gomersall,J.D., Stuart,A., 19731113, Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial, Journal of Neurology, Neurosurgery & Psychiatry, 36, 684-690, 1973	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Gordon,C.R., Kuritzky,A., Doweck,I., Spitzer,O., Shupak,A., Hering,R., 19930610, Vestibulo-ocular reflex in migraine patients: the effect of sodium valproate, Headache, 33, 129-132, 1993	Treatment duration < 3 months.
GOTOH,Fumio, TASHIRO,Kunio, KATSUZAWA,Naoyuki, KATAYAMA,Soichi, HIRAI,Shunsaku, OTOMO,Eiichi, Shozo,K.I.T.O., TERASHI,Akirou, Ikuo,G.O.T.O., Clinical Evaluation of Lomerizine on Migraine. Double-blind Study in Comparison with Dimetotiazine, Rinsho Hyoka (Clinical Evaluation), 23, 183-214, 1995	Article not in English.
GOTOH,Fumio, TASHIRO,Kunio, KUTSUZAWA,Naoyuki, KOGURE,Kyuya, KATAYAMA,Soichi, HIRAI,Shunsaku, Shozo,K.I.T.O., OTOMO,Eiichi, FUJISHIMA,Masatoshi, Clinical Evaluation of KB-2796 (lomerizine hydrochloride) on Migraine. Late Phase II Study, Rinsho Hyoka (Clinical Evaluation), 23, 13-37, 1995	Article not in English.
GRAHAME,R., 19981101, Drug prophylaxis in migraine. A controlled clinical trial, British Medical Journal, 2, 1203-1207, 1960	Incorrect intervention (reserpine)
Grotemeyer,K.-H., Schlake,H.-P., Husstedt,I.W., Normalization of platelet-reactivity under successful migraine-prophylaxis with metoprolol or flunarizin, Cephalalgia, 9, 435-436, 1989	Incorrect study type: cross-over trial with no random allocation to sequence group.
Hansen,K., Sorensen,P., Olesen,J., A controlled study of flunarizine in common migraine, Acta Neurologica Scandinavica, 69, 266-267, 1984	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Harizanov,M., Neykova,L., MÃ¡rquez,M., Herrero,E., Fillat,O., Torres,J., Camps,F., Ortiz,J.A., Efficacy and safety of dotarizine versus flunarizine in the prophylaxis of migraine, Neurologia, 12, 211-, 1997	Abstract only and not in English.
Hart,C.E., Dodick,D.W., Brandes,J.L., Rothrock,J.F., Jacobs,D., Neto,W., Bhattacharya,S., Schmitt,J., Migraine prophylaxis with topiramate: results of double-blind, placebo-controlled, dose-response trials, Epilepsia, 44 Suppl 9, 106-107, 2003	Abstract only - no full-text article available.

Study	Reason for Exclusion
Havanka-Kanniainen,H., Hokkanen,E., Myllyia,V.V., Long-acting propranolol in migraine prophylaxis, Clinical Pharmacology and Therapeutics, 41, 203-, 1987	Incorrect study design: no mention of random allocation to groups - presume not randomised.
Havanka-Kanniainen,H., Myllyla,V.V., Hokkanen,E., Nimodipine in the prophylaxis of migraine, a double blind study, Acta Neurologica Scandinavica, 65, 77-78, 1982	Treatment duration < 3 months.
Hedman,C., Andersen,A.R., Effects of the B1-selective adrenoceptor antagonist metoprolol on the symptomatology of classic migraine attacks, Cephalalgia, 7, 461-462, 1987	Treatment duration < 3 months
Hedman,C., Andersen,A.R., Andersson,P.G., Gilhus,N.E., Kangasniemi,P., Olsson,J.E., Strandman,E., Nestvold,K., Olesen,J., 19890323, Symptoms of classic migraine attacks: modifications brought about by metoprolol, Cephalalgia, 8, 279-284, 1988	Treatment period < 3 months
Holdorff,B., Sinn,M., Roth,G., [Propranolol for prophylaxis of migraine (author's transl)], Medizinische Klinik, 72, 1115-1118, 1977	Article not in English.
Holroyd,K.A., Penzien,D.B., Cordingley,G.E., 19910904, Propranolol in the management of recurrent migraine: a meta-analytic review, Headache, 31, 333-340, 1991	Systematic review that does not meet the quality standards set out in the NICE methods manual (limited number of databases searched, and method of searching not explicit).
Hubbe,P., Controlled clinical trials of drugs for use in the prophylaxis of migraine, Danish Medical Bulletin, 22, 92-96, 1975	Incorrect study type: narrative review
Hubbe,P., 19730323, The prophylactic treatment of migraine with an antiserotonin pizotifen, Acta Neurologica Scandinavica, 49, 108-114, 1973	Treatment duration < 3 months.
Israil,A., Ahmed,S., Rahman,K.M., Uddin,M.J., Dey,S.K., Battacharjee,M., Mondal,G., Ali,M.A., Alam,M.N., Miah,A.H., Uddin,M.S., 20130624, Efficacy of amitriptyline, pizotifen and propranolol in the prevention of migraine, Mymensingh Medical Journal, 22, 93-100, 2013	Incorrect study design: Allocation to groups was not randomised.
Jayapal,S.S.K., Maheswari,N., Use of topiramate for prophylaxis of chronic migraine in children: A systematic review, Archives of Disease in Childhood, 96, A42-, 2011	Systematic review that does not match review protocol (incorrect population - children)
Johannsson,V., Nilsson,L.R., Widelius,T., Javerfalk,T., Hellman,P., Akesson,J.A., Olerud,B., Gustafsson,C.L., Raak,A., Sandahl,G., 19871118, Atenolol in migraine prophylaxis a double-blind cross-over multicentre study, Headache, 27, 372-374, 1987	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Kalita,J., Bhoi,S.K., Misra,U.K., 20131031, Amitriptyline vs divalproate in migraine prophylaxis: a randomized controlled trial, Acta Neurologica Scandinavica, 128, 65-72, 2013	Open label trial.
Kangasniemi,P., Hedman,C., 19840823, Metoprolol and propranolol in the prophylactic treatment of classical and common migraine. A double-blind study, Cephalalgia, 4, 91-96, 1984	Treatment duration < 3 months
Kangasniemi,P., Nyrke,T., Lang,H., Petersen,E., Propranolol and femoxetine, a 5-HT uptake inhibitor, in migraine prophylaxis, Acta Neurologica Scandinavica, 65, 74-, 1982	Abstract only - no full text article available.
Kangasniemi,P., Tokola,R., Flunarizine in the prophylaxis of migraine patients without aura, Cephalalgia, 9, 425-, 1989	Abstract only: no full-text article available.

Study	Reason for Exclusion
Kangasniemi,P., 19790829, Placebo, 1-isopropylnoradrenochrome-5-monosemicarbazono and pizotifen in migraine prophylaxis, Headache, 19, 219-222, 1979	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Kangasniemi,P.J., Nyrke,T., Lang,A.H., Petersen,E., 19840224, Femoxetine - a new 5-HT uptake inhibitor - and propranolol in the prophylactic treatment of migraine, Acta Neurologica Scandinavica, 68, 262-267, 1983	Treatment duration (at target dose) < 3 months.
Kaniecki,R.G., 19971023, A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura, Archives of Neurology, 54, 1141-1145, 1997	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Kass,B., Nestvold,K., 19801120, Propranolol (Inderal) and clonidine (Catapressan) in the prophylactic treatment of migraine. A comparative trial, Acta Neurologica Scandinavica, 61, 351-356, 1980	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Keskinbora,K., Aydinli,I., 20090112, A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine, Clinical Neurology & Neurosurgery, 110, 979-984, 2008	Treatment duration (at target dose) < 3 months.
Keyvan,G., Abolfazl,M.B., 20100105, Comparison of treatment effect of sodium valproate, propranolol and tricyclic antidepressants in migraine, Pakistan Journal of Biological Sciences, 12, 1098-1101, 2009	Treatment duration not reported (treatment duration must be >= 3 months).
Klapper,J.A., Divalproex sodium in migraine prevention, Headache Quarterly, 7, 16-19, 1996	Open label trial
Klimek,A., Therapeutic effectiveness of propranolol and flunarizine in the prophylactic treatment of migraine, Therapie, 47, 137-, 1992	Abstract only - no full text article available.
Kuritzky,A., Hering,R., Prophylactic treatment of migraine with long acting propranolol - a comparison with placebo, Cephalalgia, 7, 457-458, 1987	Treatment duration < 3 months
Lutschg,J., Vassella,F., The treatment of juvenile migraine using flunarizine or propranolol, Schweizerische Medizinische Wochenschrift, 120, 1731-1736, 1990	Article not in English.
Lainez,M.J., Freitag,F.G., Pfeil,J., Ascher,S., Olson,W.H., Schwalen,S., Time course of adverse events most commonly associated with topiramate for migraine prevention, European Journal of Neurology, 14, 900-906, 2007	Pooled analysis of 3 studies already included in the review.
Lamsudin,R., Sadjimin,T., 19930913, Comparison of the efficacy between flunarizine and nifedipine in the prophylaxis of migraine, Headache, 33, 335-338, 1993	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Langohr,H.D., Reinecke,M., Gerber,W.D., Mangold,R., Migraine prophylaxis with dihydroergotamine and flunarizine, Fortschritte der Medizin, 106, 65-70, 1988	Article not in English.
Lastra,Martinez L., Herranz,Fernandez J., Arteaga Manjon,Cabez R., [Flunarizine and dihydroergotamine in the treatment of migraine in children (published erratum appears in An Esp Pediatr 1990 Jun;32(6):566)], An-Esp-Pediatr, 32, 213-218, 1990	Article not in English.
Lewis,D., Paradiso,E., 20080327, A double-blind, dose comparison study of topiramate for prophylaxis of basilar-	Comparison does not match review protocol (compared two doses of

Study	Reason for Exclusion
type migraine in children: a pilot study, Headache, 47, 1409-1417, 2007	topiramate.
Linde,K., Rossnagel,K., 20040817, Propranolol for migraine prophylaxis. [Review] [95 refs], Cochrane Database of Systematic Reviews, CD003225-, 2004	Systematic review that does not cover all aspects of review protocol (only includes drug propranolol). Use for cross-checking.
Linde,M., Mulleners,W.M., Chronicle,E.P., McCrory,D.C., Gabapentin for the prophylaxis of migraine in adults. Update of a cochrane review, Cephalalgia, 33, 251-, 2013	Abstract only: no full-text article available.
Linde,M., Mulleners,W.M., Chronicle,E.P., McCrory,D.C., 20131119, Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. [Review], Cochrane Database of Systematic Reviews, 6, CD010611-, 2013	Systematic review that does not cover all aspects of review protocol (only includes drug valproate). Use for cross-checking.
Linde,M., Mulleners,W.M., Chronicle,E.P., McCrory,D.C., 20131119, Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. [Review], Cochrane Database of Systematic Reviews, 6, CD010609-, 2013	Systematic review that does not cover all aspects of review protocol (only covers gabapentin and pregabalin). Use for cross checking.
Linde,M., Mulleners,W.M., Chronicle,E.P., McCrory,D.C., 20131119, Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults. [Review], Cochrane Database of Systematic Reviews, 6, CD010608-, 2013	Systematic review that does not cover all aspects of review protocol (only includes antiepileptics). Use for cross-checking.
Lo,Y.L., Lum,S.Y., Fook-Chong,S., Siow,H.C., 20100615, A pilot study of topiramate dosages for migraine prophylaxis in an Asian population, Journal of Headache & Pain, 11, 175-178, 2010	Comparison does not match review protocol (compared doses of topiramate).
Louis,P., Migraine prophylaxis: Double-blind trials with flunarizine., Die Therapiewoche, 34, 5661-5666, 1984	Article not in English.
Louis,P., Schoenen,J., Hedman,C., 19851119, Metoprolol v. clonidine in the prophylactic treatment of migraine, Cephalalgia, 5, 159-165, 1985	Treatment duration < 3 months.
Louis,P., Spierings,E.L., 19830421, Comparison of flunarizine (Sibelium) and pizotifen (Sandomigran) in migraine treatment: a double-blind study, Cephalalgia, 2, 197-203, 1982	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Louis,P., 19820225, A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium) in migraine, Headache, 21, 235-239, 1981	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Lucking,C.H., Oestreich,W., Schmidt,R., Soyka,D., 19881222, Flunarizine vs. propranolol in the prophylaxis of migraine: two double-blind comparative studies in more than 400 patients, Cephalalgia, 8, Suppl-6, 1988	Incorrect study design: no mention of random allocation to groups (assume unrandomised).
Ludin,H.P., A comparative trial with flunarizine and propranolol in migraine, Cephalalgia, 7, 469-470, 1987	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Ludin,H.P., 19890622, Flunarizine and propranolol in the treatment of migraine, Headache, 29, 219-224, 1989	Exclusion post hoc by Committee (Flunarizine does not have licensing authorisation in UK for any indication).
Luo,N., Di,W., Zhang,A., Wang,Y., Ding,M., Qi,W., Zhu,Y., Massing,M.W., Fang,Y., 20120911, A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate	Open label trial.

Study	Reason for Exclusion
in migraine prophylaxis, Pain Medicine, 13, 80-86, 2012	
Lutschg,J., Vassella,F., Flunarizine and propranolol in the treatment of migraine in children, Schweizerische Medizinische Wochenschrift, 120, 1731-1736, 1990	Article not in English.
Maissen,C.P., Ludin,H.P. Comparison of the effect of 5-hydroxytryptophan and propranolol in the interval treatment of migraine, Schweizerische Medizinische Wochenschrift, 121, 1585-1590, 1991	Article not in English.
Malvea,B.P., Gwon,N., Graham,J.R., 19730301, Propranolol prophylaxis of migraine, Headache, 12, 163-167, 1973	Treatment duration < 3 months.
Markley,H.G., Cheronis,J.C., Piepho,R.W., 19840730, Verapamil in prophylactic therapy of migraine, Neurology, 34, 973-976, 1984	Trial duration < 3 months.
Mathew,N.T., Rapoport,A., Saper,J., Magnus,L., Klapper,J., Ramadan,N., Stacey,B., Tepper,S., 20010628, Efficacy of gabapentin in migraine prophylaxis, Headache, 41, 119-128, 2001	Treatment duration (at target dose) < 3 months.
Mathew,N.T., 19811025, Prophylaxis of migraine and mixed headache. A randomized controlled study, Headache, 21, 105-109, 1981	Open label trial.
Matias-Guiu,J., Horga,J., Asensio,M., Castillo,J., Lainez,J.M., Herandez,M., Montiel,I., Comparison of dotarizine and pizotifen in prophilactic treatment of migraine: a crossover double-blind multicentre study, Functional Neurology, 2/3, 155-, 1996	Abstract only - no full text article available.
Maykova,T.N., Application and efficacy of levetiracetam in prophylactic treatment of migraine without aura, Journal of Headache and Pain, 14, -, 2013	Abstract only (no full text article available).
McArthur,J.C., Marek,K., Pestronk,A., McArthur,J., Peroutka,S.J., 19890323, Nifedipine in the prophylaxis of classic migraine: a crossover, double-masked, placebo-controlled study of headache frequency and side effects, Neurology, 39, t-6, 1989	Incorrect study design: no mention of random allocation to groups - assume not randomised.
Medeiros,P.L., Medeiros,F.L., Valenga,M.M., Low dose of pizotifen in migraine prophylaxis of adults: A comparative controlled trial with amitriptyline as an active control, Cephalalgia, 29, 37-38, 2009	Abstract only - no full text article available.
Mentenopoulos,G., Manafi,T., Logothetis,J., Bostantzopoulou,S., 19850916, Flunarizine in the prevention of classical migraine: a placebo-controlled evaluation, Cephalalgia, 5, Suppl-40, 1985	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Mikkelsen,B., Pedersen,K.K., Christiansen,L.V., 19860725, Prophylactic treatment of migraine with tolfenamic acid, propranolol and placebo, Acta Neurologica Scandinavica, 73, 423-427, 1986	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Mishra,S., A study on efficacy of topiramate in the preventative treatment of migraine in females with high body mass index, Cephalalgia, 31, 175-176, 2011	Abstract only - no full text article available.
Mohammadianinejad,S.E., Abbasi,V., Sajedi,S.A., Majdinasab,N., Abdollahi,F., Hajmanouchehri,R., Faraji,A., 20111207, Zonisamide versus topiramate in migraine prophylaxis: a double-blind randomized clinical trial, Clinical Neuropharmacology, 34, 174-177, 2011	Treatment period (at target dose) <12 weeks
Moja,L., Cusi,C., Sterzi,R., Canepari,C., Selective	Systematic review that does not

Study	Reason for Exclusion
Serotonin Re-uptake Inhibitors (SSRIs) for preventing migraine and tension-type headaches, Cochrane Database of Systematic Reviews, -, 2009	match review protocol (only includes SSRIs as drug treatment). Use for cross checking.
Mondrup,K., Moller,C.E., 19780218, Prophylactic treatment of migraine with clonidine. A controlled clinical trial, Acta Neurologica Scandinavica, 56, 405-412, 1977	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Moylan,R., Drugs for preventing migraine headaches in children, A cochrane review, Cephalalgia, 31, 84-, 2011	Abstract only - no full-text article available.
Mulleners,W.M., Chronicle,E.P., 20080604, Anticonvulsants in migraine prophylaxis: a Cochrane review., Cephalalgia, 28, 585-597, 2008	Systematic review that covers only part of the review protocol (anticonvulsant drugs). Use for cross checking.
Nair,K.G., 19760318, A pilot study of the value of propranolol in migraine, Journal of Postgraduate Medicine, 21, 111-113, 1975	Incorrect study design: non-comparative study.
Nattero,G., Biale,L., Savi,L., Lisuride and pizotifen in the treatment of migraine without aura, Cephalalgia, 218-219, 1991	Abstract only
NCT02169830, A prospective randomized cross-over trial of nortryptyline and topiramate in the initial treatment of vestibular migraine, Clinicaltrials.gov [www.clinicaltrials.gov], -, 2014	Trial protocol only (no results available).
Noone,J.F., 19810513, Clomipramine in the prevention of migraine, Journal of International Medical Research, 8, Suppl-52, 1980	Treatment duration < 3 months.
Noronha,M.J., Double-blind randomised cross-over trial of timolol in migraine prophylaxis in children, Cephalalgia, 5, 174-175, 1985	Treatment duration < 3 months
Olerud,B., Gustavsson,C.L., Furberg,B., 19870330, Nadolol and propranolol in migraine management, Headache, 26, 490-493, 1986	Treatment duration < 3 months.
Olesen,J., Calcium entry blockers in the prophylaxis of migraine, Annals of the New York Academy of Sciences, 522, 720-722, 1988	Incorrect study type: narrative review.
Olsson,J.E., Behring,H.C., Forssman,B., Hedman,C., Hedman,G., Johansson,F., Kinnman,J., Palhagen,S.E., Samuelsson,M., Strandman,E., 19841226, Metoprolol and propranolol in migraine prophylaxis: a double-blind multicentre study, Acta Neurologica Scandinavica, 70, 160-168, 1984	Treatment duration < 3 months
Osterman,P.O., 19770812, A comparison between placebo, pizotifen and 1-isopropyl-3-hydroxy-5-semicarbazono-6-oxo-2.3.5.6-tetrahydroindol (Divascan) in migraine prophylaxis, Acta Neurologica Scandinavica, 56, 17-28, 1977	Treatment duration < 3 months.
Ozyalcin,S.N., Talu,G.K., Kiziltan,E., Yucel,B., Ertas,M., Disci,R., 20050628, The efficacy and safety of venlafaxine in the prophylaxis of migraine, Headache, 45, 144-152, 2005	Treatment duration < 3 months.
Palferman,T.G., Gibberd,F.B., Simmonds,J.P., 19830610, Prophylactic propranolol in the treatment of headache, British Journal of Clinical Practice, 37, 28-29, 1983	Treatment duration < 3 months
Paterna,S., Martino,S.G., Campisi,D., Cascio,Ingurgio N., Marsala,B.A., Evaluation of the effects of verapamil,	Article not in English.

Study	Reason for Exclusion
flunarizine, diltiazem, nimodipine and placebo in the prevention of hemicrania. A double-blind randomized cross-over study, Clinica Terapeutica, 134, 119-125, 1990	
Pedersen,E., Moller,C.E., 19660928, Methysergide in migraine prophylaxis, Clinical Pharmacology & Therapeutics, 7, 520-526, 1966	Treatment duration < 3 months.
Peres,M.F.P., Goncalves,A.L., Ribeiro,R.T., Double-blind, placebo controlled, randomized clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention, Cephalalgia, 33, 94-95, 2013	Abstract only: no full text article available.
Pita,E., Higueras,A., Bolanos,J., Perez,N., Mundo,A., 19780724, Propranolol and migraine. A clinical trial, Archivos de Farmacologia y Toxicologia, 3, 273-278, 1977	Article not in English
Pompili,M., Serafini,G., Innamorati,M., Serra,G., Dominici,G., Fortes-Lindau,J., Pastina,M., Telesforo,L., Lester,D., Girardi,P., Tatarelli,R., Martelletti,P., 20121002, Patient outcome in migraine prophylaxis: the role of psychopharmacological agents, Patient Related Outcome Measures, 1, 107-118, 2010	Systematic review with insufficient details to assess whether quality meets standards in NICE manual. Use for cross checking.
Pradalier,A., Serratrice,G., Collard,M., Hirsch,E., Feve,J., Masson,M., Masson,C., Dry,J., Koulikovsky,G., Nguyen,G., [Beta-blockers and migraine. Efficacy of time-release propranolol versus placebo], Therapie, 45, 441-445, 1990	Article not in English.
Pradalier,A., Serratrice,G., Collard,M., Hirsch,E., Feve,J., Masson,M., Masson,C., Dry,J., Koulikovsky,G., Nguyen,G., Schbath,J., Carpentier,M.C., Betablockers and migraine: Long-acting propranolol in migraine prophylaxis, against placebo. Therapie, 45, 441-445, 1990	Article not in English
Rao,B.S., Das,D.G., Taraknath,V.R., Sarma,Y., 20001130, A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis, Neurology India, 48, 223-226, 2000	Incorrect study design: allocation to groups not randomised.
Rascol,A., Montastruc,J.-L., Rascol,O., Flunarizine versus pizotifen: a double blind study in the prophylaxis of migraine, Cephalalgia, 5, 542-, 1985	Abstract only - no full text article available.
Rascol,A., Montastruc,J.L., Rascol,O., 19860508, Flunarizine versus pizotifen: a double-blind study in the prophylaxis of migraine, Headache, 26, 83-85, 1986	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Raskin,N.H., Schwartz,R.K., The prophylaxis of migraine: A long-term controlled study, Neurology, 30, GS-25, 1980	Abstract only - no full text article available.
Raveau-Landon,C., Bousser,M.G., [Metoprolol, a new effective antimigraine agent], Presse medicale (Paris, France : 1983), 17, 1805-1809, 1988	Article not in English
Reunanen,M., Hokkanen,E., Divascan and clonidine in the prophylactic treatment of migraine. A double blind study, Acta Neurologica Scandinavica, 57, 287-288, 1978	Abstract only - no full-text article available.
Ryan,R.E.,Sr., Diamond,S., Ryan,R.E.,Jr., 19760102, Double blind study of clonidine and placebo for the prophylactic treatment of migraine, Headache, 15, 202-210, 1975	Treatment duration < 3 months.
Sarchielli,P., Messina,P., Cupini,L.M., Tedeschi,G., Di,Piero,V, Livrea,P., Pini,L.A., Bernardi,G., Bono,G., Sandrini,G., Caproni,S., Corbelli,I., Pisani,F., Beghi,E., Calabresi,P., SAMOHA Study Group, Sodium valproate in migraine without aura and medication overuse headache: a	Incorrect population: Patients were not required to have current migraine (were required to have past history of migraine).

Study	Reason for Exclusion
randomized controlled trial, European Neuropsychopharmacology, 24, 1289-1297, 2014	
Schrader,H., Stovner,L.J., Helde,G., Sand,T., Bovim,G., 20010405, Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study, BMJ, 322, 19-22, 2001	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Shafar,J., Tallett,E.R., Knowlson,P.A., 19720503, Evaluation of clonidine in prophylaxis of migraine. Double-blind trial and follow-up, Lancet, 1, 403-407, 1972	Treatment period < 3 months
Shamliyan,T.A., Choi,J.Y., Ramakrishnan,R., Miller,J.B., Wang,S.Y., Taylor,F.R., Kane,R.L., 20140508, Preventive pharmacologic treatments for episodic migraine in adults, Journal of General Internal Medicine, 28, 1225-1237, 2013	Exclude: Systematic review that does not match review protocol (excludes adolescents). Use for cross checking.
Shamliyan,T.A., Kane,R.L., Ramakrishnan,R., Taylor,F.R., Migraine in children: preventive pharmacologic treatments (Structured abstract), Health Technology Assessment Database, -, 2013	Systematic review that does not match review protocol (population is children with migraine only).
Shamliyan,T.A., Kane,R.L., Ramakrishnan,R., Taylor,F.R., 20140507, Episodic migraines in children: limited evidence on preventive pharmacological treatments. [Review], Journal of Child Neurology, 28, 1320-1341, 2013	Systematic review that does not match review protocol (population for review is children only)
SHEKELLE,R.B., OSTFELD,A.M., 19961201, Methysergide in the migraine syndrome, Clinical Pharmacology & Therapeutics, 5, 201-204, 1964	Treatment duration < 3 months
Shimell,C.J., Fritz,V.U., Levien,S.L., 19900221, A comparative trial of flunarizine and propranolol in the prevention of migraine, South African Medical Journal, Suid-Afrikaanse, 75-77, 1990	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Silberstein,S., Saper,J., Berenson,F., Somogyi,M., McCague,K., D'Souza,J., 20080306, Oxcarbazepine in migraine headache: a double-blind, randomized, placebo-controlled study, Neurology, 70, 548-555, 2008	Treatment duration (at target dose) <12 weeks.
Silcocks,P., Whitham,D., Whitehouse,W.P., 20100929, P3MC: a double blind parallel group randomised placebo controlled trial of Propranolol and Pizotifen in preventing migraine in children, Trials [Electronic Resource], 11, 71-, 2010	Trial protocol only (no results available).
Sinert,M.R., Epstein,B.J., Topiramate for use in adult migraine prophylaxis, Journal of Pharmacy Technology, 25, 100-110, 2009	Incorrect study design: narrative review.
Sjaastad,O., Stensrud,P., 19710706, 2-(2.6-dichlorophenylamino)-2-imidazoline hydrochloride (ST 155 or Catapresan) as a prophylactic remedy against migraine, Acta Neurologica Scandinavica, 47, 120-122, 1971	Treatment duration < 3 months.
Solomon,G.D., Verapamil and propranolol in migraine prohylaxis: a double-blind crossover study, Headache, 26, 325-, 1986	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Solomon,G.D., Steel,J.G., Spaccavento,L.J., 19831217, Verapamil prophylaxis of migraine. A double-blind, placebo-controlled study, JAMA, 250, 2500-2502, 1983	Abstract only - no full text article available.
Sorensen,P.S., Prophylactic effect of flunarizine versus metoprolol in migraine, Cephalalgia, 9, 355-356, 1989	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.

Study	Reason for Exclusion
Sorensen,P.S., Hansen,K., Olesen,J., Flunarizine in common migraine prophylaxis, a double-blind cross-over study, Cephalalgia, 5, 540-541, 1985	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Sorensen,P.S., Hansen,K., Olesen,J., 19860616, A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine, Cephalalgia, 6, 7-14, 1986	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Sorensen,P.S., Larsen,B.H., Rasmussen,M.J., Kinge,E., Iversen,H., Alslev,T., Nohr,P., Pedersen,K.K., Schroder,P., Lademann,A., 19920227, Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability, Headache, 31, 650-657, 1991	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Sorge,F., De,Simone R., Marano,E., Nolano,M., Orefice,G., Carrieri,P., 19880602, Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled, crossover study, Cephalalgia, 8, 1-6, 1988	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Sorge,F., Marano,E., 19850916, Flunarizine v. placebo in childhood migraine. A double-blind study, Cephalalgia, 5, Suppl-8, 1985	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Sorge,F., Simone,R., Marano,E., Orefice,G., Carrieri,P., Efficacy of flunarizine in the prophylaxis if migraine in children: a double-blind, cross-over, controlled study, Cephalalgia, 5, 174-, 1985	Abstract only: no full-text article available.
Soyka,D., Oestreich,W., Therapeutic effectiveness of flunarizine and propranolol in the interval therapy of migraine, Cephalalgia, 7 Suppl 6, 467-468, 1987	Excluded by the Committee post hoc - Flunarizine does not have a marketing authorisation in the UK for any indication.
Soyka,D., Oestreich,W., Flunarizine versus propranolol in migraine prophylaxis - A multicenter double-blind study in 12 hospitals, Nervenheilkunde, 6, 177-183, 1987	Article not in English.
Soyka,D., Oestreich,W., Flunarizine versus propranolol in interval treatment of migraine, Nervenheilkunde, 9, 45-51, 1990	Article not in English.
Spierings,E.L.H., The efficacy of the calcium entry blocker flunarizine in the prophylactic treatment of migraine, International Angiology, 3, 81-87, 1984	Incorrect study type: Narrative review
Standnes,B., 19830324, The prophylactic effect of timolol versus propranolol and placebo in common migraine: beta-blockers in migraine, Cephalalgia, 2, 165-170, 1982	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Steardo,L., Bonuso,S., Di,Stasio E., Marano,E., 19821216, Selective and non-selective beta-blockers: are both effective in prophylaxis of migraine? A clinical trial versus methysergide, Acta Neurologica, 4, 196-204, 1982	Open label trial
Steardo,L., Marano,E., Barone,P., Denman,D.W., Monteleone,P., Cardone,G., 19861118, Prophylaxis of migraine attacks with a calcium-channel blocker: flunarizine versus methysergide, Journal of Clinical Pharmacology, 26, 524-528, 1986	Exclusion post hoc by Committee (Flunarizine does not have licensing authorisation in UK for any indication).
Steiner,T.J., Cook,G.E., Joseph,R., Clifford,Rose F., Double-blind dose-ranging comparison of metoprolol with placebo in the prophylaxis of classical and common migraine, Cephalalgia, 5 Suppl 3, 558-559, 1985	Abstract only

Study	Reason for Exclusion
Steiner,T.J., Findley,L.J., Yuen,A.W., 19970718, Lamotrigine versus placebo in the prophylaxis of migraine with and without aura, Cephalalgia, 17, 109-112, 1997	Half of participants did not receive target dose for duration of treatment (received titrated dose for first 4 weeks). Results for these participants are not reported separately.
Steiner,T.J., Joseph,R., Hedman,C., Rose,F.C., 19880401, Metoprolol in the prophylaxis of migraine: parallel-groups comparison with placebo and dose-ranging follow-up, Headache, 28, 15-23, 1988	Treatment period < 3 months
Stellar,S., Ahrens,S.P., Meibohm,A.R., Reines,S.A., 19841203, Migraine prevention with timolol. A double-blind crossover study, JAMA, 252, 2576-2580, 1984	Treatment duration < 3 months
Stensrud,P., Skaug,O.E., Sjaastad,O., 19720110, Clinical trial of MY-25 (1-methyl-ergotamine-bitartrate) in migraine prophylaxis, Headache, 11, 128-131, 1971	Treatment duration < 3 months
Storey,J.R., Calder,C.S., Hart,D.E., Potter,D.L., 20020716, Topiramate in migraine prevention: a double-blind, placebo-controlled study, Headache, 41, 968-975, 2001	Treatment period (at target dose) < 3 months.
Stovner,L.J., Linde,M., Gravdahl,G.B., Erling,T., Aamodt,A.H., Sand,T., Hagen,K., Candesartan versus propranolol for migraine prophylaxis: A randomized, triple-blind, placebo-controlled, double crossover study, Cephalalgia, 33, 13-, 2013	Abstract only - no full-text article available.
Stovner,L.J., Linde,M., Gravdahl,G.B., Tronvik,E., Aamodt,A.H., Sand,T., Hagen,K., A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study, Cephalalgia, 34, 523-532, 2013	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Sudilovsky,A., Elkind,A.H., Ryan,R.E.,Sr., Saper,J.R., Stern,M.A., Meyer,J.H., 19871203, Comparative efficacy of nadolol and propranolol in the management of migraine, Headache, 27, 421-426, 1987	Treatment duration (at target dose) < 3 months.
Sudilovsky,A., Stern,M., Meyer,J.H., Comparative efficacy of nadolol and propranolol in the prophylaxis of migraine, Headache, 26, 311-312, 1986	Abstract only: no full-text article available.
Sudilovsky,A., Stern,M.A., Meyer,J.H., Nadolol: the benefits of an adequate trial duration in the prohylaxis of migraine, Headache, 26, 325-, 1986	Abstract only: no full-text article available.
Tfelt-Hansen,P., Standnes,B., Kangasneimi,P., Timolol and propranolol for common migraine prophylaxis, Acta Neurologica Scandinavica, 69, 264-265, 1984	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Tfelt-Hansen,P., Standnes,B., Kangasneimi,P., Hakkarainen,H., Olesen,J., 19840412, Timolol vs propranolol vs placebo in common migraine prophylaxis: a double-blind multicenter trial, Acta Neurologica Scandinavica, 69, 1-8, 1984	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Thomas,M., Behari,M., Ahuja,G.K., 19920305, Flunarizine in migraine prophylaxis: an Indian trial, Headache, 31, 613-615, 1991	Incorrect study design: no mention of random allocation to groups - presume not randomised.
Togha,M., Taghdiri,F., Razeghi,S., Efficacy and safety of venlafaxine for the treatment of chronic migraine: A randomized, double-blind, controlled trial, Journal of Neurology, 261, S201-, 2014	Abstract only - no full text article available.
Tran,B.N., Vivian,V.S., Burch,K.J., Can valproate prevent	Incorrect study type: Narrative

Study	Reason for Exclusion
migraine headaches?, Journal of Pharmacy Technology, 13, 163-168, 1997	review.
Tronvik,E., Stovner,L.J., Helde,G., Sand,T., Bovim,G., 20030109, Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial, JAMA, 289, 65-69, 2003	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Unalp,A., Uran,N., Ozturk,A., 20090408, Comparison of the effectiveness of topiramate and sodium valproate in pediatric migraine, Journal of Child Neurology, 23, 1377-1381, 2008	No mention of blinding and study described as 'retrospective' - presume open-label design
Vilming,S., Standnes,B., Hedman,C., 19850603, Metoprolol and pizotifen in the prophylactic treatment of classical and common migraine. A double-blind investigation, Cephalalgia, 5, 17-23, 1985	Treatment duration < 3 months
Viswanathan,K.N., Rajendiran,C., Manohar,D.S., Balaraman,V.T., Cinnarizine-propranalol in migraine prophylaxis - A double blind clinical study, Cephalalgia, 11, 166-167, 1991	Incorrect study design: allocation to groups not randomised.
WÃ¶rz,R., Reinhardt-Benmalek,B., FÃ¶h,M., Grotemeyer,K.H., Scharafinski,H.W., [Prevention of migraine using bisoprolol. Results of a double-blind study versus metoprolol], Fortschritte der Medizin, 110, 268-272, 1992	Article not in English.
Wessely,P., Baumgartner,C., Klingler,D., Kreczi,J., Meyerson,N., Sailer,L., Saltuari,L., Schutt,P., Preliminary results of a double-blind study with the new migraine prophylactic drug Gabapentin, Cephalalgia, 7, 477-478, 1987	Incorrect study design: no mention of random allocation to groups (assume not randomised).
Whewell,J., 19661223, Methysergide in prophylaxis of migraine: a clinical trial in general practice, British Medical Journal, 2, 394-395, 1966	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Worz,R., Drillisch,C., Prevention of migraine by a calcium entry blocker. Results of a double-blind trial of flunarizine vs pizotifen, Munchener medizinische Wochenschrift (1950), 125, 711-714, 1983	Article not in English.
Worz,R., Reinhardt-Benmalek,B., Foeh,M., Grotemeyer,K.H., Scharafinski,H.W., Migraine prophylaxis with bisoprolol, Headache Quarterly, 3, 64-72, 1992	Comparison does not match review protocol - within class (beta blockers).
Worz,R., Reinhardt-Benmalek,B., Foh,M., Grotemeyer,K.-H., Scharafinski,H.W., Migraine prophylaxis by bisoprolol. Results of a double-blind study in comparison with metoprolol, Fortschritte der Medizin, 110, 80-90, 1992	Article not in English.
Worz,R., Reinhardt-Benmalek,B., Grotemeyer,K.-H., Foh,M., Bisoprolol and metoprolol in the prophylactic treatment of migraine with and without aura - A randomized double-blind cross-over multicenter study, Cephalalgia, 11, 152-153, 1991	Treatment duration (at target dose) < 12 weeks.
Ziegler,D.K., Hurwitz,A., Hassanein,R.S., Kodanaz,H.A., Preskorn,S.H., Mason,J., 19870528, Migraine prophylaxis. A comparison of propranolol and amitriptyline, Archives of Neurology, 44, 486-489, 1987	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.
Ziegler,D.K., Hurwitz,A., Preskorn,S., Hassanein,R., Seim,J., 19930915, Propranolol and amitriptyline in prophylaxis of migraine. Pharmacokinetic and therapeutic effects, Archives of Neurology, 50, 825-830, 1993	Cross-over design with results not reported after each treatment period - not possible to incorporate into analysis.

Appendix G: Evidence tables

Abbreviations:

M/F=male/female, N=number of participants, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis

Table 8: Studies meeting inclusion criteria but reporting no outcomes specified in the review protocol

Bibliographic reference	Outcomes reported but not extracted
Andersson PG (1973) BC-105 and deseril in migraine prophylaxis. (A double-blind study). Headache 13: 71-3	Reduction in attack frequency (no measure of variability, such as standard deviations, reported, so data not useable), Migraine index, Number of patients free from attacks, Change in depression score, Side effects (serious adverse events not reported separately), Change in weight.
Ansell E, Fazzone T, Festenstein R et al. (1988) Nimodipine in migraine prophylaxis. Cephalalgia 8: 269-72	Migraine index, migraine frequency (effect size and associated variability not reported), blood pressure, visual symptoms
Bellavance AJ, Meloche JP (1990) A comparative study of naproxen sodium, pizotyline and placebo in migraine prophylaxis. Headache 30: 710-5	Migraine index, Headache unit index, migraine frequency (no measure of variability, such as standard deviations, reported, so data not useable), number of attacks requiring rescue medication no measure of variability, such as standard deviations, reported, so data not useable, pain intensity, severity of disability, average duration of headache (no effect sizes reported), days incapacitated, side effects (serious adverse events not reported separately).
Cleland PG, Barnes D, Elrington GM et al. (1997) Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. European Neurology 38: 31-8	Migraine attack frequency (no measure of variability, such as standard deviations, reported, so data not useable), Headache free days Reduction in attack frequency (no measure of variability, such as standard deviations, reported, so data not useable), Attack severity Reduction in attack frequency (no measure of variability, such as standard deviations, reported, so data not useable), Weight, Adverse events (serious adverse events not reported separately).
Couch JR, Amitriptyline Versus Placebo Study Group (2011)	Headache frequency (no group effect measures reported), headache

Bibliographic reference	Outcomes reported but not extracted
Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache 51: 33-51	duration, headache severity (no group effect measures reported), adverse events (serious adverse events not presented separately).
d'Amato CC, Pizza V, Marmolo T et al. (1999) Fluoxetine for migraine prophylaxis: a double-blind trial. Headache 39: 716-9	Total pain index, adverse events (serious adverse events not reported separately).
Diener HC, Scholz E, Dichgans J et al. (1989) Central effects of drugs used in migraine prophylaxis evaluated by visual evoked potentials. Annals of Neurology 25: 125-30	Visual evoked potential latencies and amplitudes.
Forsythe WI, Gillies D, Sills MA (1984) Propanolol ('Inderal') in the treatment of childhood migraine. Developmental Medicine & Child Neurology 26: 737-41	Headache frequency (no measure of variability, such as standard deviations, reported, so data not useable), Headache duration, Nausea, Vomiting, Analgesic use, Headache severity (no measure of variability, such as standard deviations, reported, so data not useable), side effects (severe adverse events not reported separately)
Gawel M (1987) A double blind, cross over study of nimodipine versus pizotyline in common and classical migraine. Cephalalgia 7: 453-4	Headache frequency (although a measure of variability is given, the units of this measure are not reported, so this data is not usable)
Gelmers HJ (1983) Nimodipine, a new calcium antagonist, in the prophylactic treatment of migraine. Headache 23: 106-9	Migraine frequency (no group measure reported), migraine intensity (no group measure reported), migraine duration, migraine index, adverse events (serious adverse events not reported separately)
Gelmers HJ, Henry P, Lucas J et al. (1989) European multicenter trial of Nimodipine in the prophylaxis of common migraine (migraine without aura). Headache 29: 633-8	Migraine days (no measure of variability, such as standard deviations, reported, so data not useable), 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, adverse events.
Gelmers HJ, Henry P, Lucas J et al. (1989) European multicenter trial of Nimodipine in the prophylaxis of classic migraine (migraine with aura). Headache 29: 639-42	Migraine days (no measure of variability, such as standard deviations, reported, so data not useable), 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, adverse events.
Ghobadi SH, Jivad N (2013) The prophylactic activity of propranol and nimodipineon migraine headache. World Journal of Medical Sciences 8: 144-6	Migraine frequency (not reported or calculable as a change from baseline as no baseline values reported), Migraine severity (not reported or calculable as a change from baseline as no baseline values reported), headache duration
Havanka-Kanniainen H, Hokkanen E, Myllyla V (1985) Efficacy of nimodipine in comparison with pizotifen (Sandomigrin) in the prophylaxis of migraine. Cephalalgia 5: 530-1	Migraine frequency (no measure of variability, such as standard deviations, reported, so data not useable), migraine intensity (no effect size reported), migraine intensity (no effect size reported), body weight
Jensen R, Brinck T, Olesen J (1994) Sodium valproate has a	Crossover design with phases not reported separately (so unable to

Bibliographic reference	Outcomes reported but not extracted
prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology 44: 647-51	incorporate in analysis) except for the outcome 'number of migraine days' (no measure of variability, such as standard deviations, reported, so data not useable).
Lofland JH, Gagne JJ, Pizzi LT et al. (2007) Impact of topiramate migraine prophylaxis on workplace productivity: results from two US randomized, double-blind, placebo-controlled, multicenter trials. Journal of Occupational & Environmental Medicine 49: 252-7	Same participants as Brandes 2004 and Silberstein 2004. Days of work lost to migraine, days worked with migraine, degree of effectiveness when working with migraine.
Ludvigsson J (1974) Propranolol used in prophylaxis of migraine in children. Acta Neurologica Scandinavica 50: 109-15	Headache frequency (no measure of variability, such as standard deviations, reported, so data not useable), number of patients showing improvement
Micieli G, Trucco M, Agostinis C et al. (1985) Nimodipine vs. pizotifen in common migraine: results of a double-blind cross-over trial. Cephalalgia 5 Suppl 3: 532-3	Headache severity (no measure of variability, such as standard deviations, reported, so data not useable), analgesic consumption (no measure of variability, such as standard deviations, reported, so data not useable), attack frequency (not reported separately across groups)
Nanda RN, Johnson RH, Gray J et al. (1978) A double blind trial of acebutolol for migraine prophylaxis. Headache 18: 20-2	Headache frequency (no measure of variability, such as standard deviations, reported, so data not useable), Plasma acebutolol concentrations
Nyrke T, Kangasniemi P, Lang AH et al. (1984) Steady-state visual evoked potentials during migraine prophylaxis by propranolol and femoxetine. Acta Neurologica Scandinavica 69: 9-14	Only reports relation between clinical outcomes and steady state visual evoked responses – clinical outcomes are reported in Kangnasniemi 1983
Orholm M, Honore PF, Zeeberg I (1986) A randomized general practice group-comparative study of femoxetine and placebo in the prophylaxis of migraine. Acta Neurologica Scandinavica 74: 235-9	Migraine frequency (not reported or calculable as a change from baseline as no baseline data reported), headache index, side effects (serious adverse events not reported separately),
Rodriguez-Leyva I, Sanchez Aguilar MCJM, Hernandez-Sierra JF et al. (2010) Topiramate vs. Amitriptyline in prophylactic treatment of migraine: A controlled clinical trial. Revista Mexicana de Neurociencia 11: 338-42	Headache frequency (no measure of variability, such as standard deviations, reported, so data not useable), reduction in pain score in response to acute medication, patient satisfaction, weight, adverse events (serious adverse events not reported separately).
Ryan RE (1968) Double-blind crossover comparison of bc-105, methysergide and placebo in the prophylaxis of migraine headache. Headache 8: 118-26	Headache frequency (no measure of variability, such as standard deviations, reported, so data not useable), headache index
Ryan RE, Sr., Ryan RE, Jr., Sudilovsky A (1983) Nadolol: its use in the prophylactic treatment of migraine. Headache 23: 26-31	Headache frequency (no measure of variability, such as standard deviations, reported, so data not useable), headache severity (no measure of variability, such as standard deviations, reported, so data not useable), side effects (serious adverse events not reported separately).

Bibliographic reference	Outcomes reported but not extracted
Ryan RE, Sr. (1984) Comparative study of nadolol and propranolol in prophylactic treatment of migraine. American Heart Journal 108: t-9	Headache frequency (no measure of variability, such as standard deviations, reported, so data not useable), Headache severity (no measure of variability, such as standard deviations, reported, so data not useable),
Saper JR, Silberstein SD, Lake AE, III et al. (1994) Double-blind trial of fluoxetine: chronic daily headache and migraine. Headache 34: 497-502	Headache intensity (no effect size reported), headache free days,, headache index, mood rating, beck depression inventory,, adverse events (population included chronic daily headache patients and serious adverse events not reported separately).
Sills M, Congdon P, Forsythe I (1982) Clonidine and childhood migraine: a pilot and double-blind study. Developmental Medicine & Child Neurology 24: 837-41	Migraine frequency (not reported or calculable as a change from baseline), Longest attack, Attack duration.
Siniatchkin M, Andrasik F, Kropp P et al. (2007) Central mechanisms of controlled-release metoprolol in migraine: a double-blind, placebo-controlled study. Cephalalgia 27: 1024-32	Number of migraine days (not reported or calculable as a change from baseline),Attack intensity (not reported or calculable as a change from baseline), Duration of headache (not reported or calculable as a change from baseline), Neurophysiological outcomes (measured using EEG)
Somerville BW, Herrmann WM (1978) Migraine prophylaxis with lisuride hydrogen maleate - A double blind study of lisuride versus placebo. Headache 18: 75-9	Frequency of attacks (reported as number of participants in each category, not possible to calculate a mean change from baseline), therapeutic response (number of participants with 0 or 0-2 attacks per month), reasons for withdrawal from trial, side effects (serious adverse events not reported separately)
Steiner TJ, Ahmed F, Findley LJ et al. (1998) S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. Cephalalgia 18: 283-6	Migraine frequency (no measure of variability, such as standard deviations, reported, so data not useable), Number of migraine days (no measure of variability, such as standard deviations, reported, so data not useable), Migraine severity (no measure of variability, such as standard deviations, reported, so data not useable), Global impression,
Zeeberg I, Orholm M, Nielsen JD et al. (1981) Femoxetine in the prophylaxis of migraine--a randomised comparison with placebo. Acta Neurologica Scandinavica 64: 452-9	Number of attacks (no measure of variability, such as standard deviations, reported, so data not useable), duration of attacks (no measure of variability, such as standard deviations, reported, so data not useable), headache index, side effects (serious adverse events not reported separately).

G.1 Included studies

Table 9: Afshari 2012

<table>
<tr><td>Bibliographic reference</td><td>Afshari D, Rafizadeh S, Rezaei M (2012) A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience 122: 60-8</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To evaluate the efficacy of low-dose topiramate compared with sodium valproate,</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Aged 18 to 65 at time of entry
- Diagnosis of migraine (with or without aura) according to IHS criteria
- 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
- 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 haematological diseases, severe liver or kidney diseases, and malignancy.

Baseline characteristics
<table>
<tr><td></td><td>Topiramate 50mg/d</td><td>Sodium valproate 400mg/d</td></tr>
<tr><td>Sex (M/F)</td><td>6/22</td><td>6/22</td></tr>
<tr><td>Age (mean, SD)</td><td>32.1 (10.2)</td><td>29.2 (9.6)</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td>Topiramate 50mg/d</td><td>Sodium valproate 400mg/d</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Afshari D, Rafizadeh S, Rezaei M (2012) A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience 122: 60-8</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><td>N</td><td>40</td><td>36</td></tr>
<tr><td>N (Analysis)</td><td>28</td><td>28</td></tr>
<tr><td>Drop outs</td><td>12
moved away (2)
adverse events (2)
lack of efficacy (8)</td><td>8
moved away (0)
adverse events (6)
lack of efficacy (2)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="3">Topiramate 25 mg/d for first week, then 50 mg/d until end of study</td></tr>
<tr><td>Comparison</td><td colspan="3">Sodium valproate 200 mg/d for first week then 400mg/d until end of study</td></tr>
<tr><td>Methods</td><td colspan="3">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.
Participants permitted to take symptomatic medications such as NSAIDs, acetaminophen, ergotamine, triptans or opioids.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">12 weeks</td></tr>
<tr><td>Location</td><td colspan="3">Hospital neurology clinic in Iran</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Change in Migraine severity
(visual analogue scale 1-10)<table>
<tr><td></td><td>Topiramate 50mg/d</td><td>Sodium valproate 400mg/d</td></tr>
<tr><td>Baseline (4 weeks before treatment)</td><td>mean=8.6
SD=1.7
N=28</td><td>mean=8.6
SD=1.7
N=28</td></tr>
<tr><td>Last 4 weeks of treatment</td><td>mean =5.2
SD=1.5
N=28</td><td>mean=6.3
SD=1.9
N=28</td></tr>
<tr><td>Change in migraine frequency from baseline</td><td>mean =-3.4*
SD=1.61*
N=28</td><td>mean =-2.3*
SD=1.81*
N=28</td></tr>
</table>*data imputed by reviewer from baseline and endpoint data</td></tr>
</table>

Bibliographic reference	Afshari D, Rafizadeh S, Rezaei M (2012) A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience 122: 60-8

Change in Migraine frequency

	Topiramate 50mg/d	Sodium valproate 400mg/d
Baseline (4 weeks before treatment)	mean=6.8 SD=2.0 N=28	mean=7.5 SD=1.9 N=28
Last 4 weeks of treatment	mean =3.0 SD=1.9 N=28	mean =3.6 SD=1.8 N=28
Change in migraine frequency from baseline	mean=-3.8* SD=1.95* N=28	mean=-3.9* SD=1.85* N=28

***data imputed by reviewer from baseline and endpoint data**

Change in acute analgesic use (units unclear)

	Topiramate 50mg/d	Sodium valproate 400mg/d
Baseline (4 weeks before treatment)	mean=1.64 SD=1.36 N=28	mean=1.42 SD=1.19 N=28
Last 4 weeks of treatment	mean=0.46 SD=0.74 N=28	mean =0.68 SD=0.51 N=28
Change in migraine frequency from baseline	mean =-1.18* SD=1.81* N=28	mean =-0.74* SD=1.03* N=28

***data imputed by reviewer from baseline and endpoint data**

Bibliographic reference	**Afshari D, Rafizadeh S, Rezaei M (2012) A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience 122: 60-8**
	Outcomes reported but not extracted: Headache duration, hepatic tests, adverse events (serious adverse events not reported separately), weight, quality of life (only reported mid-way through treatment period before 3 months of treatment)
Source of funding	Kermanshah University of Medical Sciences
Comments	Unclear allocation concealment (though study reports it was double blinded). Per protocol analysis (dropouts were substantial but were not considered - 12/40 (30%) patients in topiramate group and 8/36 (22%) patients in sodium valproate group). Units for assessing acute medication use are not clearly reported.

Table 10: Ashrafi 2014

Bibliographic reference	**Ashrafi MR, Najafi Z, Shafiei M et al. (2014) Cinnarizine versus topiramate in prophylaxis of migraines among children and adolescents: A randomized, double-blind clinical trial. Iranian Journal of Child Neurology 8: 18-27**
Study type	Randomised controlled trial
Aim	To compare the efficacy and safety of cinnarizine and topiramate in preventing paediatric migraines.
Patient characteristics	**Inclusion criteria:** - Children and adolescents, Aged 4–17 years, diagnosed with migraines (with or without aura) according to the International Headache society criteria (23); - Have experienced 1 or more migraine attacks per month or severe dysfunction in daily and school activities - No known structural brain lesions or other systemic conditions causing the headaches. **Exclusion criteria:** - Diagnosis of chronic headache, complications of migraine or migraine variant; - Focal neurologic deficit; - Severe adverse effects related to the study treatment drugs that are listed in the contraindications at the beginning or during the double-blind phase of the study; - Known concomitant serious disease (hepatic, renal, cardiovascular, or thyroid disease); - Use of prophylactic migraine therapy in at least one preceding month. **Baseline characteristics**

	Cinnarizine	**Topiramate**
Sex (M/F)	12/8	11/9
Age (mean, SD)	9.3 (2.43)	8.7 (3.03)

<table>
<tr><td>Bibliographic reference</td><td>Ashrafi MR, Najafi Z, Shafiei M et al. (2014) Cinnarizine versus topiramate in prophylaxis of migraines among children and adolescents: A randomized, double-blind clinical trial. Iranian Journal of Child Neurology 8: 18-27</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Cinnarizine</th><th>Topiramate</th></tr>
<tr><td>N</td><td>20</td><td>20</td></tr>
<tr><td>N (Analysis)</td><td>20</td><td>20</td></tr>
<tr><td>Drop outs</td><td>0</td><td>0</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Cinnarizine 37.5 mg/d (4 to 11 years), 50mg/d (12-17 years)
Could be reduced in cases of adverse events with neurologist’s permission</td></tr>
<tr><td>Comparison</td><td>Topiramate 50 mg/d
Could be reduced in cases of adverse events with neurologist’s permission</td></tr>
<tr><td>Methods</td><td>Outcomes were reported using a headache diary completed by the children with the parent’s advice. The study began with a 4 week baseline period during which previous prophylactic measures were discontinued and baseline data was collected. This was followed by a 12 week treatment phase where participants were randomly allocated to receive cinnarizine or topiramate. Acute treatment for migraine was permitted.</td></tr>
<tr><td>Length of follow up</td><td>12 weeks treatment period</td></tr>
<tr><td>Location</td><td>Iran, outpatient setting</td></tr>
<tr><td>Outcomes measures and effect size</td><td>50% responder
‘Responder’ defined as a reduction of 50% in migraine frequency in final month of treatment compared with baseline.
<table>
<tr><th>Cinnarizine</th><th>Topiramate</th></tr>
<tr><td>17/20* (85%)</td><td>13/20* (65%)</td></tr>
</table>
*calculated by reviewer from reported percentages

Change in migraine intensity –Visual analogue scale (0-10)
Migraine intensity was assessed on a visual analogue scale (0 to 10, where 0 is no pain and 10 is the worst pain imaginable) for each attack. The mean intensity per attack over 4 weeks is reported.
<table>
<tr><th></th><th>Cinnarizine</th><th>Topiramate</th></tr>
<tr><td>Baseline</td><td>mean=7.3
SD=2.12
N=20</td><td>mean=6.5
SD=2.42
N=20</td></tr>
<tr><td>Last 4 weeks of</td><td>mean=2.6</td><td>mean=3.5</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Ashrafi MR, Najafi Z, Shafiei M et al. (2014) Cinnarizine versus topiramate in prophylaxis of migraines among children and adolescents: A randomized, double-blind clinical trial. Iranian Journal of Child Neurology 8: 18-27**

treatment	SD=2.37 N=20	SD=2.74 N=20
Change in migraine intensity	mean=-4.7 95% CI=-3.67 to -5.73 SD=2.35* N=20	mean=-3.0 95% CI=-1.80 to -4.20 SD=2.74* N=20

***calculated by reviewer from reported 95% CIs and sample size**

Change in migraine frequency

Migraine frequency defined as number of migraine attacks (meeting international society criteria for migraine) per 4 weeks.

	Cinnarizine	**Topiramate**
Baseline	mean=8.0 SD=7.98 N=20	mean=7.5 SD=6.43 N=20
Last month of treatment	mean=2.0 SD=2.47 N=20	mean=2.7 SD=3.26 N=20
Change in migraine frequency	mean=-6.0 SD=6.91* N=20	mean=-4.8 SD=5.53* N=20

***calculated by reviewer from reported p values (0.001 in both cases) for paired t test**

Outcomes reported but not extracted: Adverse events (serious adverse events not reported separately)

Source of funding	Not reported
Comments	Method of randomisation and allocation concealment are not described. The study is described as ‘double blind’, but the tablet characteristics are described as ‘similar but not identical, giving potential for unblinding’. The dose reduction was permitted in cases of intolerance with the neurologist’s permission, but it is not described how this was achieved without unblinding.

Table 11: Apostol et al. 2008

<table>
<tr><td>Bibliographic reference</td><td>Apostol G, Cady RK, Laforet GA et al. (2008) Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. Headache 48: 1012-25</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To evaluate the efficacy, tolerability and safety of 3 doses of divalproex sodium extended release in the prophylaxis of migraine in adolescents.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Aged 12 to 17 at time of randomisation
- Migraine (classified based modified IHS diagnostic criteria) at least 12 months before screening
- >3 and <12 migraines per month
- 35 - 100kg
- Practicing an accepted form of birth control
- 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
- Failed >2 ‘adequate’ regimens of prophylactic antimigraine medications.

Baseline characteristics
<table>
<tr><td></td><td colspan="3">Divalproex sodium</td><td></td></tr>
<tr><td></td><td>1000mg/d</td><td>500mg/d</td><td>250mg/d</td><td>Placebo</td></tr>
<tr><td>Sex (M/F)</td><td>39/34</td><td>34/40</td><td>29/52</td><td>34/37</td></tr>
<tr><td>Age (mean, SD)</td><td>14.33 (1.66)</td><td>14.1 (1.56)</td><td>14.2 (1.69)</td><td>14.2 (1.50)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td colspan="3">Divalproex sodium</td><td></td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="5">Apostol G, Cady RK, Laforet GA et al. (2008) Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. Headache 48: 1012-25</td></tr>
<tr><td></td><td colspan="5"><table>
<tr><th></th><th>1000mg/d</th><th>500mg/d</th><th>250mg/d</th><th>Placebo</th></tr>
<tr><td>N</td><td>75</td><td>74</td><td>83</td><td>73</td></tr>
<tr><td>N (ITT analysis)</td><td>efficacy=73, safety=75</td><td>efficacy=74, safety=74</td><td>efficacy=81, safety=82</td><td>efficacy=71, safety=72</td></tr>
<tr><td>Drop outs</td><td>13
lost to follow-up (3)
adverse events (7)
withdrew consent (1)
non-compliance (1)
other reasons (1)</td><td>12
lost to follow-up (5)
lack of efficacy (3)
withdrew consent (1)
non-compliance (3)
never took study drug (1)</td><td>8
lost to follow-up (1)
adverse events (2)
withdrew consent (4)
lack of efficacy (1)
non-compliance (1)
other reasons (2)</td><td>6
lost to follow-up (4)
lack of efficacy (1)
adverse event (1)</td></tr>
</table></td></tr>
<tr><td>Intervention 1</td><td colspan="5">Divalproex extended release 1000mg/d</td></tr>
<tr><td>Intervention 2</td><td colspan="5">Divalproex extended release 500mg/d</td></tr>
<tr><td>Intervention 3</td><td colspan="5">Divalproex extended release 250mg/d</td></tr>
<tr><td>Comparison</td><td colspan="5">Placebo</td></tr>
<tr><td>Methods</td><td colspan="5">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. During titration phase (length of titration phase not specified) participants randomised to 1000mg/d received 500mg/d, participants randomised to 500mg/d and patients randomised to 250mg/d received 250mg/d. This was followed by a 12 week treatment phase. 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 pemoline) provided subjects were on a stable dose and the medication did not affect headache symptoms</td></tr>
<tr><td>Length of follow up</td><td colspan="5">12 weeks treatment</td></tr>
<tr><td>Location</td><td colspan="5">Multicentre study (38 centres in US)</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="5">Change in migraine headache days
Migraine headache days were defined as the number of days with migraine headache per 4 weeks.<table>
<tr><th></th><th colspan="3">Divalproex</th><th></th><th>Placebo</th></tr>
<tr><th></th><th>1000 mg</th><th>500 mg</th><th>250 mg</th><th>Combined doses**</th><th></th></tr>
<tr><td>Baseline</td><td>Not reported</td><td>Not reported</td><td>Not reported</td><td></td><td>Not reported</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Apostol G, Cady RK, Laforet GA et al. (2008) Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. Headache 48: 1012-25

migraine days per 4 weeks					
Change per 4 weeks during treatment	mean change=-3.1 SD=3.61 SE=0.422* N=73	mean change=-2.2 SD=3.18 SE=0.370* N=74	mean change=-2.8 SD=2.91 SE=0.323* N=81	mean change=-2.70 SD=3.24 N=228	mean change=-2.8 SD=3.02 SE=0.358* N=71

***calculated by reviewer from reported standard deviations for purpose of network meta-analysis**
****calculated by reviewer**

50% Responder rate

'Responder' defined as number of participants who had a >50% reduction in mean monthly migraine frequency during treatment phase).

Divalproex sodium				**Placebo**
1000 mg	**500 mg**	**250 mg**	**Combined doses***	
37/72 (51%)	27/74 (36%)	33/81 (41%)	97/227 (42.7%)	33/71 (46%)

***Calculated by reviewer for purposes of analysis**

Change in migraine frequency

Migraine frequency defined as the number of migraine attacks per 4 weeks.

	Divalproex sodium				**Placebo**
	1000 mg	**500 mg**	**250 mg**	**Combined doses***	
Baseline migraine frequency per 4 weeks (mean over 3 months before screening)	mean=17.3 SD=6.84	mean=18.0 SD=7.02	mean=16.6 SD=7.02		mean=16.7 SD=7.62
Change in migraine frequency (last 4	mean =-1.8 SD=1.76	mean =-2.0 SD=1.84	mean =-1.7 SD=1.84	mean=-1.83 SD=1.81	mean=-1.9 SD=2.18

Bibliographic reference	**Apostol G, Cady RK, Laforet GA et al. (2008) Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. Headache 48: 1012-25**
	weeks of treatment) N=73 N=74 N=81 N=228 N=71 ***Calculated by reviewer for purposes of analysis** **Outcomes reported but not extracted:** Median 4 week frequency of migraines at baseline and treatment phases and median change in this frequency, change from baseline in metabolic and reproductive endocrine parameters.
Source of funding	Abbott
Comments	Unclear randomisation and allocation concealment (randomisation schedule was prepared by the sponsor, but method not stated). Only 305 out of 436 participants in the 4 week baseline phase that came after screening were randomised; no explanation given as to why. Tablets were identical and placebo tablets were used to ensure that all participants took the same number of tablets. Unclear if those administering care were kept blind to treatment.

Table 12: Battistella 1990

Bibliographic reference	**Battistella PA, Ruffilli R, Moro R et al. (1990) A placebo-controlled crossover trial of nimodipine in pediatric migraine. Headache 30: 264-8**
Study type	Randomised controlled trial
Aim	To assess the efficacy of nimodipine in migraine prophylaxis in children and adolescents.
Patient characteristics	**Inclusion criteria:** - Migraine according to the criteria specified by the ad hoc committee of the international headache society. - At least one attack per month for the last 6 months (only considered moderate or severe attacks which reduced activity). **Exclusion criteria:** - None specified **Baseline characteristics** **Nimodipine** | **Placebo** Sex (M/F) 9/9 9/10 Age (mean, SD) 12.0 (3.4) 12.4 (3.3)
Number of Patients	

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Battistella PA, Ruffilli R, Moro R et al. (1990) A placebo-controlled crossover trial of nimodipine in pediatric migraine. Headache 30: 264-8</td></tr>
<tr><td></td><td colspan="2">
<table>
<tr><th></th><th>Nimodipine</th><th>Placebo</th></tr>
<tr><td>N</td><td>18</td><td>19</td></tr>
<tr><td>N (analysis)</td><td>15</td><td>15</td></tr>
<tr><td>Drop outs</td><td>3</td><td>4</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td colspan="2">Nimodipine 30-60mg/d (10-20mg three times daily according to weight - <40kg: 30mg/d, 40-50kg: 48mg/d, >50kg: 60mg/d)</td></tr>
<tr><td>Comparison</td><td colspan="2">Placebo</td></tr>
<tr><td>Methods</td><td colspan="2">Crossover design (only 1st phase reported here). Prophylactic treatment was stopped 3 months before the trial. Trial began with 4 weeks medication-free observation period for baseline measures. This is was followed by 12 week treatment period where patients received medication according to the group that they were randomised to (nimodipine or placebo). Acetaminophen was allowed for acute treatment of migraine.</td></tr>
<tr><td>Length of follow up</td><td colspan="2">12 weeks treatment period (part of a longer cross over trial but only the first phase is reported here)</td></tr>
<tr><td>Location</td><td colspan="2">Italy, University research setting</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="2">Change in migraine/headache frequency
Attack frequency was measured per 4 weeks during baseline phase and in the last 4 weeks of the 12 week treatment period. Only attacks that results in a reduction in everyday activity (moderate to severe intensity) were counted.
<table>
<tr><th></th><th>Nimodipine 30-60mg/d</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=3.3
SD=0.9
N=15</td><td>mean=3.0
SD=0.9
N=15</td></tr>
<tr><td>12 weeks</td><td>mean=2.8
SD=0.9
N=15</td><td>mean=2.5
SD=0.9
N=15</td></tr>
<tr><td>Change in migraine frequency</td><td>mean=-0.5*
SD=0.9*
N=15</td><td>mean=-0.5*
SD=0.9*
N=15</td></tr>
</table>
*data imputed by reviewer from baseline and endpoint data

Outcomes reported but not extracted: Headache duration</td></tr>
<tr><td>Source of funding</td><td colspan="2">Not reported</td></tr>
</table>

Bibliographic reference	**Battistella PA, Ruffilli R, Moro R et al. (1990) A placebo-controlled crossover trial of nimodipine in pediatric migraine. Headache 30: 264-8**
Comments	Both patients and clinicians were blinded to treatment allocation. Allocation to groups was at random, but randomisation method was not reported. Methods for concealment of allocation were not described. Some of the participants were outside of the age range for the review (12 and over), although the mean age for each group was >12.

Table 13: Battistella 1993

Bibliographic reference	**Battistella PA, Ruffilli R, Cernetti R et al. (1993) A placebo-controlled crossover trial using trazodone in pediatric migraine. Headache 33: 36-9**
Study type	Randomised controlled trial
Aim	To assess the efficacy of trazodone in migraine prophylaxis in children and adolescents.
Patient characteristics	**Inclusion criteria:** - Migraine according to the criteria specified by 'current classification criteria' (no further details reported) - Symptoms for at least the last 6 months - At least 3 attacks per month (unclear over what timeframe) **Exclusion criteria:** - None specified **Baseline characteristics (not reported separately for each group)** Sex (M/F): 22/18 Age (mean, SD): 12.6 (3.8)
Number of Patients	<table><tr><th></th><th>Trazodone</th><th>Placebo</th></tr><tr><td>N</td><td>20</td><td>20</td></tr><tr><td>N (analysis)</td><td>18</td><td>17</td></tr><tr><td>Drop outs</td><td>2</td><td>3</td></tr></table>
Intervention	Trazodone 1mg/kg/d
Comparison	Placebo
Methods	Crossover design (only 1st phase reported here). Prophylactic treatment was stopped 3 months before the trial. The trials started with a 4-week run-in period where baseline data was collected, followed by a 12 week treatment period where patients received medication according to the group that they were randomised to (trazodone or placebo). A further cross over phase was also included (results not reported here). Acetaminophen was allowed for acute

<table>
<tr><td>Bibliographic reference</td><td>Battistella PA, Ruffilli R, Cernetti R et al. (1993) A placebo-controlled crossover trial using trazodone in pediatric migraine. Headache 33: 36-9</td></tr>
<tr><td></td><td>treatment of migraine.</td></tr>
<tr><td>Length of follow up</td><td>12 weeks treatment period (part of a longer cross over trial but only the first phase is reported here)</td></tr>
<tr><td>Location</td><td>Italy, University research setting</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in Migraine/headache frequency
Attack frequency was measured per 4 weeks during baseline phase and in the last 4 weeks of the 12 week treatment period. Only attacks that results in a reduction in everyday activity (moderate to severe intensity) were counted.
<table>
<tr><th></th><th>Trazodone 1mg/kg/d</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=4.0
sd.=1.0*
N=18</td><td>mean=3.5
SD=0.5*
N=18</td></tr>
<tr><td>12 weeks</td><td>mean=2.2
SD=0.7*
N=18</td><td>mean=1.8
SD=0.6*
N=18</td></tr>
<tr><td>Change in migraine frequency</td><td>mean=-1.8**
SD=0.89**
N=18</td><td>mean=-1.7**
SD=0.56**
N=18</td></tr>
</table>
*standard deviations estimated by reviewer from graph
**data imputed by reviewer from baseline and endpoint data

Outcomes reported but not extracted: Headache duration</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Both patients and clinicians were blinded to treatment allocation. Allocation to groups was at random, but randomisation method was not reported. Methods for concealment of allocation were not described. Some of the participants were outside of the age range for the review (12 and over), although the mean age for each group was >12. Standard deviations reported in the text and plotted on graph are inconsistent – used those plotted as more plausible based on variability in other studies.</td></tr>
</table>

Table 14: Bavrasad 2010

Bibliographic reference	**Bavrasad R, Nejad SEM, Yarahmadi AR et al. (2010) Assessment of the middle dose of topiramate in comparison with sodium valproate for migraine prophylaxis: A randomized-double-blind study. International Journal of Pharmacology 6: 670-5**

<table>
<tr><td>Bibliographic reference</td><td>Bavrasad R, Nejad SEM, Yarahmadi AR et al. (2010) Assessment of the middle dose of topiramate in comparison with sodium valproate for migraine prophylaxis: A randomized-double-blind study. International Journal of Pharmacology 6: 670-5</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To compare the effectiveness and acceptability of sodium valproate and topiramate for migraine prophylaxis.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Migraine according to the criteria specified by the international headache society.
- 1-6 attacks per month for at least the last year.
- Aged 20-50
- Body-mass index 19-29 kg/m2
- Weight 45-85 kg
- Good general health (medical history, physical examination, ECG, urine and blood screening)
- Females must have had a negative pregnancy test and use reliable contraception.
- Female sex was not listed as an explicit inclusion criteria, but all participants were female (see baseline characteristics)

Exclusion criteria:
- Tension-type headache more than 2 days per month.
- Known allergy to the drugs in the trial.
- Blood donation in the previous month.
- Breastfeeding.
- Migraine prophylaxis in the previous 2 months.
- Previous proven inefficacy of sodium valproate prophylaxis.
- Drug over use (urine screen – further details not provided).
- Regular use of prescribed or over-the-counter medication except oral contraceptive pill and usual acute migraine treatment.

Baseline characteristics
<table>
<tr><th></th><th>Topiramate</th><th>Sodium Valproate</th></tr>
<tr><td>Sex (M/F)</td><td>0/36</td><td>0/38</td></tr>
<tr><td>Age (mean, SD)</td><td>30.1 (6.0)</td><td>31.2 (5.0)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Topiramate</th><th>Sodium Valproate</th></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Bavrasad R, Nejad SEM, Yarahmadi AR et al. (2010) Assessment of the middle dose of topiramate in comparison with sodium valproate for migraine prophylaxis: A randomized-double-blind study. International Journal of Pharmacology 6: 670-5</td></tr>
<tr><td></td><td colspan="2"><table>
<tr><td>N</td><td>36</td><td>38</td></tr>
<tr><td>N (analysis)</td><td>35</td><td>35</td></tr>
<tr><td>Drop outs</td><td>1
Paraesthesia (1)</td><td>2
Drowsiness and nausea (1)
Pregnancy (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="2">Topiramate 50 to 75mg/d</td></tr>
<tr><td>Intervention 2</td><td colspan="2">Sodium Valproate 400 to 600 mg/d</td></tr>
<tr><td>Methods</td><td colspan="2">Baseline phase not described. There was a titration phase of 2-4 weeks where doses were gradually increased to 75mg/d or 600mg/d (topiramate and sodium valproate, respectively) or the maximum tolerated dose. The treatment phase was 12 weeks treatment at this dose. Not stated whether acute medication was permitted during the trial.</td></tr>
<tr><td>Length of follow up</td><td colspan="2">12 weeks treatment period (at maintenance dose)</td></tr>
<tr><td>Location</td><td colspan="2">Iran, University research setting</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="2">Change in migraine severity
Severity was measured on a scale of 0 to 10.<table>
<tr><th></th><th>Topiramate 50 to 75mg/d</th><th>Sodium Valproate 400 to 600mg/d</th></tr>
<tr><td>Baseline period</td><td>mean=9.30
SD=1.45
N=35</td><td>mean=9.20
SD=1.36
N=35</td></tr>
<tr><td>During treatment period (12 weeks)</td><td>mean=4.70
SD=1.24
N=35</td><td>mean=4.15
SD=0.864
N=35</td></tr>
<tr><td>Change in migraine severity</td><td>mean=-4.6*
SD=1.36*
N=35</td><td>mean=-5.05*
SD=1.19*
N=35</td></tr>
</table>*data imputed by reviewer from baseline and endpoint data

Change in Migraine frequency
Migraine frequency was defined as the number of migraine attacks per month<table>
<tr><th></th><th>Topiramate 50 to 75mg/d</th><th>Sodium Valproate 400 to 600mg/d</th></tr>
<tr><td>Baseline period</td><td>mean=10.07</td><td>mean=10.14</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Bavrasad R, Nejad SEM, Yarahmadi AR et al. (2010) Assessment of the middle dose of topiramate in comparison with sodium valproate for migraine prophylaxis: A randomized-double-blind study. International Journal of Pharmacology 6: 670-5**

	SD=2.32 N=35	SD=1.98 N=35
During treatment period (12 weeks)	mean=4.58 SD=1.1 N=35	mean=4.81 SD=1.7 N=35
Change in migraine frequency	mean=-5.49* SD=2.01* N=35	mean=-5.33* SD=1.86* N=35

***data imputed by reviewer from baseline and endpoint data**

Outcomes reported but not extracted: Headache duration, number with 50% reduction in headache frequency (only reported for young and middle age groups), adverse events (serious adverse events not reported separately), Quality of life (means and standard deviations only reported at baseline)

Source of funding	Not reported
Comments	Baseline period was not clearly described. Randomisation was done by GlaxoWellcome (randomisation method not described). Allocation concealment was not described, but as the study was double blind it is likely that allocation concealment occurred. Participants and investigators were blinded to treatment allocation until the end of the study.

Table 15: Bidabadi 2010

Bibliographic reference	**Bidabadi E, Mashouf M (2010) A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Paediatric Drugs 12: 269-75**
Study type	Randomised controlled trial
Aim	To compare the efficacy and tolerability of propranolol and sodium valproate in the prevention of migraine in the paediatric population.
Patient characteristics	**Inclusion criteria:** - 5–15 years of age. - Meet the diagnostic criteria for paediatric migraine without aura as defined by the International Headache Society. **Exclusion criteria:** - Chronic daily headaches

<table>
<tr><td>Bibliographic reference</td><td>Bidabadi E, Mashouf M (2010) A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Paediatric Drugs 12: 269-75</td></tr>
<tr><td></td><td>- More than one headache type, including cluster headaches, medication overuse headache, and tension headache.
- Increased pain with the Valsalva manoeuvre.
- Coexisting medical, neurologic, or psychiatric disorder.
- Changed school performance.
- Neuroimaging studies indicative of a focal neurologic lesion.
- Previous treatment with three or more migraine prophylactic medications.
- History of previous propranolol or sodium valproate use.
- Contraindications for propranolol or sodium valproate use (e.g. asthma, hepatic disease).
- History of non-compliance with previous migraine medications.

Baseline characteristics
<table>
<tr><th></th><th>Propranolol</th><th>Sodium Valproate</th></tr>
<tr><td>Sex (M/F)</td><td>19/11</td><td>21/9</td></tr>
<tr><td>Age (mean, SD)</td><td>9.79 (2.80)</td><td>9.93 (2.57)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Propranolol</th><th>Sodium Valproate</th></tr>
<tr><td>N</td><td>32</td><td>31</td></tr>
<tr><td>N (Analysis)</td><td>30</td><td>30</td></tr>
<tr><td>Drop outs</td><td>2
Reasons not reported separately for each group</td><td>1
Reasons not reported separately for each group</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Propranolol 2mg/kg/d
(in children who weighed =<35 kg the maximum dosage was 30 mg twice daily; in those who weighed =>35 kg the maximum dosage was 60 mg twice daily)</td></tr>
<tr><td>Comparison</td><td>Sodium valproate 15mg/kg/d</td></tr>
<tr><td>Methods</td><td>Participants were weaned off migraine prophylaxis at least 3 months before starting the study. Outcome data was collected using a follow up questionnaire at monthly visits (not a headache diary), and there was no prospective baseline period (baseline data collected by questionnaire at the beginning of the study. Propranolol was started at a dosage of 3 mg/kg/day in two divided doses, and sodium valproate was started at a dosage of 30 mg/kg/day in two divided doses. The propranolol dosage was adjusted to 2 mg/kg/day (in children who weighed =<35 kg the maximum dosage was 30 mg twice daily; in those who weighed =>35 kg the maximum dosage was 60 mg twice</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Bidabadi E, Mashouf M (2010) A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Paediatric Drugs 12: 269-75</td></tr>
<tr><td></td><td>daily), and the sodium valproate dosage was adjusted to 15 mg/kg/day after the first follow-up visit (1 month later). Treatment with propranolol or sodium valproate was discontinued when one of the following endpoints was reached: successful treatment (<3 headaches per month) for a 4- to 6-month period (primary endpoint); 3 months of a persistent unsuccessful or incomplete response to treatment (>4 headaches per month), or intolerable side effects of the drugs. Upon recognition of the above endpoints, the child was slowly tapered off the drug. Data reported here is based on efficacy at 4 months of treatment.</td></tr>
<tr><td>Length of follow up</td><td>4 months treatment duration (actual follow up was variable depending on response (see methods), but data at 4 months follow up reported here).</td></tr>
<tr><td>Location</td><td>Iran, outpatient setting</td></tr>
<tr><td>Outcomes measures and effect size</td><td>50% responder
‘Responder’ was defined as number of participants with 50% reduction in headache frequency per month at the end of treatment compared with baseline.
<table>
<tr><th>Propranolol 2mg/kg/d</th><th>Sodium Valproate 15mg/kg/d</th></tr>
<tr><td>25/30* (83.3%)</td><td>19/30* (63.3%)</td></tr>
</table>
*calculated by reviewer from reported percentages

Change in headache frequency
Headache frequency defined as number of headaches per month.
<table>
<tr><th></th><th>Propranolol 2mg/kg/d</th><th>Sodium Valproate 15mg/kg/d</th></tr>
<tr><td>Baseline</td><td>mean=13.86
SD=2.11
N=30</td><td>mean=13.23
SD=2.43
N=30</td></tr>
<tr><td>4th month of treatment</td><td>mean=4.23
SD=3.24
N=30</td><td>mean=5.83
SD=4.04
N=30</td></tr>
<tr><td>Change in migraine frequency</td><td>mean=-9.63*
SD=2.85*
N=30</td><td>mean=-7.4**
SD=3.52*
N=30</td></tr>
</table>
*data imputed by reviewer from baseline and endpoint data

Outcomes reported but not extracted: Headache duration, reduction in headache severity by at least one grade.</td></tr>
<tr><td>Source of funding</td><td>None.</td></tr>
</table>

Bibliographic reference	**Bidabadi E, Mashouf M (2010) A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Paediatric Drugs 12: 269-75**
Comments	Method of randomisation and allocation were unclear. Participants and investigators were blinded to allocation; this was maintained by provided drugs that were identical in appearance; drugs were provided and coded by a nurse who was not part of the study. A per protocol analysis was conducted, but drop-out rate was low and so this is unlikely to have had a large impact on the results. Outcome data was collected using retrospective questionnaires and a retrospective baseline period was used – potentially less accurate than a headache diary.

Table 16: Bostani 2013

Bibliographic reference	**Bostani A, Rajabi A, Moradian N et al. (2013) The effects of cinnarizine versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience 123: 487-93**
Study type	Randomised controlled trial
Aim	To compare the efficacy and safety of low-dose cinnarizine and sodium valproate in migraine prophylaxis.
Patient characteristics	**Inclusion criteria:** - Migraine with or without aura according international headache society criteria. - History of migraine for at least 1 year. - 4-10 migraines per month. - Pain-free intervals of 48 hours between attacks. - Age of onset <50 years. - Aged 18-65 - Withdrawal of concomitant migraine prophylactic treatment 1 month before the trial. - Able to fill in headache diary correctly and reliably. **Exclusion criteria:** - Suffering from another type of headache. - >8 treatment days of ergots, nonsteroidal anti-inflammatory drugs or triptans per month. - Administration of other migraine medication. - Dependency on alcohol or other drugs. - History of hemiplegic ophthalmoplegic or basilar migraine. - Pregnancy, lactation or inability to use contraception (females of childbearing age). - Serious medical conditions such as cardiovascular disease, significant haematological disease, decreased renal or hepatic function, depression, movement disorder, malignancy or hypersensitivity to calcium channel blockers. **Baseline characteristics**

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Bostani A, Rajabi A, Moradian N et al. (2013) The effects of cinnarizine versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience 123: 487-93</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><th></th><th>Cinnarizine 50mg/d</th><th>Sodium valproate 400mg/d</th></tr>
<tr><td>Sex (M/F)</td><td>17/33</td><td>16/38</td></tr>
<tr><td>Age (mean, SD)</td><td>32.38 (7.81)</td><td>31.85 (7.76)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="3"><table>
<tr><th></th><th>Cinnarizine 50mg/d</th><th>Sodium valproate 400mg/d</th></tr>
<tr><td>N</td><td>65</td><td>67</td></tr>
<tr><td>N (analysis)</td><td>50</td><td>54</td></tr>
<tr><td>Drop outs</td><td>15
Adverse events (12)
Insufficient response (2)
Moved away (1)</td><td>13
Adverse events (12)
Moved away (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="3">Cinnarazine 50mg/d</td></tr>
<tr><td>Comparison</td><td colspan="3">Sodium valproate 400mg/d</td></tr>
<tr><td>Methods</td><td colspan="3">Details of the baseline period are not provided. Patients received a randomly allocated treatment for 12 weeks. And reported migraine attacks, duration, severity, adverse events and use of acute medication in a headache diary. Acute medication use was permitted during the trial.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">12 weeks treatment period</td></tr>
<tr><td>Location</td><td colspan="3">Iran, Neurology clinic</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">50% responder
50% responder defined as participants with migraine frequency reduction of at least 50% between baseline period and last 4 weeks of treatment.<table>
<tr><th>Cinnarizine 50mg/d</th><th>Sodium valproate 400mg/d</th></tr>
<tr><td>16/50 (32%)</td><td>36/54 (66.7%)</td></tr>
</table>
Migraine severity
Severity assessed using a 0-10 visual analogue scale, with 0 equivalent to no pain and 10 indicating the worst pain imaginable. Mean severity across migraine attacks calculated throughout each period.<table>
<tr><th></th><th>Cinnarizine 50mg/d</th><th>Sodium valproate 400mg/d</th></tr>
<tr><td>Baseline</td><td>mean=7.4
SD=1.55</td><td>mean=7.57
SD=1.45</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Bostani A, Rajabi A, Moradian N et al. (2013) The effects of cinnarizine versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience 123: 487-93

	N=50	N=54
Last 4 weeks of 12 week treatment	mean=5.52 SD=1.6 N=50	mean=4.67 SD=1.66 N=54
Change in migraine severity	mean=-1.88* SD=1.58* N=50	mean=-2.9* SD=1.57* N=54

***data imputed by reviewer from baseline and endpoint data**

Migraine frequency

Frequency defined as the number of attacks in the assessment period.

	Cinnarizine 50mg/d	**Sodium valproate 400mg/d**
Baseline	mean=6.16 SD=4.22 N=50	mean=7.30 SD=6.12 N=54
Last 4 weeks of 12 week treatment	mean=3.92 SD=1.82 N=50	mean=3.28 SD=2.07 N=54
Change in migraine frequency	mean=-2.24* SD=3.67* N=50	mean=-4.02* SD=5.39* N=54

***data imputed by reviewer from baseline and endpoint data**

Quality of life - MIDAS score

	Cinnarizine 50mg/d	**Sodium valproate 400mg/d**
Baseline	mean=19.96 SD=10.89 N=50	mean=19.76 SD=10.89 N=54
End of treatment (12 weeks)	mean=11.5 SD=7.14 N=50	mean=10.17 SD=7.13 N=54

Bibliographic reference	Bostani A, Rajabi A, Moradian N et al. (2013) The effects of cinnarizine versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience 123: 487-93

Change in quality of life	mean=-8.46* SD=9.58* N=50	mean=-9.59* SD=9.58* N=54

***data imputed by reviewer from baseline and endpoint data**

Quality of life – HIT-6 score

	Cinnarizine 50mg/d	**Sodium valproate 400mg/d**
Baseline	mean=60.54 SD=10.8 N=50	mean=62.04 SD=9.48 N=54
End of treatment (12 weeks)	mean=52.2 SD=10.35 N=50	mean=49.13 SD=8.58 N=54
Change in quality of life	mean=-8.34* SD=10.58* N=50	mean=-12.91* SD=9.06* N=54

***data imputed by reviewer from baseline and endpoint data**

Change in acute medication use

Acute analgesic use defined as number of analgesics used per episode (unclear whether refers to number of doses, or number types of acute medication).

	Cinnarizine 50mg/d	**Sodium valproate 400mg/d**
Baseline	mean=1.7 SD=0.707 N=50	mean=1.63 SD=0.654 N=54
Last 4 weeks of 12 week treatment	mean=1.10 SD=0.647 N=50	mean=0.76 SD=0.581 N=54
Change in migraine	mean=-0.6* SD=10.58*	mean=-0.87* SD=0.62*

Bibliographic reference	**Bostani A, Rajabi A, Moradian N et al. (2013) The effects of cinnarizine versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience 123: 487-93**
	frequency | N=50 | N=54 ***data imputed by reviewer from baseline and endpoint data** **Outcomes reported but not extracted:** Headache duration, migraine-associated symptoms, adverse events (serious adverse events not reported separately).
Source of funding	Kermanshah University of Medical Sciences
Comments	Per protocol analysis (dropouts not taken into account). Randomisation was via computer. Patients and clinicians were blinded to treatment allocation by pre-printed medication code labels. Details of baseline data collection not reported.

Table 17: Brandes 2004, Brandes 2006

Bibliographic reference	**Brandes JL, Saper JR, Diamond M et al. (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291: 965-73** **Brandes JL, Kudrow DB, Rothrock JF et al. (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clinic Proceedings 81: 1311-9**
Study type	Randomised controlled trial
Aim	To assess the efficacy and safety of topiramate for migraine prevention.
Patient characteristics	**Inclusion criteria:** - Established history of migraine with or without aura (IHS criteria) for at least 6 months before screening - Aged 12 to 65 years - Between 3 and 12 migraines, but not more than 15 headache days (migraine or non-migraine 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,

<table>
<tr><td>Bibliographic reference</td><td>Brandes JL, Saper JR, Diamond M et al. (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291: 965-73

Brandes JL, Kudrow DB, Rothrock JF et al. (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clinic Proceedings 81: 1311-9</td></tr>
<tr><td></td><td>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 or St John’s wort
- History of nephrolithiasis
- Have taken topiramate for more than 2 weeks or had participated in a topiramate trial
- Received an experimental drug or used an experimental device within 30 days of screening

Baseline characteristics
<table>
<tr><th></th><th>Topiramate 200mg/d</th><th>Topiramate 100mg/d</th><th>Topiramate 50mg/d</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>11/106</td><td>11/109</td><td>20/97</td><td>20/94</td></tr>
<tr><td>Age (mean, SD)</td><td>39.1 (12.71)</td><td>39.1 (12.58)</td><td>39.0 (12.09)</td><td>39.3 (11.96)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Topiramate 200mg/d</th><th>Topiramate 100mg/d</th><th>Topiramate 50mg/d</th><th>Placebo</th></tr>
<tr><td>N</td><td>121</td><td>122</td><td>120</td><td>120</td></tr>
<tr><td>N (ITT analysis)</td><td>117</td><td>120</td><td>117</td><td>114</td></tr>
<tr><td>Drop outs</td><td>51
participant choice (5)
lost to follow up (3)
adverse events (25)
lack of efficacy (12)
other (2)</td><td>59
participant choice (6)
lost to follow up (4)
adverse events (32)
lack of efficacy (11)
other (4)</td><td>61
participant choice (8)
lost to follow up (9)
adverse events (20)
lack of efficacy (15)
other (6)</td><td>57
participant choice (7)
lost to follow up (6)
adverse events (14)
lack of efficacy (21)
other (3)</td></tr>
</table></td></tr>
<tr><td>Intervention 1</td><td>Topiramate 200mg/d Median daily dose actually taken = 150.2mg/d (69.2% achieved target dose)</td></tr>
<tr><td>Intervention 2</td><td>Topiramate 100mg/d Median daily dose actually taken = 85.6mg/d (85.8% achieved target dose)</td></tr>
<tr><td>Intervention 3</td><td>Topiramate 50mg/d Median daily dose actually taken = 46.5mg/d (97.4% achieved target dose)</td></tr>
<tr><td>Comparison</td><td>Placebo 85.1% achieved target dose</td></tr>
<tr><td>Methods</td><td>Eligible participants entered into washout period up to 14 days. This followed by 28 day prospective baseline phase</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Brandes JL, Saper JR, Diamond M et al. (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291: 965-73

Brandes JL, Kudrow DB, Rothrock JF et al. (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clinic Proceedings 81: 1311-9</td></tr>
<tr><td></td><td>during which headache and medication record information completed by participants. Rescue medication permitted during this time. Participants randomised after baseline phase. 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 permitted included aspirin acetaminophen, NSAIDs, ergot derivatives, triptans and opioids.</td></tr>
<tr><td>Length of follow up</td><td>26 weeks (8 weeks titration phase, 18 weeks at maximum tolerated or assigned dose)</td></tr>
<tr><td>Location</td><td>Multicentre study (52 North American clinical centres)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in migraine headache days
A migraine day was defined as a calendar day in which a patient had a migraine headache lasting at least 30 minutes.
<table>
<tr><td></td><td colspan="4">Topiramate</td><td>Placebo</td></tr>
<tr><td></td><td>200 mg</td><td>100 mg</td><td>50 mg</td><td>Combined doses*</td><td></td></tr>
<tr><td>Baseline</td><td>mean=6.1
SD=2.54
N=117</td><td>mean=6.9
SD=3.00
N=120</td><td>mean=6.4
SD=2.88
N=117</td><td></td><td>mean=6.7
SD=2.84
N=114</td></tr>
<tr><td>Change in migraine days per 4 weeks assessed throughout treatment period</td><td>mean=-2.9
SD=3.46*
SE=0.32
N=117</td><td>mean=-2.6
SD=3.40*
SE=0.31
N=120</td><td>mean=-1.7**
SD=3.99*
SE=0.3**
N=177</td><td>mean=-2.3
SD=3.7
N=414</td><td>mean=-1.3
SD=3.42*
SE=0.32
N=114</td></tr>
</table>
*Calculated by reviewer
**data read by reviewer from graph

50% Responder rate
Number of participants who had a >50% reduction in mean 4 weekly migraine frequency. Assessed throughout 26-week treatment period.</td></tr>
</table>

Bibliographic reference	**Brandes JL, Saper JR, Diamond M et al. (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291: 965-73** **Brandes JL, Kudrow DB, Rothrock JF et al. (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clinic Proceedings 81: 1311-9**

Topiramate				**Placebo**
200 mg/d	**100 mg/d**	**50 mg/d**	**Combined doses***	
55/117 (47%)	59/120 (49%)	46/117 (39%)	160/354 (45.2%)	26/114 (30%)

***calculated by reviewer for purpose of analysis**

Change in migraine intensity

Migraine severity was rated on a 3-point scale: 1=mild, 2=moderate, 3=severe.

	Topiramate				**Placebo**
	200 mg/d	**100 mg/d**	**50 mg/d**	**Combined doses****	
Baseline	mean=2.3 SD=0.39 N=117	mean=2.2 SD=0.37 N=120	mean=2.3 SD=0.38 N=117		mean=2.2 SD=0.45 N=114
Change in migraine intensity Assessed throughout 26-week treatment period	mean=-0.1 SE=0.04 SD=0.433* N=117	mean=-0.2 SE=0.04 SD=0.438* N=120	mean=-0.1 SE=0.04 SD=0.427* N=114	mean=-0.134 SD=0.434 N=351	mean=-0.1 SE=0.04 SD=0.427* N=114

***calculated by reviewer from standard error and sample size**

****calculated by reviewer for purpose of analysis**

Change in Migraine frequency

Migraine frequency was defined as the number of migraine periods in 4 weeks.

	Topiramate				**Placebo**
	200 mg	**100 mg**	**50 mg**	**Combined doses****	

Bibliographic reference	**Brandes JL, Saper JR, Diamond M et al. (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291: 965-73** **Brandes JL, Kudrow DB, Rothrock JF et al. (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clinic Proceedings 81: 1311-9**

Per 4 weeks during baseline	mean=5.1 SD=2.0 N=117	mean=5.8 SD=2.58 N=120	mean=5.4 SD=2.4 N=117		mean=5.6 SD=2.2 N=114
Per 4 weeks during treatment period	mean=3.0 SD=2.2 N=117	mean=3.5 SD=3.5 N=120	mean=4.1 SD=3.6 N=117		mean=4.5 SD=2.9 N=114
Change in migraine frequency per 4 weeks assessed throughout 26 week treatment period	mean=-2.1 SD=2.11 N=117	mean=-2.3 SD=3.14 N=120	mean=-1.3 SD=3.17 N=117	mean=-1.903 SD=2.877 N=354	mean=-1.1 SD=2.62 N=114

***data imputed by reviewer from baseline and endpoint data**

****calculated by reviewer for purpose of analysis**

Quality of life – MSQ

	Topiramate			**Placebo**
	200 mg	**100 mg**	**50 mg**	
Role restrictive, baseline	mean=49.8 SE=1.6 N=107	mean=47.0 SE=1.6 N=111	mean=48.4 SE=1.6 N=110	mean=51.9 SE=1.7 N=106
Role restrictive, endpoint	mean=77.9 SE=1.9 N=107	mean=75.8 SE=1.9 N=111	mean=71.9 SE=1.9 N=110	mean=67.2 SE=1.8 N=106
Role prevention, baseline	mean=67.6 SE=1.8 N=107	mean=65.4 SE=1.8 N=111	mean=63.7 SE=1.8 N=110	mean=69.9 SE=1.8 N=106

Bibliographic reference	**Brandes JL, Saper JR, Diamond M et al. (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291: 965-73** **Brandes JL, Kudrow DB, Rothrock JF et al. (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clinic Proceedings 81: 1311-9**

Role prevention, endpoint	mean=87.2 SE=1.7 N=107	mean=85.5 SE=1.7 N=111	mean=82.6 SE=1.7 N=110	mean=80.8 SE=1.6 N=106
Role emotional function, baseline	mean=52.6 SE=2.2 N=107	mean=51.7 SE=2.2 N=111	mean=53.4 SE=2.2 N=110	mean=57.7 SE=2.2 N=106
Role emotional function, endpoint	mean=82.7 SE=2.1 N=107	mean=82.9 SE=2.1 N=111	mean=77.6 SE=2.1 N=110	mean=74.1 SE=2.0 N=106

Quality of life – SF36

	Topiramate			**Placebo**
	200 mg	**100 mg**	**50 mg**	
Role Physical, baseline	mean=48.5 SE=3.9 N=107	mean=42.5 SE=3.9 N=111	mean=48.5 SE=3.9 N=110	mean=52.9 SE=4.0 N=106
Role Physical, endpoint	mean=69.1 SD=3.7 N=107	mean=68.5 SE=3.7 N=111	mean=69.1 SE=3.7 N=110	mean=64.6 SE=3.6 N=106
Vitality, baseline	mean=48.1 SE=2.1 N=107	mean=48.9 SE=2.0 N=111	mean=51.1 SE=2.0 N=110	mean=54.5 SE=2.1 N=106
Vitality, endpoint	mean=54.6 SE=2.0 N=107	mean=54.4 SE=2.0 N=111	mean=54.8 SE=2.0 N=110	mean=56.2 SE=2.0 N=106
Physical functioning, baseline	mean=80.9 SE=1.9 N=107	mean=81.9 SE=1.9 N=111	mean=81.7 SE=1.9 N=110	mean=84.7 SE=1.9 N=106

Bibliographic reference	**Brandes JL, Saper JR, Diamond M et al. (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291: 965-73** **Brandes JL, Kudrow DB, Rothrock JF et al. (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clinic Proceedings 81: 1311-9**				
	Physical functioning, endpoint	mean=84.3 SE=1.8 N=107	mean=87.1 SE=1.8 N=111	mean=86.0 SE=1.8 N=110	mean=58.7 SE=2.2 N=106
	Bodily pain, baseline	mean=53.8 SE=2.2 N=107	mean=54.2 SE=2.2 N=111	mean=58.9 SE=2.2 N=110	mean=58.7 SE=2.2 N=106
	Bodily pain, endpoint	mean=65.3 SE=2.1 N=107	mean=65.8 SE=2.1 N=111	mean=65.5 SE=2.1 N=110	mean=63.4 SE=2.0 N=106
	General health, baseline	mean=70.2 SE=1.8 N=107	mean=69.6 SE=1.7 N=111	mean=68.7 SE=1.7 N=110	mean=71.2 SE=1.8 N=106
	General health, endpoint	mean=74.7 SE=1.8 N=107	mean=72.6 SE=1.8 N=111	mean=70.8 SE=1.8 N=110	mean=71.2 SE=1.8 N=106
	Social functioning, baseline	mean=69.9 SE=2.2 N=107	mean=71.0 SE=2.1 N=111	mean=71.3 SE=2.1 N=110	mean=71.2 SE=1.8 N=106
	Social functioning, endpoint	mean=69.9 SE=2.2 N=107	mean=77.3 SE=2.0 N=111	mean=79.6 SE=2.0 N=110	mean=77.7 SE=2.0 N=106
	Role emotional, baseline	mean=78.5 SE=2.0 N=107	mean=71.0 SE=3.7 N=111	mean=66.6 SE=3.7 N=110	mean=75.1 SE=3.8 N=106
	Role emotional, endpoint	mean=76.6 SE=3.1 N=107	mean=78.1 SE=3.2 N=111	mean=76.4 SE=3.2 N=110	mean=77.6 SE=3.0 N=106
	Mental health,	mean=72.0	mean=71.2	mean=69.8	mean=73.2

Bibliographic reference	**Brandes JL, Saper JR, Diamond M et al. (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291: 965-73** **Brandes JL, Kudrow DB, Rothrock JF et al. (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clinic Proceedings 81: 1311-9**

baseline	SE=1.7 N=107	SE=1.7 N=111	SE=1.7 N=110	SE=1.7 N=106
Mental health, endpoint	mean=72.1 SE=1.6 N=107	mean=71.7 SE=1.6 N=111	mean=71.7 SE=1.6 N=110	mean=73.4 SE=1.6 N=106

Change in acute medication use

Acute medication use was assessed by measuring the number of days requiring acute medication per 4 weeks.

	Topiramate				**Placebo**
	200 mg	**100 mg**	**50 mg**	**Combined doses (200mg and 100mg) ****	
Number of days per 4 weeks requiring rescue medication during baseline period	mean=5.8 SD=2.52 N=117	mean=6.2 SD=2.52 N=120	mean=5.7 SD=2.72 N=117		mean=5.8 SD=2.67 N=114
Change in number of days requiring rescue medication per 4 weeks, assessed during 26-week treatment period.	mean=-2.2 SE=0.29 SD=3.14* N=117	mean=-2.1 SE=0.29 SD=3.18* N=120	not reported	mean=-2.15 SD=3.15 N=237	mean=-1.0 SE=0.29 SD=3.09* N=114

***calculated by reviewer from reported standard errors and sample size**

****calculated by reviewer for purpose of analysis**

Outcomes reported but not extracted: Mean migraine duration; specific adverse events, SF36 other domains (not selected a priori for analysis)

Bibliographic reference	**Brandes JL, Saper JR, Diamond M et al. (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291: 965-73** **Brandes JL, Kudrow DB, Rothrock JF et al. (2006) Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clinic Proceedings 81: 1311-9**
Source of funding	Johnson and Johnson Pharmaceuticals
Comments	Participants were allocated to groups according to a computer-generated randomization schedule. Study medication was packaged and labelled according to a medication code schedule generated before the trial. Each bottle had a 2-part tear-off label; study medication identification was concealed and could be revealed only in case of emergency. An interactive voice response system was used to assign randomization numbers to patients, and treatment assignments were not revealed to study patients, investigators, clinical staff, or study monitors until all patients had completed therapy and the database had been finalized. 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 (47% dropout rate). 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. 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. Previous preventive medications used or years used not reported.

Table 18: Diener 1996

Bibliographic reference	**Diener HC, Foh M, Iaccarino C et al. (1996) Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study group. Cephalalgia 16: 441-7**
Study type	Randomised controlled trial
Aim	To assess the efficacy of cyclandelate and propranolol for migraine prophylaxis (data for cyclandelate group not reported here as does not match interventions specified in review protocol).
Patient characteristics	**Inclusion criteria:** - Age 18 to 60 - Migraine with or without aura according to the international headache society criteria. - Migraine history of at least 12 months. - Mean number of attacks between 2 and 10 within the last 3 months. - 2 – 10 attacks in prospective baseline period. **Exclusion criteria:**

<table>
<tr><td>Bibliographic reference</td><td>Diener HC, Foh M, Iaccarino C et al. (1996) Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study group. Cephalalgia 16: 441-7</td></tr>
<tr><td></td><td>- Pregnant or lactating women.
- Psychiatric disorders.
- Concomitant non-migraine headaches 3 times per month within the last 3 months.
- Use of centrally-acting drugs or migraine prophylactic drugs during the 4 weeks preceding the trial
- Contraindication to beta blocker or cyclandelate.
- Use of acute migraine drugs for more than 12 days per month.

Baseline characteristics
<table>
<tr><th></th><th>Propranolol</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>18/60</td><td>14/41</td></tr>
<tr><td>Age (mean, SD)</td><td>40 (13)</td><td>39 (11)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Propranolol</th><th>Placebo</th></tr>
<tr><td>N</td><td>78</td><td>55</td></tr>
<tr><td>N (ITT analysis)</td><td>78</td><td>55</td></tr>
<tr><td>Drop outs</td><td>12
Not drug related (3)
Lack of efficacy (3)
Adverse events (6)</td><td>8
Not drug related (7)
Lack of efficacy (0)
Adverse events (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Propranolol 120mg/d</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Methods</td><td>The study started with a 4 week baseline period without prophylactic treatment to collect baseline measurements. Participants were subsequently randomised to receive propranolol or placebo* (3:2 ratio). Following randomisation, there was a 2 week run in period, with propranolol treatment at a dose of 120mg/d (this run in period was necessary to gradually increase the dose of cyclandelate*). Subsequently, there was a treatment period of 12 weeks followed by a run out period of 2 weeks. Acute medication was permitted for up to 12 days/month during the trial.

*The trial also compared cyclandelate (data not extracted here as cyclandelate was not an intervention included in the review protocol).</td></tr>
<tr><td>Length of follow up</td><td>12 week treatment period.</td></tr>
<tr><td>Location</td><td>Multicentre study, location unclear</td></tr>
</table>

Bibliographic reference	**Diener HC, Foh M, Iaccarino C et al. (1996) Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. The Study group. Cephalalgia 16: 441-7**
Outcomes measures and effect size	**50% responder** Responder was defined as a reduction in migraine frequency in the last 4 weeks of treatment of >50% compared with baseline. Migraine frequency was defined as number of attacks per 4 weeks. **Propranolol**: 33/78 (42.3%) **Placebo**: 17/55 (30.9%) **Outcomes reported but not extracted:** Headache duration, blood pressure, blood chemistry, adverse events (serious adverse events not reported separately)
Source of funding	Not reported.
Comments	Method of random sequence generation and allocation concealment not described (though allocation concealment likely to have occurred as trial was double blind). Study described as double blind. Headache diaries were analysed by the treating physicians before breaking randomisation code.

Table 19: Diener 2004

Bibliographic reference	**Diener HC, Tfelt-Hansen P, Dahlof C et al. (2004) Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. Journal of Neurology 251: 943-50**
Study type	Randomised controlled trial
Aim	To evaluate the efficacy of topiramate for migraine prophylaxis.
Patient characteristics	**Inclusion criteria:** - Aged between 12 and 65 years old - 3 to 12 migraine periods and no more than 15 headache (including migraine) days during baseline period. - History of migraine with or without aura (according to international headache society 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 or uncontrolled diabetes - Other contraindications for using beta-blockers **Baseline characteristics**

	Topiramate 200mg/d	Topiramate 100mg/d	Propranolol 160mg/d	Placebo
Sex (M/F)	28/115	29/110	24/119	34/109

<table>
<tr><td>Bibliographic reference</td><td colspan="5">Diener HC, Tfelt-Hansen P, Dahlof C et al. (2004) Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. Journal of Neurology 251: 943-50</td></tr>
<tr><td></td><td>Age (mean, SD)</td><td>42.6 (11.29)</td><td>39.8 (10.88)</td><td>40.6 (11.13)</td><td>40.4 (10.11)</td></tr>
<tr><td>Number of Patients</td><td colspan="5"><table>
<tr><th></th><th>Topiramate 200mg/d</th><th>Topiramate 100mg/d</th><th>Propranolol 160mg/d</th><th>Placebo</th></tr>
<tr><td>N</td><td>144</td><td>141</td><td>144</td><td>146</td></tr>
<tr><td>N (ITT analysis)</td><td>143</td><td>139</td><td>143</td><td>143</td></tr>
<tr><td>Drop outs</td><td>79
participant choice (8)
lost to follow up (1)
adverse events (63)
lack of efficacy (2)
other (4)</td><td>47
participant choice (5)
lost to follow up (0)
adverse events (37)
lack of efficacy (1)
other (2)</td><td>42
participant choice (3)
lost to follow up (1)
adverse events (29)
lack of efficacy (3)
other (5)</td><td>47
participant choice (7)
lost to follow up (1)
adverse events (15)
lack of efficacy (13)
other (8)</td></tr>
</table></td></tr>
<tr><td>Intervention 1</td><td colspan="5">Topiramate 200mg/d Median daily dose actually received for randomised period (i.e. titration & maintenance) 124.2mg/d. Target dose achieved in 53%.</td></tr>
<tr><td>Intervention 2</td><td colspan="5">Topiramate 100mg/d Median daily dose actually received for randomised period (i.e. titration & maintenance) 87.9mg/d Target dose achieved in 87%.</td></tr>
<tr><td>Intervention 3</td><td colspan="5">Propranolol 160mg/d Median daily dose actually received for randomised period (i.e. titration & maintenance) 129.6mg/d Target dose achieved in 78%.</td></tr>
<tr><td>Comparison</td><td colspan="5">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)</td></tr>
<tr><td>Methods</td><td colspan="5">Study started 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 record information recorded. Participants randomised after baseline phase. 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 experienced unacceptable tolerability problems. Not reported what happened in placebo group. Titration continued for 8 weeks then participants given 18 weeks treatment at target dose. Permitted use of “acute rescue medication (i.e. aspirin, paracetamol, NSAIDs, ergot derivatives, triptans and opioids) for migraine attacks as needed”.</td></tr>
<tr><td>Length of follow up</td><td colspan="5">26 weeks</td></tr>
<tr><td>Location</td><td colspan="5">Tertiary care headache centres, multicentre study (61 centres in 13 countries)</td></tr>
<tr><td>Outcomes measures and</td><td colspan="5"></td></tr>
</table>

Bibliographic reference	**Diener HC, Tfelt-Hansen P, Dahlof C et al. (2004) Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. Journal of Neurology 251: 943-50**

effect size

Change in migraine days

Migraine days defined as calendar days with migraine.

	Topiramate			**Propranolol**	**Placebo**
	200 mg	**100 mg**	**Combined doses***	**160 mg**	
Baseline	mean=6.2 SD=2.76 N=143	mean=5.8 SD=2.21 N=139		mean=6.1 SD=2.70 N=143	mean=6.1 SD=2.60 N=143
Change in number of migraine days per 28 days in treatment period	mean=-1.3 SD=3.46* SE=0.25 N=143	mean=-1.8 SD=3.40* SE=0.25 N=139	mean=-1.55 SD=3.43 n=282	mean=-1.9 SD=2.99* SE=0.25 N=143	mean=-1.1 SD=2.87* SE=0.24 N=143

***calculated by reviewer**

50% responder rate

50% responder defined as participants who had a >50% reduction in monthly migraine frequency during treatment phase) compared with the baseline phase.

Topiramate			**Propranolol**	**Placebo**
200 mg	**100 mg**	**Combined doses****	**160 mg**	
35/143	37/139	72/282 (25.5%)	43/143	22/143

****calculated by reviewer for purpose of analysis**

Change in migraine frequency

Migraine frequency defined as number of migraine periods per 28 days.

	Topiramate			**Propranolol**	**Placebo**
	200 mg	**100 mg**	**Combined doses****	**160 mg**	
Baseline	mean=5.3 SD=2.24 N=143	mean=4.9 SD=1.97 N=139		mean=5.1 SD=2.17 N=143	mean=5.2 SD=2.24 N=143
Change migraine	mean=-1.1	mean=-1.6	mean=-1.35	mean=-1.6	mean=-0.8

Bibliographic reference	Diener HC, Tfelt-Hansen P, Dahlof C et al. (2004) Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. Journal of Neurology 251: 943-50

frequency in treatment period	SE=0.22 SD=2.63* N=143	SE=0.22 SD=2.59* N=139	SD=2.61 N=282	SE=0.21 SD=2.51* N=143	SE=0.21 SD=2.51* N=143

***calculated by reviewer from reported standard errors**
****calculated by reviewer for purpose of analysis**

Change in acute medication use

Acute medication use defined as number of days of acute medication use per 28 days,

	Topiramate			**Propranolol**	**Placebo**
	200 mg	**100 mg**	**Combined doses****	**160 mg**	
Baseline	mean=5.5 SD=2.62 N=143	mean=5.0 SD=2.21 N=139		mean=5.4 SD=2.54 N=143	mean=5.3 SD=2.52 N=143
Change in acute medication use in treatment period	mean=-0.9 SE=0.21 SD=2.51* N=143	mean=-1.5 SE=0.21 SD=2.48* N=139	mean=-1.20 SD=2.51 N=282	mean=-1.6 SE=0.21 SD=2.51* N=143	mean=-0.8 SE=0.2 SD=2.36* N=143

***calculated by reviewer from reported standard errors**
****calculated by reviewer for purpose of analysis**

Outcomes reported but not extracted: 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

Source of funding	Johnson and Johnson Pharmaceuticals
Comments	Unclear randomisation and allocation concealment. Study was described as 'double blind'. Only 63% of participants completed the treatment regimen. Group using Topiramate 200mg/d had a much higher dropout rate than other groups. 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, withdrawals due to adverse events. 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.

Table 20: Diener 2007

<table>
<tr><td>Bibliographic reference</td><td>Diener HC, Bussone G, Van Oene JC et al. (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study.[Erratum appears in Cephalalgia. 2007 Aug;27(8):962]. Cephalalgia 27: 814-23</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To evaluate the efficacy and tolerability of topiramate for the prevention of chronic migraine.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Aged 18 to 65
- Diagnosis of chronic migraine according to the international classification of headache disorders criteria (=> 15 migraine headaches per 4 weeks)
- Met criteria at least during the last 3 months before entry into the trial.
- Migraine history of at least 1 year.
- =>12 migraine days in the baseline period.

Exclusion criteria:
- Patients presenting with another primary chronic headache or any secondary headache except medication overuse headache.
- Onset of migraine over the age of 50.
- Severe depression.
- Taking antidepressants unless the antidepressant was used for 3 months at a stable dose, and the patient intended to continue use throughout the trial.
- Use of prophylactic migraine medication unless the drug had been used for 3 months (at a stable dose for at least 1 month), and the patient continued to use throughout the trial.
- History of topiramate use
- Use of any anticonvulsant in the last 30 days.
- Use of a carbonic anhydrase inhibitor.

Baseline characteristics
<table>
<tr><th></th><th>Topiramate 100mgd</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>8/24</td><td>7/20</td></tr>
<tr><td>Age (mean, SD)</td><td>47.8 (9.4)</td><td>44.4 (9.6)</td></tr>
<tr><td>With/without medication overuse</td><td>23/4</td><td>23/9</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Diener HC, Bussone G, Van Oene JC et al. (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study.[Erratum appears in Cephalalgia. 2007 Aug;27(8):962]. Cephalalgia 27: 814-23</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><th></th><th>Topiramate 100mg/d</th><th>Placebo</th></tr>
<tr><td>N</td><td>32</td><td>27</td></tr>
<tr><td>N (ITT analysis)</td><td>32</td><td>27</td></tr>
<tr><td>Drop outs</td><td>8
Insufficient tolerability (1)
Insufficient tolerability and efficacy (5)
Insufficient efficacy (2)
Withdrew consent (0)</td><td>13
Insufficient tolerability (3)
Insufficient tolerability and efficacy (0)
Insufficient efficacy (8)
Withdrew consent (2)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="3">Topiramate 100mg/d</td></tr>
<tr><td>Comparison</td><td colspan="3">Placebo</td></tr>
<tr><td>Methods</td><td colspan="3">A 4-week baseline period was followed by 4-week titration phase and a 12 week maintenance phase. There was then a taper-down phase lasting up to 7 weeks. Titration occurred at a rate of 25mg/week up to a 100mg/d. In the first 8 weeks of treatment, clinicians were permitted to increase or decrease the dose within the range of 50-200mg/d. Participants were allowed to take acute medication for migraine.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">12 week treatment period at maintenance dose.</td></tr>
<tr><td>Location</td><td colspan="3">USA, Multicentre (neurology departments)</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Change in migraine days<table>
<tr><th></th><th>Topiramate 100mgd</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=15.5
SD=4.6
N=32</td><td>mean=13.4
SD=8.8
N=27</td></tr>
<tr><td>Change in migraine headache days in the last 4 weeks of treatment</td><td>mean=-3.5
SD=6.3
N=32</td><td>mean=0.2
SD=4.7
N=27</td></tr>
<tr><td>Change in migraine headache days in the last 4 weeks of treatment (medication</td><td>mean=-3.5
SD=7.1
N=23</td><td>mean=-0.8
SD=4.8
N=23</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Diener HC, Bussone G, Van Oene JC et al. (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study.[Erratum appears in Cephalalgia. 2007 Aug;27(8):962]. Cephalalgia 27: 814-23

overuse headache patients only)		

Quality of life - MIDAS

	Topiramate 100mgd	**Placebo**
Baseline	mean=67 SD=87 N=25	mean=61 SD=99 N=14
Change in migraine headache days in the last 4 weeks of treatment	mean=-26 SD=61 N=32	mean=3 SD=21 N=27

Change in acute analgesic use

Acute medication use was defined as the number of days requiring acute medication.

	Topiramate 100mgd	**Placebo**
Baseline	mean=13.3 SD=6.8 N=32	mean=14.7 SD=6.5 N=27
Change in migraine headache days in the last 4 weeks of treatment	mean=-3.0 SD=5.9 N=32	mean=-0.7 SD=6.2 N=27
Change in migraine headache days in the last 4 weeks of treatment **(medication overuse headache patients only)**	mean=-3.7 SD=6.7 N=23	mean=-0.5 SD=6.5 N=23

Bibliographic reference	**Diener HC, Bussone G, Van Oene JC et al. (2007) Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study.[Erratum appears in Cephalalgia. 2007 Aug;27(8):962]. Cephalalgia 27: 814-23**
	Serious adverse events **What constituted a serious adverse event was not explicitly reported.** **Topiramate 100mgd**: 1/32 (hospitalisation for surgery for carpal tunnel decompression) **Placebo**: 1/27 (hospitalisation for neurogenic muscle spasm) **Outcomes reported but not extracted:** Satisfaction, 50% responder defined as 50% reduction in headache days (rather than frequency), blood pressure, body weight.
Source of funding	Not reported (though it is reported that the study was sponsored and the data analysed by the sponsor)
Comments	Randomisation was by computer before the study started in blocks of 4 (2 per treatment), and subjects were assigned to the next available randomisation number in the block. Randomisation was stratified according to the presence or absence of medication overuse in the baseline period. Details of allocation concealment are not reported. The study is described as 'double blind', though details of how blinding was maintained are not provided. Quality of life was also assessed using the MSQ and HIT-6 questionnaires, but these data are not reported other than to say that there were no significant differences, indicating potential reporting bias.

Table 21: Diener 2009

Bibliographic reference	**Diener HC, Gendolla A, Feuersenger A et al. (2009) Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia 29: 921-7**
Study type	Randomised controlled trial
Aim	To evaluate telmisartan for migraine prophylaxis.
Patient characteristics	**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.

<table>
<tr><td>Bibliographic reference</td><td>Diener HC, Gendolla A, Feuersenger A et al. (2009) Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia 29: 921-7</td></tr>
<tr><td></td><td>- 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
- 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, percutaneous transluminal coronary angioplasty or unstable angina within the past 3 months
- Any other serious disorders.

Baseline characteristics
<table>
<tr><th></th><th>Telmisartan</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>8/32</td><td>5/39</td></tr>
<tr><td>Age (mean, SD)</td><td>39.8 (11.7)</td><td>41.6 (12.9)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Telmisartan</th><th>Placebo</th></tr>
<tr><td>N</td><td>48</td><td>47</td></tr>
<tr><td>N (per protocol analysis)</td><td>40</td><td>44</td></tr>
<tr><td>Drop outs</td><td>2</td><td>3</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Telmisartan (Micardis; Boehringer Ingelheim) 80mg/d (presumed per day, though not explicitly stated)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Diener HC, Gendolla A, Feuersenger A et al. (2009) Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia 29: 921-7</td></tr>
<tr><td>Comparison</td><td>Matching placebo 80mg</td></tr>
<tr><td>Methods</td><td>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.</td></tr>
<tr><td>Length of follow up</td><td>12 week treatment period</td></tr>
<tr><td>Location</td><td>Headache clinic, Germany</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in migraine days
Migraine days defined as number of days per 4 weeks with 1hr or more of migraine symptoms.
<table>
<tr><th></th><th>Telmisartan 80mg/d</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=6.18
SD=2.89
N=40</td><td>mean=7.59
SD=3.59
N=44</td></tr>
<tr><td>Last 4 weeks of treatment</td><td>mean=4.53
SD=3.41
N=40</td><td>mean=6.45
SD=4.47
N=44</td></tr>
<tr><td>Change in migraine days</td><td>mean=-1.65
SD=3.46
SE=0.547*
N=40</td><td>mean=-1.14
SD=3.78
SE=0.570*
N=44</td></tr>
</table>
*calculated by reviewer from reported standard deviation for network meta-analysis

Change in acute analgesic use
Acute medication use was defined as the number of doses of analgesia per 4 weeks.
<table>
<tr><th></th><th>Telmisartan 80mg/d</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Last 4 weeks of treatment</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Change in analgesic use</td><td>mean=-0.31
95%CI=-1.43 to 0.82
SD=3.72*</td><td>mean=-0.25
95%CI=-1.35 to 1.43
SD=4.70*</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Diener HC, Gendolla A, Feuersenger A et al. (2009) Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia 29: 921-7**
	<table><tr><td></td><td>N=42</td><td>N=44</td></tr></table> ***data calculated by reviewer from reported 95% CIs** **Outcomes reported but not extracted:** Responder rate (>50% reduction in headache *days*), change from baseline in headache hours, change from baseline in triptan use, blood pressure at baseline and end of the study, adverse events (serious adverse events not reported separately)
Source of funding	Unrestricted grant from Boehringer Ingelheim
Comments	The method of randomisation and allocation concealment were unclear. Patients and physicians were blinded to group allocation. Per protocol analysis was 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). However, the number of dropouts was small and similar across groups, so this is unlikely to have had a substantial effect on results. 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.

Table 22: Dodick 2009

Bibliographic reference	**Dodick DW, Freitag F, Banks J et al. (2009) Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clinical Therapeutics 31: 542-59**
Study type	Randomised controlled trial
Aim	To compare the efficacy and tolerability of topiramate and amitriptyline in the prophylactic treatment of migraine.
Patient characteristics	**Inclusion criteria:** Aged =>18 History of migraine with or without aura according to international headache society criteria. Migraine for at least 6 months before the beginning of the trial. 3 to 12 migraines per month in the 3 months before the trial and 3 to 12 migraines in the baseline period. No more than 15 headache days (migraine and non-migraine) in the baseline period. **Exclusion criteria:** Previously failed >2 adequate trials of migraine prevention medication (where adequate trials were of at least 3 months duration at doses recommended for headache relief) Previously failed adequate trials of topiramate or amitriptyline where failure was due to adverse events or lack of efficacy. Use of acute medication on more than 15 days per month. Onset over the age of 50.

<table>
<tr><td>Bibliographic reference</td><td>Dodick DW, Freitag F, Banks J et al. (2009) Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clinical Therapeutics 31: 542-59</td></tr>
<tr><td></td><td>Migraine aura only (without headache).
Cluster headache history.
Progressive neurological condition other than migraine.
Condition more painful than headache.
History of medical condition for which amitriptyline is contraindicated.
History of an unstable medical condition in the last 2 years or major psychiatric condition in the last 6 months that could impair participation in the study or require the use of medications not permitted in the study.
History of drug or alcohol abuse in the last 2 years.
History of nephrolithiasis, active liver disease, or liver function test => 2 times normal.
Pregnant or nursing women and those who are not practicing an accepted form of contraception.

Baseline characteristics
<table>
<tr><th></th><th>Topiramate</th><th>Amitriptyline</th></tr>
<tr><td>Sex (M/F)</td><td>23/149</td><td>27/132</td></tr>
<tr><td>Age (mean, SD)</td><td>39.7 (10.7)</td><td>37.9 (11.3)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Topiramate</th><th>Amitriptyline</th></tr>
<tr><td>N</td><td>178</td><td>169</td></tr>
<tr><td>N (ITT analysis)</td><td>172</td><td>159</td></tr>
<tr><td>N (safety analysis)</td><td>177</td><td>169</td></tr>
<tr><td>Drop outs</td><td>76
Subject’s choice (15)
Protocol violation (8)
Lost to follow up (9)
Limiting adverse events (34)
Lack of efficacy (2)
Other (2)</td><td>74
Subject’s choice (13)
Protocol violation (2)
Lost to follow up (9)
Limiting adverse events (34)
Lack of efficacy (0)
Other (6)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Topiramate 50-100mg/d</td></tr>
<tr><td>Intervention 1</td><td>Amitriptyline 50-100mg/d</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Dodick DW, Freitag F, Banks J et al. (2009) Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clinical Therapeutics 31: 542-59</td></tr>
<tr><td>Methods</td><td>The trial started with a washout period of 14-28 days during which any previously used migraine prevention medication use was stopped. This was followed by a 28 day baseline period, where baseline measures were taken using a headache diary. Following assessment of eligibility, participants were then randomised to receive either amitriptyline or topiramate for the next 26 weeks, which consisted of a 4 week titration phase and a 22 week treatment phase at the target dose. In the titration phase, for both treatments, patients initially received 25mg/d, This was increased by 25mg/d each week at the investigators discretion up to a minimum of 50mg/d and maximum of 100mg/d. After the maintenance phase there was a taper-down period at the investigators discretion (approximately 2 weeks). Acute medication use was permitted for up to 4 days per week. Participants were encouraged to continue normal patterns of non-migraine medication use, diet, and lifestyle.

Intention to treat analysis used a last observation carried forward method. The intention to treat population was all participants with at least one post-treatment efficacy measurement point. The safety population was all participants with at least one post-treatment safety measurement point</td></tr>
<tr><td>Length of follow up</td><td>22 week treatment period (at target dose)</td></tr>
<tr><td>Location</td><td>USA outpatient setting (multicentre)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in migraine days
Migraine days were defined as days with migraine headache (not including other headache types) as reported in a headache diary. Least squared mean was calculated using an analysis of co-variance with treatment and centre as factors and baseline migraine frequency as a co-variate.
<table>
<tr><th></th><th>Topiramate 50-100mg/d</th><th>Amitriptyline 50-100mg/d</th><th>Mean difference</th></tr>
<tr><td>Baseline</td><td>mean=7.4
SD=2.9
N=172</td><td>mean=7.1
SD=2.6
N=159</td><td></td></tr>
<tr><td>Change in 28 days preceding end of maintenance treatment</td><td>least squared mean=-3.2
SD=not reported
N=172</td><td>least squared mean=-3.1
SD=not reported
N=159</td><td>mean difference=-0.1
95% CI=-0.9 to 0.7
SE=0.41</td></tr>
</table>
Change in Migraine frequency
Migraine frequency was defined as the number of migraine episodes in the 28 day period. If symptoms recurred in the</td></tr>
</table>

Bibliographic reference	**Dodick DW, Freitag F, Banks J et al. (2009) Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clinical Therapeutics 31: 542-59**

same 24 hour period, this was considered part of the same episode. Least squared mean was calculated using an analysis of co-variance with treatment and centre as factors and baseline migraine frequency as a co-variate.

	Topiramate 50-100mg/d	Amitriptyline 50-100mg/d	Mean difference
Baseline	mean=6.3 SD=2.5 N=172	mean=6.0 SD=2.3 N=159	
Change in 28 days preceding end of maintenance treatment	least squared mean=-2.6 SD=not reported N=172	least squared mean=-2.7 SD=not reported N=159	mean difference=0.1 95% CI=-0.6 to 0.7

Quality of life – MIDAS

The questionnaire was administered at the beginning of the baseline period at the end of the treatment period to assess headache related disability.

	Topiramate 50-100mg/d	Amitriptyline 50-100mg/d
Beginning of baseline period	mean=26.4 SD=19.6 N=152 (not ITT analysis)	mean=25.5 SD=20.4 N=143 (not ITT analysis)
Change at end of maintenance treatment	mean=-12.1 SD=23.4 N=152 (not ITT analysis)	mean=-14.2 SD=20.7 N=143 (not ITT analysis)

Quality of life – MSQ

The questionnaire was administered at the beginning of the baseline period and at every visit during treatment. The scores are normalised on a scale of 0-100. Better scores indicate better quality of life.

	Topiramate 50-100mg/d	Amitriptyline 50-100mg/d	Mean difference
Beginning of baseline period	mean RR=55.8 SD RR=16.3 mean RP=68.8	mean RR=55.7 SD RR=15.2 mean RP=72.2	

Bibliographic reference	**Dodick DW, Freitag F, Banks J et al. (2009) Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clinical Therapeutics 31: 542-59**

	SD RP=20.1 mean EF=55.9 SD EF=26.6 N=172	SD RP=17.8 mean EF=57.8 SD EF=24.9 N=159	
Change at last visit during treatment	mean RR=23.7 SD RR=not reported least squared mean RP=16.7 SD RP=not reported mean EF=25.6 SD EF=not reported N=172	mean RR=18.4 SD RR=not reported least squared mean RP=12.5 SD RP=not reported mean EF=20.5 SD EF=not reported N=159	mean difference RR=5.3 95% CI RR=1.2 to 9.4 mean difference RP=4.2 95% CI RP=0.8 to 7.5 mean difference EF=5.1 95% CI EF=0.5 to 9.7

Quality of life – Q-LES-Q-SF

The questionnaire was administered at the beginning of the baseline period and at every visit during treatment. The scores from the first 14 items are normalised on a scale of 0-100 (results from the final 2 items were analysed separately (not reported). Better scores indicate better quality of life.

	Topiramate 50-100mg/d	Amitriptyline 50-100mg/d	Mean difference
Beginning of baseline period	mean=65.9 SD=15.7 N=172	mean=65.3 SD=13.4 N=159	
Change at last visit during treatment	mean=4.6 SD=23.4 N=172	mean=4.9 SD=not reported N=159	mean difference=-0.3 95% CI=-3.1 to 2.6

Serious adverse events

A serious adverse event was defined as an event that was fatal or immediately life threatening, permanently or significantly disabling, resulted in or prolonged hospitalisation, or was a congenital anomaly or birth defect.

Topiramate 50-100mg/d	**Amitriptyline 50-100mg/d**
4/177	8/169

Bibliographic reference	**Dodick DW, Freitag F, Banks J et al. (2009) Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clinical Therapeutics 31: 542-59**
	Outcomes reported but not extracted: Change in headache days, number of responders where responder was defined as 50% reduction in migraine or headache days, use of acute medication (measures of variability, such as standard deviations, and so the data was not useable), migraine severity (measures of variability, such as standard deviations, and so the data was not useable), severity of migraine related nausea, vomiting, photophobia and phonophobia, functional disability, specific adverse events, weight, laboratory parameters
Source of funding	Ortho-McNeil Janssen Scientific affairs.
Comments	Randomisation was via computer-generated sequence in permuted blocks of 4 for each site. Drugs were identical in appearance and the trial was double blind. Blinding was ensured by participants taking the same number of capsules morning and evening irrespective of group (using placebo capsules as required). Allocation concealment is not explicitly described, but as this was a double blind trial, this is likely to have occurred. High dropout rate (43.2%), though similar across groups. Analysis of Quality of life MIDAS scores could not use intention to treat analysis as it was only measured once in the treatment period (at the end), so participants who had dropped out before that measurement could not be included.

Table 23: Feuerstein 1990

Bibliographic reference	**Feuerstein, T, Quebe-Fehling, E. A double-blind, placebo-controlled, parallel-group, multicenter study of the safety and efficacy of gabapentin (CI-945) as a prophylactic interval therapy in patients with common migraine (Protocols 879-201, -205, -206, -207, -209). Research Report No. RR 4301-00066. Freiburg: Goedecke AG Research and Development. 1990;(RR 4301-00066).**
Study type	Randomised controlled trial
Aim	To investigate the effectiveness of gabapentin in patients with therapy-resistance common migraine.
Patient characteristics	Inclusion criteria: Therapy-resistant common migraine (defined by the Ad hoc committee on Classification of headache). At least 8 migraine attacks per month (1 centre) or at least 2 attacks per month (other 4 centres) Exclusion criteria: Pregnant or nursing females. Severe liver or kidney insufficiency or other severe progressive accompanying illness. Other prophylactic migraine medication. Baseline characteristics

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Feuerstein, T, Quebe-Fehling, E. A double-blind, placebo-controlled, parallel-group, multicenter study of the safety and efficacy of gabapentin (CI-945) as a prophylactic interval therapy in patients with common migraine (Protocols 879-201, -205, -206, -207, -209). Research Report No. RR 4301-00066. Freiburg: Goedecke AG Research and Development. 1990;(RR 4301-00066).</td></tr>
<tr><td></td><td></td><td>Gabapentin</td><td>Placebo</td></tr>
<tr><td></td><td>Sex (M/F)</td><td>11/35</td><td>10/33</td></tr>
<tr><td></td><td>Age (mean, range)</td><td>42 (20 to 68)</td><td>42 (23 to 68)</td></tr>
<tr><td>Number of Patients</td><td colspan="3"></td></tr>
<tr><td></td><td></td><td>Gabapentin</td><td>Placebo</td></tr>
<tr><td></td><td>N</td><td>46</td><td>43</td></tr>
<tr><td></td><td>N (per-protocol analysis)</td><td>22</td><td>31</td></tr>
<tr><td></td><td>Drop outs</td><td>15
Non-compliance (5)
Non-compliance and lack of efficacy (1)
Adverse reactions (3)
Adverse reactions and lack of efficacy (1)
Lack of efficacy (1)
Non-compliance, adverse reactions and lack of efficacy (1)
Other (3)</td><td>10
Non-compliance (5)
Non-compliance and lack of efficacy (0)
Adverse reactions (1)
Adverse reactions and lack of efficacy (0)
Lack of efficacy (1)
Non-compliance, adverse reactions and lack of efficacy (0)
Other (3)</td></tr>
<tr><td>Intervention</td><td colspan="3">Gabapentin 900mg/d</td></tr>
<tr><td>Comparison</td><td colspan="3">Placebo</td></tr>
<tr><td>Methods</td><td colspan="3">On entry to the study, retrospective baseline data was collected for the last 3 months (according to patient recall). Patients were randomised to receive gabapentin or placebo for 12 weeks. Prophylactic medication was permitted in the retrospective baseline period. Acute analgesics were permitted but limited to 20 tablets per month. Psychotropics, vasodilators or beta-blockers were not permitted.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">12 week treatment duration</td></tr>
<tr><td>Location</td><td colspan="3">Austria and Germany (multicentre), outpatient/research centre setting</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Change in migraine frequency
Migraine frequency defined as number of attacks per 28 days.</td></tr>
<tr><td></td><td></td><td>Gabapentin 900mg/d</td><td>Placebo</td></tr>
<tr><td></td><td>3 month</td><td>mean=6.1</td><td>mean=6.3</td></tr>
</table>

Bibliographic reference	**Feuerstein, T, Quebe-Fehling, E. A double-blind, placebo-controlled, parallel-group, multicenter study of the safety and efficacy of gabapentin (CI-945) as a prophylactic interval therapy in patients with common migraine (Protocols 879-201, -205, -206, -207, -209). Research Report No. RR 4301-00066. Freiburg: Goedecke AG Research and Development. 1990;(RR 4301-00066).**
	retrospective baseline: SD=2.3, N=22 / SD=5.5*, N=31 Treatment period: mean=4.7, SD=2.8, N=22 / mean=5.6, SD=5.6*, N=31 Change in migraine frequency: mean=-1.4, SD=2.6, N=22 / mean=-0.7, SD=2.1, N=31 *substantially higher standard deviations in the placebo group than the gabapentin group are explained by two participants with very high baseline values (>20 attacks per month) in the placebo group Outcomes reported but not extracted: Duration of migraine attacks, change in number of patients with aura symptoms, adverse events (serious adverse events not reported separately), subjective rating of improvement, laboratory values, average pain (no measure of variability such as standard deviation, reported, so data not usable), maximum pain (not group summary effect reported)
Source of funding	Goedecke AG (pharmaceutical company) internal research and development report
Comments	Randomisation was in blocks of 10. Each centre was randomised separately. The method of randomisation and details of allocation concealment are not reported. The trial is described as 'double blind', but further details are not provided. The trial used a retrospective baseline, requiring patients to recall headache symptoms in the last 3 months, and therefore introducing potential recall bias. Additionally, prophylactic medication was permitted in the retrospective baseline period, and so baseline values may underestimate the 'true' values without treatment.

Table 24: Freitag 1984

Bibliographic reference	**Freitag FG, Diamond S (1984) Nadolol and placebo comparison study in the prophylactic treatment of migraine. Journal of the American Osteopathic Association 84: 343-7**
Study type	Randomised controlled trial
Aim	To evaluate the efficacy of nadolol in reducing the frequency and severity of migraine headaches.
Patient characteristics	**Inclusion criteria:** - Diagnosis of migraine according to the Ad hoc committee for the classification of headache criteria.

<table>
<tr><td>Bibliographic reference</td><td>Freitag FG, Diamond S (1984) Nadolol and placebo comparison study in the prophylactic treatment of migraine. Journal of the American Osteopathic Association 84: 343-7</td></tr>
<tr><td></td><td>Exclusion criteria:
- None reported.

Baseline characteristics
<table>
<tr><th></th><th>Nadolol</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>5/19</td><td>1/7</td></tr>
<tr><td>Age (mean, range)</td><td>34.9* (24-57)</td><td>40.5* (28-57)</td></tr>
</table>
*Calculated by reviewer from mean ages for males and females specified separately</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Nadolol 80mg/d</th><th>Nadolol 160mg/d</th><th>Nadolol 240mg/d</th><th>Placebo</th></tr>
<tr><td>N</td><td>8</td><td>8</td><td>8</td><td>8</td></tr>
<tr><td>N (analysis, presumed)</td><td>8</td><td>8</td><td>8</td><td>8</td></tr>
<tr><td>Drop outs</td><td>None reported</td><td>None reported</td><td>None reported</td><td>None reported</td></tr>
</table>
</td></tr>
<tr><td>Intervention 1</td><td>Nadolol 80mg/d</td></tr>
<tr><td>Intervention 2</td><td>Nadolol 160mg/d</td></tr>
<tr><td>Intervention 3</td><td>Nadolol 240mg/d</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Methods</td><td>Previous prophylactic treatment was stopped at the start of the trial. The trial began with an 8-week placebo-controlled baseline period to allow washout of previous medication, exclusion of placebo responders (not clear how identified), and recording of baseline measures. This was followed by a 12 week treatment period where participants were randomised to receive either nadolol (one of 3 doses) or placebo. Use of acute migraine medication was permitted, but participants were encouraged not to use it daily or almost daily.</td></tr>
<tr><td>Length of follow up</td><td>20 week treatment duration</td></tr>
<tr><td>Location</td><td>USA, setting not reported</td></tr>
<tr><td>Outcomes measures and effect size</td><td>50% responder
There was no statistically significant difference between the dose groups, and so the authors combined all of the patients treated with nadolol in the analysis. 50% responder was defined as the number of participants with at least a 50% reduction</td></tr>
</table>

Bibliographic reference	**Freitag FG, Diamond S (1984) Nadolol and placebo comparison study in the prophylactic treatment of migraine. Journal of the American Osteopathic Association 84: 343-7**
	in headache frequency in the last 4 weeks of treatment compared with the baseline period. **Nadolol (80 to 240 mg/d)**: 6/22 (27%) **Placebo**: 0/8 (0%) **Outcomes reported but not extracted:** number with 50% reduction in pain, number with 50% reduction in intensity, number with 50% improvement in relief, adverse events (only reported for nadolol group)
Source of funding	Not reported
Comments	Allocation to groups was randomised, but details of random sequence generation or allocation concealment are not reported. The trial was double blind – identical tablets were used to ensure blinding of participants. Blinding of investigators is not described explicitly. No reporting of dropouts.

Table 25: Freitag 2002

Bibliographic reference	**Freitag FG, Collins SD, Carlson HA et al. (2002) A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology 58: 1652-9**
Study type	Randomised controlled trial
Aim	To evaluate the efficacy and safety of extended-release divalproex sodium compared with placebo in prophylactic monotherapy treatment of migraine headache.
Patient characteristics	**Inclusion criteria:** - Aged >=12 years - Women of childbearing potential were required to practice contraception. - Onset of migraine 6 or months before screening. - 2 or more migraine headaches per month in the 3 months before screening. **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 > 2 adequate trials of prophylactic anti-migraine medication within 5 half-lives of that medication before entering the baseline phase.

<table>
<tr><td>Bibliographic reference</td><td>Freitag FG, Collins SD, Carlson HA et al. (2002) A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology 58: 1652-9</td></tr>
<tr><td></td><td>Baseline characteristics
<table>
<tr><th></th><th>Divalproex sodium 500 or 1000mg/d</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>25/90</td><td>25/97</td></tr>
<tr><td>Age (mean, SD)</td><td>19.6 +12.24</td><td>20.8 +12.29</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Divalproex sodium 500 or 1000mg/d</th><th>Placebo</th></tr>
<tr><td>N</td><td>122</td><td>115</td></tr>
<tr><td>N (analysis)</td><td>119</td><td>115</td></tr>
<tr><td>Drop outs</td><td>21
adverse events (10)
ineffectiveness (2)
loss to follow up (1)
non-compliance (3)
other (5)</td><td>14
adverse events (10)
ineffectiveness (1)
loss to follow up (1)
non-compliance (1)
other (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Extended release Divalproex sodium (Depakote) 500mg/d or 1000mg/d</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Methods</td><td>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.

2 week titration phase followed by 10 week treatment. During 1st week of titration participants received 500mg divalproex (or placebo). After week 1 of titration participants received 1000mg/d divalproex (or placebo). During 2nd week the investigator had the option or reducing the subject’s dose to 500mg/d for the remaining period if deemed necessary because of intolerance.

Treatment with symptomatic medications was allowed on as-needed basis for treatment of individual headaches during the study.</td></tr>
<tr><td>Length of follow up</td><td>12 weeks treatment duration</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Freitag FG, Collins SD, Carlson HA et al. (2002) A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology 58: 1652-9</td></tr>
<tr><td>Location</td><td>Not reported</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Serious adverse events
<table>
<tr><th></th><th>Divalproex 500 or 1000mg/d</th><th>Placebo</th></tr>
<tr><td>Incidence during treatment</td><td>2/122</td><td>4/115</td></tr>
</table>
Outcomes reported but not extracted: Change in migraine days (no measure of variability, such as standard deviation, reported so data not useable), Change in migraine frequency (no measure of variability, such as standard deviation, reported so data not useable), Migraine headache rate and days for last 4 weeks of treatment, baseline rescue medications used, specific adverse events.</td></tr>
<tr><td>Source of funding</td><td>Abbot Laboratories</td></tr>
<tr><td>Comments</td><td>Study does not report standard deviations for results relating to mean change in headache rate and days.

1 week termination phase followed the 12 week treatment phase. 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.</td></tr>
</table>

Table 26: Holroyd 2010

Bibliographic reference	**Holroyd KA, Cottrell CK, O'Donnell FJ et al. (2010) Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ 341: c4871**
Study type	Randomised controlled trial
Aim	To determine if the addition of preventive drug treatment (β blocker), brief behavioural migraine management, or their combination improves the outcome of optimised acute treatment in the management of migraine (behavioural management arm and combination therapy not extracted here).
Patient characteristics	**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 - Diary confirmed criteria for severity of migraine during the optimised acute treatment run-in of at least 3 migraines with disability per 30 days

<table>
<tr><td>Bibliographic reference</td><td>Holroyd KA, Cottrell CK, O'Donnell FJ et al. (2010) Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ 341: c4871</td></tr>
<tr><td></td><td>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 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

Baseline characteristics
<table>
<tr><th></th><th>B-blocker 40-180 mg/d</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>8/45</td><td>10/45</td></tr>
<tr><td>Age (mean, SD)</td><td>37.7 (10.1)</td><td>39.5 (10.2)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>B-blocker 40-180 mg/d</th><th>Placebo</th></tr>
<tr><td>N</td><td>53</td><td>55</td></tr>
<tr><td>N (ITT analysis)</td><td>53</td><td>55</td></tr>
<tr><td>Drop outs</td><td>28 (18 at 5 months follow up)</td><td>25 (15 at 5 months follow up)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>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).</td></tr>
<tr><td>Comparison</td><td>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 maintained to nadolol placebo. Participants initially received a</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Holroyd KA, Cottrell CK, O'Donnell FJ et al. (2010) Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ 341: c4871</td></tr>
<tr><td></td><td>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)

Additional comparators were Behavioural migraine management plus B blocker and behavioural migraine management and placebo (not extracted here as do not meet criteria for review).</td></tr>
<tr><td>Methods</td><td>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 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.</td></tr>
<tr><td>Length of follow up</td><td>12 months treatment duration</td></tr>
<tr><td>Location</td><td>Outpatient setting, USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in Migraine days
Migraine days defined as number of days with migraine per 30 days.
<table>
<tr><th></th><th>Propranolol or nadolol</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=8.6
SD=3.3
N=53</td><td>mean=8.4
SD=3.5
N=55</td></tr>
<tr><td>Change in migraine days – 5 months</td><td>mean=-3.9
95%CI=-4.2 to -3.5
SE=0.179*
SD=1.30*
N=53</td><td>mean=-3.3
95%CI=-3.6 to -3.0
SE=0.153*
SD=1.14*
N=55</td></tr>
<tr><td>Change in migraine days – 12 months</td><td>mean=-4.5
95%CI=-5.1 to -4.0
SD=1.11*
N=53</td><td>mean=-3.9
95%CI=-4.3 to -3.5
SD=1.51*
N=55</td></tr>
</table>
*calculated by reviewer from reported 95%CIs</td></tr>
</table>

Bibliographic reference	Holroyd KA, Cottrell CK, O'Donnell FJ et al. (2010) Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ 341: c4871

50% responder rate

'Responder' defined as participants with =>50% reduction in migraine frequency per 30 days in month 5 compared with baseline.

	Propranolol or nadolol	Placebo
>=50% reduction in migraines at month 5	18/35 (34%)	22/40 (40%)

Change in Migraine frequency

Migraine frequency defined as number migraine attacks per 30 days (with at least 24hr pain-free period between distinct attacks).

	Propranolol or nadolol	Placebo
Baseline migraines per 30 days	mean=5.2 SD=1.9 N=53	mean=5.5 SD=1.9 N=55
Change in number of migraines frequency – 5 months	mean=-2.1 95%CI=-2.2 to -1.9 SD=0.56* N=53	mean=-2.1 95%CI=-2.2 to -1.9 SD=0.57* N=55
Change in migraine frequency – 12 months	mean=-2.5 95%CI=-2.8 to -2.2 SD=1.11* N=53	mean=-2.5 95%CI=-2.6 to -2.3 SD=0.57* N=55

***calculated by reviewer from reported 95%Cis**

Migraine specific quality of life

	Propranolol or nadolol	Placebo
Baseline	N=40.3 SD=13.4	mean=40.3 SD=13.4

Bibliographic reference	**Holroyd KA, Cottrell CK, O'Donnell FJ et al. (2010) Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ 341: c4871**
	<table><tr><td></td><td>N=53</td><td>N=55</td></tr><tr><td>Change in quality of life at 5 months</td><td>mean=-7.1 95%CI=-7.7 to -6.6 SD=2.04* N=53</td><td>mean=-7.1 95%CI=-7.8 to -6.3 SD=2.84* N=55</td></tr><tr><td>Change in quality of life - 10 months</td><td>mean=-8.5 95%CI=-9.4 to -7.6 SD=3.34* N=53</td><td>mean=-8.8 95%CI=-9.5 to -8.1 SD=2.65* N=55</td></tr></table> ***calculated by reviewer from reported 95%Cis** **Outcomes reported but not extracted:** Resting heart rate at baseline, month 5, 10 and 16, adverse events (serious adverse events not reported separately).
Source of funding	National Institutes of Health provided primary support for the trial, Merck Pharmaceuticals and GlaxoSmithKline Pharmaceuticals donated triptans.
Comments	2 different beta blockers were used: at end of study 87% were taking propranolol and 13% were taking nadolol. Used and intention to treat analysis. Use of acute medication was permitted. A computer generated randomisation sequence was used; this was supplied in sealed opaque envelopes by statistician unconnected with study. Randomisation was stratified by sex and by site. The study was described as 'double blind'. Dropout rate was high (30.6% at 5 months, 49% at 10 months), although an intention to treat analysis was conducted which partly mitigates this.

Table 27: Klapper 1997, Green 2005

Bibliographic reference	**Klapper J (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study.[Erratum appears in Cephalalgia 1997 Nov;17(7):798]. Cephalalgia 17: 103-8** **Green MW, Giordano S, Jiang P et al. (2005) Effect of divalproex on metabolic parameters is dose related in migraine prophylaxis. Headache 45: 1031-7**
Study type	Randomised controlled trial

<table>
<tr><td>Bibliographic reference</td><td>Klapper J (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study.[Erratum appears in Cephalalgia 1997 Nov;17(7):798]. Cephalalgia 17: 103-8

Green MW, Giordano S, Jiang P et al. (2005) Effect of divalproex on metabolic parameters is dose related in migraine prophylaxis. Headache 45: 1031-7</td></tr>
<tr><td>Aim</td><td>To evaluate the efficacy and safety of divalproex sodium for monotherapy for migraine prophylaxis.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Migraine with or without aura (IHS classification) for at least 6 months
- Averaged >2 migraine attacks per month over last 3 months
- Aged >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.

Baseline characteristics
<table>
<tr><td></td><td colspan="3">Divalproex</td><td></td></tr>
<tr><td></td><td>1500mg/d</td><td>1000mg/d</td><td>500mg/d</td><td>Placebo</td></tr>
<tr><td>Sex (M/F)</td><td>*3/41</td><td>*5/38</td><td>*3/42</td><td>*4/40</td></tr>
<tr><td>Age (mean, range)</td><td>40.7 (23 to 76)</td><td>41.5 (21 to 70)</td><td>40.8 (17 to 65)</td><td>40.2 (19 to 67)</td></tr>
</table>
Calculated by reviewer from reported percentages</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td colspan="3">Divalproex</td><td></td></tr>
<tr><td></td><td>1500mg/d</td><td>1000mg/d</td><td>500mg/d</td><td>Placebo</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="5">Klapper J (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study.[Erratum appears in Cephalalgia 1997 Nov;17(7):798]. Cephalalgia 17: 103-8

Green MW, Giordano S, Jiang P et al. (2005) Effect of divalproex on metabolic parameters is dose related in migraine prophylaxis. Headache 45: 1031-7</td></tr>
<tr><td></td><td>N</td><td>44</td><td>43</td><td>45</td><td>44</td></tr>
<tr><td></td><td>N (ITT analysis)</td><td>44</td><td>40</td><td>45</td><td>42</td></tr>
<tr><td></td><td>Drop outs</td><td>13
ineffectiveness (0)
intolerance (11)
personal reasons (2)
non-compliance (0)
lost to follow up (0)</td><td>10
ineffectiveness (0)
intolerance (6)
personal reasons (2)
non-compliance (2)
lost to follow up (0)</td><td>6
ineffectiveness (0)
intolerance (6)
personal reasons (0)
non-compliance (0)
lost to follow up (0)</td><td>8
ineffectiveness (4)
intolerance (2)
personal reasons (1)
non-compliance (0)
lost to follow up (1)</td></tr>
<tr><td>Intervention 1</td><td colspan="5">Divalproex (DVPX Depakote) 1500mg/d</td></tr>
<tr><td>Intervention 2</td><td colspan="5">Divalproex (DVPX Depakote) 1000mg/d</td></tr>
<tr><td>Intervention3</td><td colspan="5">Divalproex (DVPX Depakote) 500mg/d</td></tr>
<tr><td>Comparison</td><td colspan="5">Placebo</td></tr>
<tr><td>Methods</td><td colspan="5">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.

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 4 days (every 8 days for 500mg) until the assigned dose achieved. Doses then remained fixed for study period.

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.</td></tr>
<tr><td>Length of follow up</td><td colspan="5">12 weeks treatment period</td></tr>
<tr><td>Location</td><td colspan="5">Not reported</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Klapper J (1997) Divalproex sodium in migraine prophylaxis: a dose-controlled study.[Erratum appears in Cephalalgia 1997 Nov;17(7):798]. Cephalalgia 17: 103-8

Green MW, Giordano S, Jiang P et al. (2005) Effect of divalproex on metabolic parameters is dose related in migraine prophylaxis. Headache 45: 1031-7</td></tr>
<tr><td>Outcomes measures and effect size</td><td>50% responder
50% responder defined as number of patients with >50% reduction in the number of migraine attacks per 4 weeks during treatment compared with baseline.
<table>
<tr><th></th><th>Divalproex 1500 mg/d</th><th>Divalproex 1000 mg/d</th><th>Divalproex 500 mg/d</th><th>Placebo</th></tr>
<tr><td>No. of participants with >50% reduction in migraine attacks during treatment phase</td><td colspan="3">57*/129 (not reported separately for each group)</td><td>9*/42</td></tr>
</table>
*calculated by reviewer from reported percentages

Outcomes reported but not extracted: Change in migraine frequency (no measure of variability such as standard deviation reported, so data not usable), No. of patients with >50% reduction in migraine attacks impairing usual activities, 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, no. of patients with >50% reduction in attacks requiring acute medication, specific adverse events (serious adverse events not reported separately).</td></tr>
<tr><td>Source of funding</td><td>Abbott Laboratories</td></tr>
<tr><td>Comments</td><td>Baseline 4 migraine attack characteristics are higher in the placebo arm than other arms. Randomisation and allocation concealment not reported.

Efficacy analyses based on the intent to treat dataset of all randomised patients providing headache data during experimental phase.</td></tr>
</table>

Table 28: Lakshmi 2007

Bibliographic reference	**Lakshmi CV, Singhi P, Malhi P et al. (2007) Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial. Journal of Child Neurology 22: 829-35**
Study type	Randomised controlled trial

<table>
<tr><td>Bibliographic reference</td><td>Lakshmi CV, Singhi P, Malhi P et al. (2007) Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial. Journal of Child Neurology 22: 829-35</td></tr>
<tr><td>Aim</td><td>To evaluate the safety and efficacy of topiramate for migraine prophylaxis in children.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria:
- Aged 8 to 14.
- Diagnosed with migraine with or without aura according to the 2004 International headache society criteria.
- Frequency of 2 or more migraines per month for the 3 months before entering the trial.
Exclusion criteria:
- Headaches other than migraine.
- Comorbid medical conditions.
- Already taking migraine prophylaxis.

Baseline characteristics
<table><tr><td></td><td>Topiramate</td><td>Placebo</td></tr><tr><td>Sex (M/F)</td><td>18/3</td><td>11/10</td></tr><tr><td>Age (mean, SD)</td><td>10.95 (1.53)</td><td>10.14 (1.35)</td></tr></table></td></tr>
<tr><td>Number of Patients</td><td><table><tr><td></td><td>Topiramate</td><td>Placebo</td></tr><tr><td>N</td><td>22</td><td>22</td></tr><tr><td>N (Analysis)</td><td>21</td><td>21</td></tr><tr><td>Drop outs</td><td>1</td><td>1</td></tr></table></td></tr>
<tr><td>Intervention</td><td>Topiramate 100mg/d or maximum tolerated dose</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Methods</td><td>How baseline data was collected (retrospectively or prospectively) is not described. The study started with a titration period of 4 weeks, where topiramate dose was increased by 25mg per week to 100mg/d or the maximum tolerated dose. This was followed by a maintenance phase of 12 weeks.</td></tr>
<tr><td>Length of follow up</td><td>12 treatment at maintenance dose.</td></tr>
<tr><td>Location</td><td>India, outpatient setting.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>50% responder
‘Responder’ defined as participants with =>50% reduction in migraine frequency per 28 days in treatment period compared with baseline.
<table><tr><td>Topiramate 100mg/d</td><td>Placebo</td></tr></table></td></tr>
</table>

Bibliographic reference	Lakshmi CV, Singhi P, Malhi P et al. (2007) Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial. Journal of Child Neurology 22: 829-35

20/21* (95.2%)	11/21* (52.4%)

***Calculated from reported percentages by reviewer**

Change in migraine frequency

Migraine frequency was defined as the number of migraine attacks per 28 days.

	Topiramate 100mg/d	**Placebo**
Baseline	mean=16.14 SD=9.35 N=21	mean=13.38 SD=7.48 N=21
During treatment	mean=4.27 SD=1.95 N=21	mean=7.48 SD=5.94 N=21
Change in migraine frequency	mean=-11.87* SD=8.54* N=21	mean=-5.9* SD=6.84* N=21

***data imputed by reviewer from baseline and endpoint data**

Quality of life - PedMIDAS

	Topiramate 100mg/d	**Placebo**
Baseline	mean=50.66 SD=32.1 N=21	mean=42.66 SD=27.5 N=21
End of study	mean=10.42 SD=6.39 N=21	mean=23.7 SD=19.1 N=21
Change in Quality of life	mean=-40.24* SD=29.43* N=21	mean=-18.96* SD=24.80* N=21

***data imputed by reviewer from baseline and endpoint data**

Bibliographic reference	**Lakshmi CV, Singhi P, Malhi P et al. (2007) Topiramate in the prophylaxis of pediatric migraine: a double-blind placebo-controlled trial. Journal of Child Neurology 22: 829-35**
	Outcomes reported but not extracted: Adverse events (serious adverse events not reported separately), Migraine duration, Body weight, School absenteeism, Migraine severity (no effect size reported – just reported as 'not significantly different'), Acute medication use (no effect size reported – just reported as 'not significantly different')
Source of funding	Not reported.
Comments	Randomisation was by use of random number tables. The original sequence and the code numbers were placed in sealed envelopes and opened other after the data analysis was completed. Participants, parents and investigators (baseline and follow up) were all blind to treatment allocation. The drug and placebo were similar in appearance, packing taste and other factors. Details of how baseline data was collected is not reported. Analysis was per protocol, but because there was only 1 dropout per group, this is unlikely to have impacted the results. Potential reporting bias – effect sizes not reported for outcomes that were not significantly different (severity and acute medication use)

Table 29: Lewis 2009

Bibliographic reference	**Lewis D, Winner P, Saper J et al. (2009) Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics 123: 924-34**
Study type	Randomised controlled trial
Aim	To evaluate the efficacy and safety of topiramate for migraine prophylaxis for migraine prevention in adolescents.
Patient characteristics	**Inclusion criteria**: - Aged between 12 and 17 years - History of migraine (IHS criteria for paediatric migraine) for > 6 months - Average of 3 to 12 migraine episodes on no more than 14 headache days (migraine and non-migraine) 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

<table>
<tr><td>Bibliographic reference</td><td>Lewis D, Winner P, Saper J et al. (2009) Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics 123: 924-34</td></tr>
<tr><td></td><td>
- Participants had taken flunarizine within the 4 months before study screening, were taking non-stable doses of psychostimulant or used corticosteroids, local anaesthetics or Botox for migraine, or had a history of using antipsychotics or centrally acting sympathomimetics in non-stable doses
- Baseline serum ammonia levels >2 times upper limit of normal
- History of any condition that could have impaired reliable participation in the study.

Baseline characteristics
<table>
<tr><td></td><td colspan="2">Topiramate</td><td></td></tr>
<tr><td></td><td>100mg/d</td><td>50mg/d</td><td>Placebo</td></tr>
<tr><td>Sex (M/F)</td><td>18/17</td><td>10/25</td><td>12/21</td></tr>
<tr><td>Age (mean, SD)</td><td>14.2+1.5</td><td>14.2+1.6</td><td>14.4+1.7</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td colspan="2">Topiramate</td><td></td></tr>
<tr><td></td><td>100mg/d</td><td>50mg/d</td><td>Placebo</td></tr>
<tr><td>N</td><td>35</td><td>35</td><td>33</td></tr>
<tr><td>N (ITT analysis)</td><td>35</td><td>35</td><td>33</td></tr>
<tr><td>Drop outs</td><td>5
subject choice (1)
adverse event (3)
other (1)</td><td>6
loss to follow up (1)
adverse event (3)
other (2)</td><td>6
subject choice (1)
adverse event (1)
pregnancy (1)
lack of efficacy (2)
other (2)</td></tr>
</table>
</td></tr>
<tr><td>Intervention 1</td><td>Topiramate 100mg/d, Mean +SD daily dose actually taken = 73.6 +18.7mg/d (91% achieved target dose, 51% taking target dose at end of study)</td></tr>
<tr><td>Intervention 2</td><td>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)</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Methods</td><td>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.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Lewis D, Winner P, Saper J et al. (2009) Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics 123: 924-34</td></tr>
<tr><td></td><td>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 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 permitted included non-prescription analgesics, NSAIDs, ergot derivatives, triptans and dihydroergotamine mesylate. Treatment could not exceed 14 days per month.</td></tr>
<tr><td>Length of follow up</td><td>16 week treatment period</td></tr>
<tr><td>Location</td><td>Multicentre study (31 US and non-US sites)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in Migraine days
Migraine days defined as number of days with migraine per month. 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.
<table>
<tr><td></td><td colspan="3">Topirmate</td><td></td></tr>
<tr><td></td><td>100 mg/d</td><td>50 mg/d</td><td>Combined doses***</td><td>Placebo</td></tr>
<tr><td>Baseline</td><td>mean=6.9
SD=3.02
N=35</td><td>mean=6.4
SD=2.86
N=35</td><td></td><td>mean=6.1
SD=3.02
N=33</td></tr>
<tr><td>Last 4 weeks of treatment at target dose</td><td>mean=2.0
SD=2.86
N=35</td><td>mean=2.8
SD=3.33
N=35</td><td></td><td>mean=3.5
SD=3.47
N=33</td></tr>
<tr><td>Change in migraine days</td><td>mean=-4.9*
SD=2.94*
SE=0.497**
N=35</td><td>mean=-3.6*
SD=3.12*
SE=0.527**
N=35</td><td>mean=-4.25
SD=3.08
N=70</td><td>mean=2.6*
SD=3.27*
0.553**
N=33</td></tr>
</table>
*data imputed by reviewer from baseline and endpoint data
**calculated by reviewer from reported standard deviations for purpose of network meta-analysis</td></tr>
</table>

Bibliographic reference	**Lewis D, Winner P, Saper J et al. (2009) Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics 123: 924-34**

***** calculated by reviewer**

50% responder

50% responder defined as participants achieving >50% reduction in mean monthly migraine frequency during last 12 weeks of treatment at target dose compared with baseline.

Topiramate			
100 mg/d	**50 mg/d**	**Combined dose****	**Placebo**
29*/35 (83%)	16*/35 (46%)	45/70 (64.3%)	15*/33 (45%)

***calculated by reviewer from reported percentages**

****calculated by reviewer for purpose of analysis**

Change in Migraine frequency

Migraine frequency defined as number of migraine episodes per month. Migraine episode defined as all recurrences of migraine symptoms within 48 hours of onset.

	Topiramate			
	100 mg/d	**50 mg/d**	**Combined doses****	**Placebo**
Baseline	mean=4.3 SD=1.59 N=35	mean=4.1 SD=1.74 N=35		mean=4.1 SD=1.48 N=33
Last 4 weeks of treatment at target dose	mean=1.1 SD=1.53 N=35	mean=1.9 SD=1.95 N=35		mean=2.1 SD=2.03 N=33
Change in migraine frequency	mean=-3.2* SD=1.56* N=35	mean=-2.2* SD=1.85* N=35	mean=-2.7 SD=1.76 N=70	mean=2.0* SD=1.82 * N=33

***data imputed by reviewer from baseline and endpoint data**

****calculated by reviewer for purpose of analysis**

Bibliographic reference	**Lewis D, Winner P, Saper J et al. (2009) Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics 123: 924-34**
	Outcomes reported but not extracted: 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)
Source of funding	National Institutes of Health, Ortho-McNeil Janssen Scientific Affairs
Comments	Method of randomisation and allocation concealment were unclear. Study described as 'double blind' but details of blinding not reported. 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 at least 1 post-baseline efficacy assessment.

Table 30: Lipton 2011

Bibliographic reference	**Lipton RB, Silberstein S, Dodick D et al. (2011) Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia 31: 18-30**
Study type	Randomised controlled trial
Aim	To evaluate whether topiramate prevents development of chronic daily headache in a population with high-frequency episodic migraine. A secondary objective was to assess topiramate as a preventative treatment in this population.
Patient characteristics	**Inclusion criteria**: - Aged 18-65 - 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

Bibliographic reference	**Lipton RB, Silberstein S, Dodick D et al. (2011) Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia 31: 18-30**

- 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 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/mm3 or 2x ULN, platelet count <80,000/mm3, 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, propoxyphene or alcohol.

Baseline characteristics

	Topiramate 100mg/d	**Placebo**
Sex (M/F)	21/138	15/156
Age (mean, SD)	39.6 (10.6)	40.9 (11.2)

Number of Patients

	Topiramate 100mg/d	**Placebo**
N	188	197
N (ITT analysis)	177	175
Dropouts	69 Lost to follow up (25) Limiting adverse event (21) Subject choice (11) Lack of efficacy (6) Significant protocol violation (2)	86 Lost to follow up (29) Limiting adverse event (18) Subject choice (22) Lack of efficacy (8) Significant protocol violation (5)

Bibliographic reference	**Lipton RB, Silberstein S, Dodick D et al. (2011) Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia 31: 18-30**
	other (4) / other (4)
Intervention	Topiramate 100mg (2 x 25mg tablets twice per day) Mean daily dose actually taken = 89.5+14.2 mg/d
Comparison	Placebo Mean daily dose actually taken = 90.5+14.9 mg/d
Methods	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. Topiramate doses started at 25mg/d and increased by 25mg weekly (for a total of 6 weeks) until participants 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.
Length of follow up	26 weeks treatment duration
Location	Multicentre study (87 sites)
Outcomes measures and effect size	**Change in migraine days** Migraine days defined as number of days with migraine per 28 days.

	Topiramate 100 mg/d	**Placebo**
Baseline	mean=11.6 SD=2.0 N=159	mean=11.8 SD=2.2 N=171
Change in migraine days during treatment	mean=-6.6 SD=3.5 SE=0.278* N=159	mean=-5.3 SD=3.6 SE=0.275* N=171

***calculated by reviewer from reported standard deviations for purpose of network meta-analysis**

Migraine specific quality of life - MIDAS

	Topiramate 100 mg/d	**Placebo**
Change in Migraine disability assessment score from baseline during treatment (MIDAS)	mean=-29.7 SD=33.05 N=159	mean=-22.6 SD=36.89 N=171

Bibliographic reference	**Lipton RB, Silberstein S, Dodick D et al. (2011) Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia 31: 18-30**

Change in use of acute medication

Acute medication use was defined as number of days with acute medication use per 28 days.

	Topiramate 100 mg/d	**Placebo**
Baseline	mean=8.6 SD=3.2 N=159	mean=8.6 SD=3.5 N=171
Change in acute medication use during treatment	mean=-4.8 SD=3.5 N=159	mean=-3.8 SD=3.7 N=171

Serious adverse events

Topiramate 100 mg/d	**Placebo**
3/176	5/185

***calculated by reviewer**

Outcomes reported but not extracted: Number reporting >15 headache days per month, 50% responder (no number per group or effect size reported), Headache (not specifically migraine) days per 28 days, 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

Source of funding	Ortho McNeil Janssen Scientific Affairs
Comments	Participants were assigned to groups by a predetermined computer-generated randomisation schedule that was prepared before the study. Medication code numbers were also pre-printed on study medication and participants were allocated medication according to the randomisation schedule. Participants and clinicians were blind to group allocation. Tablets were identical in appearance and number. Study reports “approximately 10% of subjects had baseline migraine rates <9 or >15 per month”, but this was an exclusion criteria. The efficacy population for this study was defined as randomised subjects who had 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.

Bibliographic reference	**Lipton RB, Silberstein S, Dodick D et al. (2011) Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia 31: 18-30**
	The dropout rate was high (40.3%) and higher in the placebo group than the topiramate group. 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.

Table 31: Mansoureh 2008

Bibliographic reference	**Mansoureh T, Rahmat JM, Nilavari K et al. (2008) Cinnarizine in refractory migraine prophylaxis: Efficacy and tolerability. A comparison with Divalproex. Journal of Headache and Pain 9: 77-82**
Study type	Randomised controlled trial
Aim	To assess the efficacy and safety of cinnarizine in patients with migraine refractory to propranolol and tricyclic antidepressants in comparison with Divalproex.
Patient characteristics	**Inclusion criteria**: - Aged 16-60 years - 3-10 migraine attacks per month for the last 2 months - Migraine (with or without aura as defined by international headache society criteria) present for at least 1 year - Onset of migraine before age of 50 - Migraine refractory to all previous prophylaxis including propranolol and tricyclics (no further details of how this was assessed provided) **Exclusion criteria:** - Use of prophylactic migraine therapy in previous month - Previous or current history of alcohol or drug addiction - Interval headaches - Extra pyramidal disorders - Serious disease - Pregnancy or lactation - Child bearing potential without adequate contraception - Hypersensitivity to cinnarizine or valproate **Baseline characteristics:**

	Cinnarizine (N=67)	**Divalproex (N=58)**
Sex (M/F)	11/56	13/45

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Mansoureh T, Rahmat JM, Nilavari K et al. (2008) Cinnarizine in refractory migraine prophylaxis: Efficacy and tolerability. A comparison with Divalproex. Journal of Headache and Pain 9: 77-82</td></tr>
<tr><td></td><td colspan="2"><table>
<tr><td>Age (mean, range)</td><td>34.5 (13-60)</td><td>33.6 (16-55)</td></tr>
<tr><td>Attack frequency per month (mean, range)</td><td>7.4 (3-10)</td><td>6.9 (3-10)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="2"><table>
<tr><th></th><th>Cinnarizine</th><th>Divalproex</th></tr>
<tr><td>N</td><td>67</td><td>58</td></tr>
<tr><td>N (ITT analysis)</td><td>67</td><td>58</td></tr>
<tr><td>Dropouts</td><td>25</td><td>21</td></tr>
</table></td></tr>
<tr><td>Intervention 1</td><td colspan="2">Cinnarizine 75mg per day</td></tr>
<tr><td>Intervention 2</td><td colspan="2">Divalproex sodium 600 mg per day</td></tr>
<tr><td>Methods</td><td colspan="2">Baseline phase: 4 weeks with no prophylactic treatment. Acute treatment was allowed to control attacks.
Treatment phase: 12 weeks. Patients reported outcomes in headache diary. Not reported whether acute medication was permitted.</td></tr>
<tr><td>Length of follow up</td><td colspan="2">12 weeks treatment phase. No further follow up.</td></tr>
<tr><td>Location</td><td colspan="2">Iran, Neurology department</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="2">50% responder (decrease of > 50% migraine frequency compared to baseline)<table>
<tr><th>Cinnarizine</th><th>Divalproex</th></tr>
<tr><td>41/67</td><td>37/58</td></tr>
</table>
Outcomes reported but not extracted: Migraine frequency (standard deviations not reported in baseline period, so not possible to calculate variability in change from baseline), Migraine intensity (standard deviations not reported in baseline period, so not possible to calculate variability in change from baseline), Number of days without attack, Time between consecutive attacks, adverse events (serious adverse events not reported separately).</td></tr>
<tr><td>Source of funding</td><td colspan="2">Not reported</td></tr>
<tr><td>Comments</td><td colspan="2">Block randomisation in groups of 6 (no further details of randomisation procedure). Patient and clinician were blinded. No details of procedures for allocation concealment, but likely to be maintained given patient and clinician were blinded. Tablets were similar but not identical in appearance. High dropout rates (average 37%) but similar across groups. Analysis was per protocol.</td></tr>
</table>

Table 32: Mathew 1995

<table>
<tr><td>Bibliographic reference</td><td>Mathew NT, Saper JR, Silberstein SD et al. (1995) Migraine prophylaxis with divalproex. Archives of Neurology 52: 281-6</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To compare the effectiveness and safety of divalproex sodium and placebo in the prophylaxis of migraine headache.</td></tr>
<tr><td>Patient characteristics</td><td>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.

Baseline characteristics
<table>
<tr><th></th><th>Divalproex 500 or 1000mg/d</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>14/56</td><td>16/21</td></tr>
<tr><td>Age (mean)</td><td>47</td><td>43</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Divalproex 500 or 1000mg/d</th><th>Placebo</th></tr>
<tr><td>N</td><td>70</td><td>37</td></tr>
<tr><td>N (analysis)</td><td>69</td><td>36</td></tr>
<tr><td>Dropouts</td><td>12
intolerance to study medication (9) loss to follow up (2)
ineffective treatment (1)</td><td>5
intolerance to study medication (2)
intercurrent illness (1)
non-compliance (1)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Mathew NT, Saper JR, Silberstein SD et al. (1995) Migraine prophylaxis with divalproex. Archives of Neurology 52: 281-6</td></tr>
<tr><td></td><td></td><td></td><td>personal reasons (1)</td></tr>
<tr><td>Intervention</td><td colspan="3">Divalproex sodium (Depakote) 500mg/d or 1000mg/d</td></tr>
<tr><td>Comparison</td><td colspan="3">Placebo</td></tr>
<tr><td>Methods</td><td colspan="3">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.

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.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">12 weeks</td></tr>
<tr><td>Location</td><td colspan="3">United states (multi-site headache/neurology clinics)</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">50% Responder rate
Number achieving >50% reduction in migraine frequency per 4 weeks in treatment period compared with baseline
<table>
<tr><th>Sodium valproate</th><th>Placebo</th></tr>
<tr><td>33/69</td><td>5/36</td></tr>
</table>
Migraine frequency
<table>
<tr><th></th><th>Divalproex 500mg/d or 1000mg/d</th><th>Placebo</th></tr>
<tr><td>Number of migraines per 28 days (baseline)</td><td>mean=6.0
SE=0.25*
SD=2.08**
N=69</td><td>mean=6.4
SE=0.25*
SD=1.5**
N=36</td></tr>
<tr><td>Number of migraines per 28 days (Last 4 weeks of treatment)</td><td>mean=3.0*
SE=0.2*
SD=1.55**
N=60</td><td>mean=5.7*
SE=0.25*
SD=1.41**
N=32</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Mathew NT, Saper JR, Silberstein SD et al. (1995) Migraine prophylaxis with divalproex. Archives of Neurology 52: 281-6**
	Change in number of migraines per 28 days after treatment compared with baseline: mean=-3.00*** SD=1.87*** N=60 vs mean=-0.7*** SD=1.46*** N=32 ***Estimated by reviewer from figure** ****Standard deviations calculated by reviewer from reported standard errors** *****data imputed by reviewer from baseline and endpoint data** **Outcomes reported but not extracted:** Migraine days (no measure of variability such as standard deviation reported, therefore result not useable in analysis), migraine duration (no measure of variability such as standard deviation reported, therefore result not useable in analysis), migraine intensity (no measure of variability such as standard deviation reported, therefore result not useable in analysis), Migraine intensity related to functional ability, Frequency of migraine with nausea, vomiting, aura, photophobia, phonophobia; specific adverse events.
Source of funding	Abbot Laboratories
Comments	Detail of randomisation and allocation concealment not reported. Study described as 'double blind' but details of blinding not provided. Analysis was per protocol, but drop-out rate was relatively low (<15%) and similar across groups, so unlikely to have had an impact.

Table 33: Mei 2004

Bibliographic reference	**Mei D, Capuano A, Vollono C et al. (2004) Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. Neurological Sciences 25: 245-50**
Study type	Randomised controlled trial
Aim	To evaluate the efficacy and tolerability of topiramate in the prophylactic treatment of migraine.
Patient characteristics	**Inclusion criteria**: - Diagnosis of migraine with and without aura according to 1988 IHS criteria. - Frequency of crises ranging from 2 to 6 per month. - Subjects on continuing medication for other pathologies were included and did not modify the dosages during the study. **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.

<table>
<tr><td>Bibliographic reference</td><td>Mei D, Capuano A, Vollono C et al. (2004) Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. Neurological Sciences 25: 245-50</td></tr>
<tr><td></td><td>- 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.

Baseline characteristics
<table>
<tr><th></th><th>Topiramate 100mg</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>16/19</td><td>17/20</td></tr>
<tr><td>Age (mean, SD)</td><td>39.74 (12.02)</td><td>38.7 (11.04)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Topiramate 100mg</th><th>Placebo</th></tr>
<tr><td>N</td><td>58</td><td>57</td></tr>
<tr><td>N (analysis)</td><td>35</td><td>37</td></tr>
<tr><td>Dropouts</td><td>23</td><td>20</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Topiramate 100mg/d</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Methods</td><td>In the month preceding the trial 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. Topiramate 25mg/day initially was 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</td></tr>
<tr><td>Length of follow up</td><td>12 weeks treatment at maintenance dose.</td></tr>
<tr><td>Location</td><td>Headache clinic, Italy</td></tr>
<tr><td>Outcomes measures and effect size</td><td>50% responder rate
Number with >=50% reduction in migraine frequency between baseline and last 4 weeks of treatment
<table>
<tr><th>Topiramate 100mg</th><th>Placebo</th></tr>
<tr><td>22/35* (63%)</td><td>8/37* (21%)</td></tr>
</table>
*calculated by reviewer from reported percentages

Outcomes reported but not extracted: Migraine frequency (no measure of variability, such as standard deviation reported, so data not usable), Use of acute medication (no measure of variability, such as standard deviation reported for placebo arm, so data not usable), mean cumulative migraine rate at baseline, 4, 8, 12 and 16 weeks Number of days of</td></tr>
</table>

Bibliographic reference	**Mei D, Capuano A, Vollono C et al. (2004) Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. Neurological Sciences 25: 245-50**
	disability (subject absent from work/ unable to do all non-work activities) at baseline, 4, 8,12 and 16 weeks.
Source of funding	Not reported
Comments	Appears to be a per-protocol analysis – there was a high drop-out rate in both groups, and so this is a potential source of bias Randomisation was in a 1/1 ratio with balanced blocks of 2 using a computer- generated random number scheme. Allocation concealment was unclear. The study is described as 'double blind' but details of blinding are not reported.

Table 34: Nadelmann 1986

Bibliographic reference	**Nadelmann JW, Phil M, Stevens J et al. (1986) Propranolol in the prophylaxis of migraine. Headache 26: 175-82**
Study type	Randomised controlled trial
Aim	To assess the efficacy of propranolol for migraine prophylaxis.
Patient characteristics	**Inclusion criteria:** - Fulfilled criteria for classic or common migraine as specified by the ad hoc committee for classification of headache. - History of at least 4 migraine headaches per month. - At least 4 headaches per month in the baseline period. **Exclusion criteria:** - Any other type of migraine other than classic or common. - Any other type of headache known to be associated with migraine. - Contraindications to beta-blockers. **Baseline characteristics** **Not reported separately for each group.**

Sex (M/F)	9/53
Age (range)	18-60

Number of Patients

	Propranolol	**Placebo**
N	28	29
N (analysis)	27	24
Drop outs	1	5

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Nadelmann JW, Phil M, Stevens J et al. (1986) Propranolol in the prophylaxis of migraine. Headache 26: 175-82</td></tr>
<tr><td></td><td colspan="3"><table><tr><td></td><td>Reasons for dropout not reported separately for each phase in the crossover trial</td><td>Reasons for dropout not reported separately for each phase in the crossover trial</td></tr></table></td></tr>
<tr><td>Intervention 1</td><td colspan="3">Propranolol 60 to 320mg/d</td></tr>
<tr><td>Comparison</td><td colspan="3">Placebo</td></tr>
<tr><td>Methods</td><td colspan="3">This was a randomised crossover trial, although only the first phase of the trial is reported here. The trial started with a 4 week baseline phase to establish baseline measures followed by a dose finding period, where propranolol dose was established. All patients started on a dose of 80mg/d and adjusted upwards to a maximum of 320mg/d. Downward adjustment was also permitted if ‘clinically warranted’. Following the dose finding period, participants were randomised to receive propranolol or placebo for 12 weeks. The participants crossed over treatment for a further 12 weeks (no washout period). The second phase of the cross over trial is not reported here. Use of acute medication for migraine was permitted.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">12 weeks</td></tr>
<tr><td>Location</td><td colspan="3">USA, type of setting not reported</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Use of acute medication
Medication to treat migraine was given a score (simple analgesic: 1 unit, narcotic: 2 units, Ergot compound: 3 units). A ‘relief medication unit’ was index was calculated as the number of relief medication units divided by the total number of days.<table><tr><td></td><td>Propranolol 60-320mg/d</td><td>Placebo</td></tr><tr><td>End of baseline phase (unclear over what period measurement was over)</td><td colspan="2">Not reported separately for each group
mean=3.39
SD=1.92
N=64</td></tr><tr><td>Change at 12 weeks of treatment (unclear over what period measurement was over)</td><td>mean=-0.80
SD=2.15
N=27</td><td>mean=-1.36
SD=2.20
N=24</td></tr></table>
Outcomes reported but not extracted: Headache unit index (HUI), weight, heart rate, blood pressure, side effects (severe adverse events not reported separately).</td></tr>
<tr><td>Source of funding</td><td colspan="3">Not reported</td></tr>
<tr><td>Comments</td><td colspan="3">Treatment allocation was randomly assigned, although the details of randomisation method are not reported. Methods to</td></tr>
</table>

Bibliographic reference	Nadelmann JW, Phil M, Stevens J et al. (1986) Propranolol in the prophylaxis of migraine. Headache 26: 175-82
	ensure allocation concealment are not reported. The treatment phase of the trial is described as double blind, although one investigator (responsible for titration of drugs to target doses) was unblinded.

Table 35: Pradalier 1989

Bibliographic reference	Pradalier A, Serratrice G, Collard M et al. (1989) Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. Cephalalgia 9: 247-53
Study type	Randomised controlled trial
Aim	To evaluate the efficacy and safety of long-acting propranolol in the prophylactic treatment of migraine.
Patient characteristics	**Inclusion criteria**: - Migraine for at least 2 years with or without aura according to 1988 IHS classification. - Age 18-65 years. - Duration of symptoms 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. - Bradycardia of <50 beats/min - Raynaud phenomenon - High blood pressure. - Resistant to 2 previously well-followed prophylactic treatments **Baseline characteristics**

	Propranolol 160mg/d	Placebo
Sex (M/F)	9/31	9/25
Age (mean, SD)	37.1 (1.7)	37.7 (1.8)

Number of Patients

	Propranolol 160mg/d	Placebo
N	40 (31 entered treatment phase)	34 (24 entered treatment phase)
N (analysis)	22	19
Dropouts	9	5

Intervention	Long-acting propranolol, oral capsule (160mg) once daily at lunch time, for 12 weeks

<table>
<tr><td>Bibliographic reference</td><td>Pradalier A, Serratrice G, Collard M et al. (1989) Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. Cephalalgia 9: 247-53</td></tr>
<tr><td>Comparison</td><td>placebo, oral capsule once daily at lunch time, for 12 weeks</td></tr>
<tr><td>Methods</td><td>All patients completed a 4 week placebo run-in period followed by a 12 week treatment period. Could take their usual medication to alleviate migraine attacks</td></tr>
<tr><td>Length of follow up</td><td>12 weeks treatment</td></tr>
<tr><td>Location</td><td>Multicentre, France</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in migraine frequency
Migraine frequency defined as number of ‘crises’ per month (crisis not defined).
<table>
<tr><th></th><th>Propranolol 160mg/d</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=6.11
SD=0.93
N=35*</td><td>mean=6.00
SD=1.37
N=27*</td></tr>
<tr><td>Month preceding day 84 of treatment</td><td>mean=3.15
SD=0.77
N=22*</td><td>mean=6.41
SD=1.70
N=19*</td></tr>
<tr><td>Change in migraine frequency</td><td>mean=-2.96**
SD=0.86**
N=22*</td><td>mean=+0.41**
SD=1.56**
N=19*</td></tr>
</table>
*number of participants not reported for this outcome – inferred by reviewer from number reported for outcome ‘heart rate’.
**data imputed by reviewer from baseline and endpoint data

Outcomes reported but not extracted: 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, adverse events (serious adverse events not reported separately).</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Randomisation method unclear. Allocation concealment unclear. Unclear missing data. Crisis not defined.

Reported that the analysis was based on ITT principle but it is unclear that this was the case (no details provided and number of participants reported in analysis are consistent with per protocol analysis).</td></tr>
</table>

Table 36: Schellenberg 2007

Bibliographic reference	**Schellenberg R, Lichtenthal A, Wohling H et al. (2008) Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? Headache 48: 118-25**
Study type	Randomised controlled trial
Aim	To evaluate the efficacy of nebivolol and metoprolol for the prophylactic treatment of migraine.
Patient characteristics	**Inclusion criteria:** - Diagnosis of migraine with or without aura (ICHD-II codes 1.1-1.2). - Aged 18 – 65 years. - Minimum of 1 year history of migraine. - Onset before the age of 50. - Written record of attacks for the previous 3 months. - Minimum of 2 attacks per month for the previous 3 months. - 2 to 6 migraines in month before baseline period. - Adequate acute symptomatic relief of attacks. - Current contraception accepted and to remain unchanged during trial. **Exclusion criteria:** - Prophylactic migraine treatment in the last 3 months. - Concomitant beta blocker for calcium antagonist use. - Concomitant non-drug migraine treatment. - Use of acute treatment for more than 10 days per month. - Change of current acute migraine treatment. - History of sensitivity to nebivolol or metoprolol. - History of alcohol or controlled substance abuse. - Pregnancy or breast feeding. - Fecund females without contraception. - Congestive heart failure or any serious cardiological condition. - Heart rate < 50 bpm. - Systolic blood pressure <100mmHg. - Peripheral arterial occlusive disease. - Uncontrolled diabetes mellitus. - History of bronchospasm. - Clinically relevant abnormal laboratory values. - Participation in another trial in the last 30 days.

<table>
<tr><td>Bibliographic reference</td><td>Schellenberg R, Lichtenthal A, Wohling H et al. (2008) Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? Headache 48: 118-25</td></tr>
<tr><td></td><td>- Any other severe condition.

Baseline characteristics
<table>
<tr><th></th><th>Metoprolol</th><th>Nebivolol</th></tr>
<tr><td>Sex (M/F)</td><td>0/13</td><td>4/12</td></tr>
<tr><td>Age (mean, SD)</td><td>41 (7)</td><td>38 (13)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Metoprolol</th><th>Nebivolol</th></tr>
<tr><td>N</td><td>14</td><td>16</td></tr>
<tr><td>N (ITT analysis)</td><td>14</td><td>16</td></tr>
<tr><td>Drop outs</td><td>1 (reason not reported)</td><td>1 (reason not reported)</td></tr>
</table></td></tr>
<tr><td>Intervention 1</td><td>Metoprolol 142.5mg/d</td></tr>
<tr><td>Comparison</td><td>Nebivolol 5mg/d</td></tr>
<tr><td>Methods</td><td>The first 12 weeks of the study were to determine eligibility, the last 3 weeks of which was used as a 4 week baseline period. After baseline there was a 2-week titration period for metoprolol (not required for nebivolol). This was followed by 14 weeks of treatment at the target dose for both drugs, and then a 2-week down-titration period (not used in analysis). Acute analgesia was permitted and monitored as an outcome.</td></tr>
<tr><td>Length of follow up</td><td>14 weeks treatment at target dose</td></tr>
<tr><td>Location</td><td>Germany, outpatient setting</td></tr>
<tr><td>Outcomes measures and effect size</td><td>50% responder rate
‘Responder’ defined as participants with 50% reduction in the number of attacks from baseline to last 4 weeks of treatment.
<table>
<tr><th>Metoprolol 142.5mg/d</th><th>Nebivolol 5mg/d</th></tr>
<tr><td>8/14* (57%)</td><td>8/16* (50%)</td></tr>
</table>
*calculated by reviewer from reported percentages

Change in migraine frequency
Migraine frequency defined as the number of attacks in 4 weeks.
<table>
<tr><th></th><th>Metoprolol 142.5mg/d</th><th>Nebivolol 5mg/d</th></tr>
<tr><td>Baseline</td><td>mean=3.4
SD=1.0</td><td>mean=3.3
SD=1.0</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Schellenberg R, Lichtenthal A, Wohling H et al. (2008) Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? Headache 48: 118-25

	N=14	N=16
Last 4 weeks of treatment	mean=1.3 SD=1.0 N=14	mean=1.6 SD=1.5 N=16
Change in migraine frequency	mean=-2.1* SD=1.0* N=14	mean=-1.7* SD=1.32* N=16

***data imputed by reviewer from baseline and endpoint data**

Quality of life – SF36

	Metoprolol 142.5mg/d	**Nebivolol 5mg/d**
Baseline – Physical health	mean=37 SD=8 N=14	mean=39 SD=11 N=16
End of treatment – Physical health	mean=46 SD=7 N=14	mean=50 SD=10 N=16
Change in quality of life (physical health)	mean=+9* SD=7.55* N=14	mean=+11* SD=10.54* N=16
Baseline – Mental health	mean=39 SD=11 N=14	mean=37 SD=11 N=16
End of treatment – Mental health	mean=48 SD=8 N=14	mean=45 SD=13 N=16
Change in quality of life (mental health)	mean=+9* SD=9.85* N=14	mean=+8* SD=12.12* N=16

***data imputed by reviewer from baseline and endpoint data**

Bibliographic reference	**Schellenberg R, Lichtenthal A, Wohling H et al. (2008) Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? Headache 48: 118-25**
	Outcomes reported but not extracted: Patients using pain medication at endpoint (no baseline data available to calculate change in acute medication use), severity at endpoint (no baseline data available to calculate change in severity), attacks during weeks 0-4, duration of migraine attacks, adverse events (serious adverse events not reported separately), global impression, Quality of life (MIDAS) – no mean scores reported, only numbers of participants in each category.
Source of funding	Berlin-Chemie AG (support for 1st author)
Comments	Randomisation was computer-generated in blocks of 4. Details of allocation concealment are not reported, but the study is described as 'double blind' and so is likely to have occurred. Drugs were identical and placebo tablets were used to ensure that all participants received the same number of tablets at all treatment phases.

Table 37: Silberstein 2004

Bibliographic reference	**Silberstein SD, Neto W, Schmitt J et al. (2004) Topiramate in migraine prevention: results of a large controlled trial. Archives of Neurology 61: 490-5** **Silberstein SD (2003) Efficacy and safety of topiramate in migraine prevention: A dose-ranging, placebo-controlled, double-blind, multicenter trial. Advanced Studies in Medicine 3: S565-S568** **Silberstein SD, Loder E, Forde G et al. (2006) The impact of migraine on daily activities: effect of topiramate compared with placebo. Current Medical Research & Opinion 22: 1021-9**
Study type	Randomised controlled trial
Aim	To assess the efficacy and safety of topiramate as a migraine-preventive therapy.
Patient characteristics	**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),

<table>
<tr><td>Bibliographic reference</td><td>Silberstein SD, Neto W, Schmitt J et al. (2004) Topiramate in migraine prevention: results of a large controlled trial. Archives of Neurology 61: 490-5

Silberstein SD (2003) Efficacy and safety of topiramate in migraine prevention: A dose-ranging, placebo-controlled, double-blind, multicenter trial. Advanced Studies in Medicine 3: S565-S568

Silberstein SD, Loder E, Forde G et al. (2006) The impact of migraine on daily activities: effect of topiramate compared with placebo. Current Medical Research & Opinion 22: 1021-9</td></tr>
<tr><td></td><td>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.

Baseline characteristics
<table>
<tr><td></td><td colspan="3">Topiramate</td><td></td></tr>
<tr><td></td><td>200mg/d</td><td>100mg/d</td><td>50mg/d</td><td>Placebo</td></tr>
<tr><td>Sex (M/F)</td><td>18/94</td><td>13/112</td><td>10/107</td><td>12/103</td></tr>
<tr><td>Age (mean, SD)</td><td>40.5 (11.4)</td><td>40.6 (11.0)</td><td>40.2 (11.5)</td><td>40.4 (11.5)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td colspan="3">Topiramate</td><td></td></tr>
<tr><td></td><td>200mg/d</td><td>100mg/d</td><td>50mg/d</td><td>Placebo</td></tr>
<tr><td>N</td><td>117</td><td>128</td><td>125</td><td>117</td></tr>
<tr><td>N (ITT analysis)</td><td>112</td><td>125</td><td>117</td><td>115</td></tr>
<tr><td>Dropouts</td><td>72
no post-baseline efficacy data (5)
participant choice (8)
lost to follow up (6)
adverse events (38)
lack of efficacy (8)
other (7)</td><td>45
no post-baseline efficacy data (3)
participant choice (6)
lost to follow up (2)
adverse events (24)
lack of efficacy (6)
other (4)</td><td>57
no post-baseline efficacy data (8)
participant choice (10)
lost to follow up (4)
adverse events (21)
lack of efficacy (10)
other (4)</td><td>48
no post-baseline efficacy data (8)
participant choice (3)
lost to follow up (5)
adverse events (11)
lack of efficacy (21)
other (6)</td></tr>
</table></td></tr>
<tr><td>Intervention 1</td><td>Topiramate 200mg/d. Mean daily dose actually taken = 116.2 +46.9mg/d (58.0% achieved target dose)</td></tr>
<tr><td>Intervention 2</td><td>Topiramate 100mg/d. Mean daily dose actually taken = 78.3 +21.2mg/d (87.2% achieved target dose)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Silberstein SD, Neto W, Schmitt J et al. (2004) Topiramate in migraine prevention: results of a large controlled trial. Archives of Neurology 61: 490-5

Silberstein SD (2003) Efficacy and safety of topiramate in migraine prevention: A dose-ranging, placebo-controlled, double-blind, multicenter trial. Advanced Studies in Medicine 3: S565-S568

Silberstein SD, Loder E, Forde G et al. (2006) The impact of migraine on daily activities: effect of topiramate compared with placebo. Current Medical Research & Opinion 22: 1021-9</td></tr>
<tr><td>Intervention 3</td><td>Topiramate 50mg/d. Mean daily dose actually taken = 44.7 +6.4mg/d (96.9% achieved target dose)</td></tr>
<tr><td>Comparison</td><td>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</td></tr>
<tr><td>Methods</td><td>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 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.</td></tr>
<tr><td>Length of follow up</td><td>26 weeks treatment duration (18 weeks at maintenance dose)</td></tr>
<tr><td>Location</td><td>Multicentre study (49 US outpatient treatment centres)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in Migraine days
Migraine days defined as the number of days with migraine per month.
<table>
<tr><td></td><td colspan="3">Topiramate</td><td></td><td></td></tr>
<tr><td></td><td>200mg/d</td><td>100mg/d</td><td>50mg/d</td><td>Combined doses***</td><td>Placebo</td></tr>
<tr><td>Monthly migraine days(baseline)</td><td>mean=6.6
SD=3.1
N=112</td><td>mean=6.4
SD=2.7
N=125</td><td>mean=6.4
SD=2.7
N=117</td><td></td><td>mean=6.6
SD=2.6
N=115</td></tr>
<tr><td>Monthly migraine days (during treatment)</td><td>mean=3.9
SD=3.4
N=112</td><td>mean=3.7
SD=3.3
N=125</td><td>mean=3.7
SD=3.3
N=117</td><td></td><td>mean=5.3
SD=3.6
N=115</td></tr>
<tr><td>Change in migraine days</td><td>mean=-2.7*
SD=3.26*
SE=0.308**
N=112</td><td>mean=-2.7*
SD=3.04*
SE=0.271**
N=125</td><td>mean=-2.7*
SD=3.04*
SE=0.281**
N=117</td><td>mean=-2.7
SD=3.10
N=354</td><td>mean=-1.3*
SD=3.22*
SE=0.300**
N=115</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Silberstein SD, Neto W, Schmitt J et al. (2004) Topiramate in migraine prevention: results of a large controlled trial. Archives of Neurology 61: 490-5** **Silberstein SD (2003) Efficacy and safety of topiramate in migraine prevention: A dose-ranging, placebo-controlled, double-blind, multicenter trial. Advanced Studies in Medicine 3: S565-S568** **Silberstein SD, Loder E, Forde G et al. (2006) The impact of migraine on daily activities: effect of topiramate compared with placebo. Current Medical Research & Opinion 22: 1021-9**

***data imputed by reviewer from baseline and endpoint data**
****calculated by reviewer from reported standard deviations for purpose of network meta-analysis**
*****calculated by reviewer**

50% responder

50% responders were defined as patients with a reduction in headache frequency of at least 50%.

Topiramate				
200mg/d	**100mg/d**	**50mg/d**	**Combined doses****	**Placebo**
59*/112 (52.3%)	68*/125 (54%)	42*/117 (35.9%)	169/354 (47.7%)	26*/115 (22.6%

***calculated by reviewer from reported percentages**
****calculated by reviewer for purpose of analysis**

Change in migraine frequency

Migraine headache frequency was defined as a migraine headache that started, ended, or recurred within 24 hours). If the headache persisted for longer than 24 hours, it was considered a new migraine period.

	Topiramate				
	200mg/d	**100mg/d**	**50mg/d**	**Combined doses****	**Placebo**
Monthly frequency (baseline)	mean=5.6 SD=2.6 N=112	mean=5.4 SD=2.2 N=125	mean=5.4 SD=2.4 N=117		mean=5.6 SD=2.3 N=115
Monthly frequency (during treatment)	mean=3.3 SD=2.9 N=112	mean=3.3 SD=2.9 N=125	mean=4.1 SD=3.6 N=117		mean=4.6 SD=3.0 N=115
Change in	mean=-2.3*	mean=-2.1*	mean=-1.3*	mean=-1.90	mean=-1.0*

Bibliographic reference	**Silberstein SD, Neto W, Schmitt J et al. (2004) Topiramate in migraine prevention: results of a large controlled trial. Archives of Neurology 61: 490-5** **Silberstein SD (2003) Efficacy and safety of topiramate in migraine prevention: A dose-ranging, placebo-controlled, double-blind, multicenter trial. Advanced Studies in Medicine 3: S565-S568** **Silberstein SD, Loder E, Forde G et al. (2006) The impact of migraine on daily activities: effect of topiramate compared with placebo. Current Medical Research & Opinion 22: 1021-9**

migraine frequency	SD=2.76* N=112	SD=2.62* N=125	SD=3.17* N=117	SD=2.88 N=354	SD=2.72* N=115

***data imputed by reviewer from baseline and endpoint data**
****calculated by reviewer for purpose of analysis**

Change in use of acute pharmacological treatment

Acute medication use was assessed as the number of days requiring acute medication use per month.

	Topiramate				
	200mg/d	**100mg/d**	**50mg/d**	**Combined doses****	**Placebo**
Baseline	mean=6.1 SD=2.6 N=112	mean=5.9 SD=2.5 N=125	mean=5.8 SD=2.5 N=117		mean=6.1 SD=3.0 N=115
During treatment	mean=4.0 SD=2.8 N=112	mean=4.0 SD=3.4 N=125	mean=4.5 SD=3.1 N=117		mean=5.2 SD=3.3 N=115
Change in acute medication use	mean=-2.1* SD=2.71* N=112	mean=-1.9* SD=3.05* N=125	mean=-1.3* SD=2.85* N=117	mean=-1.77 SD=2.89 N=354	mean=-0.9* SD=3.16* N=115

***data imputed by reviewer from baseline and endpoint data**
****calculated by reviewer for purpose of analysis**

Quality of life – MSQ

	Topiramate 200mg/d	**Topiramate 100mg/d**	**Topiramate 50mg/d**	**Placebo**

Bibliographic reference	**Silberstein SD, Neto W, Schmitt J et al. (2004) Topiramate in migraine prevention: results of a large controlled trial. Archives of Neurology 61: 490-5** **Silberstein SD (2003) Efficacy and safety of topiramate in migraine prevention: A dose-ranging, placebo-controlled, double-blind, multicenter trial. Advanced Studies in Medicine 3: S565-S568** **Silberstein SD, Loder E, Forde G et al. (2006) The impact of migraine on daily activities: effect of topiramate compared with placebo. Current Medical Research & Opinion 22: 1021-9**

End of baseline period	mean RR=50.0 se RR=1.7 mean RP=68.4 se RP=1.8 mean EF=54.5 SD EF=2.3 N=112	mean RR=49.0 se RR=1.6 mean RP=69.5 se RP=1.7 mean EF=55.0 SD EF=2.2 N=125	mean RR=50.1 se RR=1.7 mean RP=67.8 se RP=1.8 mean EF=55.1 SD EF=2.3 N=117	mean RR=50.6 se RR=1.7 mean RP=67.4 se RP=1.8 mean EF=52.3 SD EF=2.3 N=115
Mean of visits during treatment	mean RR=75.8 se RR=2.0 mean RP=84.4 se RP=1.7 mean EF=81.2 se EF=2.2 N=112	mean RR=77.2 se RR=1.7 mean RP=88.3 se RP=1.4 mean EF=84.4 SD EF=1.9 N=125	mean RR=72.2 se RR=1.8 mean RP=84.3 se RP=1.5 mean EF=78.5 SD EF=2.0 N=117	mean RR=65.8 se RR=1.8 mean RP=80.6 se RP=1.5 mean EF=72.9 SD EF=2.0 N=115

Outcomes reported but not extracted: Specific adverse events, Quality of life – specific domains of SF-36 questionnaire.

Source of funding	Johnson and Johnson Pharmaceuticals
Comments	Medication code labels were pre-printed. No further details of how random sequence was generated. Patients and clinicians were blinded to treatment allocation. High dropout rate (45.6%) with higher dropout rate in topiramate 200mg/d group compared with other groups, largely due to adverse events. 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.

Table 38: Silberstein 2006

<table>
<tr><td>Bibliographic reference</td><td>Silberstein SD, Hulihan J, Karim MR et al. (2006) Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study.[Erratum appears in Clin Ther. 2006 Sep;28(9):1482]. Clinical Therapeutics 28: 1002-11</td></tr>
<tr><td>Study type</td><td>Randomised controlled trial</td></tr>
<tr><td>Aim</td><td>To evaluate the efficacy and safety of topiramate for preventative therapy for migraine.</td></tr>
<tr><td>Patient characteristics</td><td>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 corticosteroids, 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.

Baseline characteristics:
<table>
<tr><td></td><td>Topiramate 200mg/d</td><td>Placebo</td></tr>
<tr><td>Sex (M/F)</td><td></td><td></td></tr>
<tr><td>Age (mean, SD)</td><td>39.9+11.8</td><td>41.7+9.4</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td>Topiramate 200mg/d</td><td>Placebo</td></tr>
<tr><td>N</td><td>140</td><td>73</td></tr>
<tr><td>N (ITT analysis)</td><td>138</td><td>73</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Silberstein SD, Hulihan J, Karim MR et al. (2006) Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study.[Erratum appears in Clin Ther. 2006 Sep;28(9):1482]. Clinical Therapeutics 28: 1002-11</td></tr>
<tr><td></td><td>Dropouts</td><td>45
No post baseline efficacy data (2)
Participant choice (8)
Lost to follow up (7)
Adverse events (21)
Lack of efficacy (4)
Protocol violation (2)
Other (1)</td><td>13
Participant choice (1)
Lost to follow up (0)
Adverse events (4)
Lack of efficacy (2)
Protocol violation (2)
Other (4)</td></tr>
<tr><td>Intervention</td><td colspan="2">Topiramate 200mg/d Mean daily dose actually taken = 161.3 mg/d (61.3% achieved target dose)</td></tr>
<tr><td>Comparison</td><td colspan="2">Placebo Mean daily dose actually taken = 185.6 mg/d (86.4% achieved target dose)</td></tr>
<tr><td>Methods</td><td colspan="2">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. Rescue medications permitted during study.</td></tr>
<tr><td>Length of follow up</td><td colspan="2">20 weeks (8 week titration and 12 week maintenance period)</td></tr>
<tr><td>Location</td><td colspan="2">Out-patient setting, USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="2">50% Responder rate
‘Responder’ was defined as participants with a 50% reduction in the number of migraine periods in the treatment phase compared with baseline. 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
<table>
<tr><th>Topiramate 200mg/d</th><th>Placebo</th></tr>
<tr><td>55/138 (39.9%)</td><td>25/73 (34.2%)</td></tr>
</table>
Serious adverse events
<table>
<tr><th>Topiramate 200mg/d</th><th>Placebo</th></tr>
<tr><td>0/138</td><td>0/73</td></tr>
</table>
Outcomes reported but not extracted: Change in migraine frequency (no measure of variability such as standard deviation reported, so data not usable), adverse events (serious adverse events not reported separately), number of</td></tr>
</table>

Bibliographic reference	**Silberstein SD, Hulihan J, Karim MR et al. (2006) Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study.[Erratum appears in Clin Ther. 2006 Sep;28(9):1482]. Clinical Therapeutics 28: 1002-11**
	patients with a >75% reduction in migraine frequency
Source of funding	Ortho McNeil Neurologics
Comments	Unclear method of randomisation and allocation concealment. Study described as 'double blind', but details of blinding not reported. Results reported using ITT population. 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.

Table 39: Silberstein 2007

Bibliographic reference	**Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. Headache. 2007; 47(2):170-180.** **Dodick DW, Silberstein S, Saper J et al. (2007) The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache 47: 1398-408** **Silberstein S, Lipton R, Dodick D et al. (2009) Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache 49: 1153-62**
Study type	Randomised controlled trial
Aim	To evaluate the efficacy and safety of topiramate in the treatment of chronic migraine.
Patient characteristics	**Inclusion criteria**: - Adults (age 18 to 65) - 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 - 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

<table>
<tr><td>Bibliographic reference</td><td>Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. Headache. 2007; 47(2):170-180.

Dodick DW, Silberstein S, Saper J et al. (2007) The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache 47: 1398-408

Silberstein S, Lipton R, Dodick D et al. (2009) Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache 49: 1153-62</td></tr>
<tr><td></td><td>- Overuse of acute migraine medication (defined as use in excess of 4 days per week during prospective baseline period)
- History of hepatic disorder or nephrolithiasis; progressive neurologic disorder other than migraine
- Pregnant or nursing.

Baseline characteristics:
<table>
<tr><th></th><th>Topiramate 100mg/d</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>25/128</td><td>20/133</td></tr>
<tr><td>Age (mean, SD)</td><td>37.8 (12.38)</td><td>38.6 (11.80)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Topiramate 100mg/d</th><th>Placebo</th></tr>
<tr><td>N</td><td>165</td><td>163</td></tr>
<tr><td>N (ITT analysis)</td><td>153</td><td>153</td></tr>
<tr><td>Dropouts</td><td>73
Lack of efficacy (21)
Subject choice (13)
Protocol violation (5)
Limiting adverse event (18)
Lost to follow up (15)
Other (1)</td><td>73
Lack of efficacy (30)
Subject choice (10)
Protocol violation (6)
Limiting adverse event (10)
Lost to follow up (16)
Other (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Topiramate 100mg/d
Mean +SD dose used during study period 74.6+17.7mg/d (72.5% achieved target dose)</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. Headache. 2007; 47(2):170-180.

Dodick DW, Silberstein S, Saper J et al. (2007) The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache 47: 1398-408

Silberstein S, Lipton R, Dodick D et al. (2009) Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache 49: 1153-62</td></tr>
<tr><td></td><td>Mean +SD dose used during study period 88.2+16.7mg/d (80.4% achieved target dose)</td></tr>
<tr><td>Methods</td><td>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 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.</td></tr>
<tr><td>Length of follow up</td><td>26 weeks (56 days pre-treatment phase, 16 weeks treatment phase, 2 weeks ‘taper/exit period’.</td></tr>
<tr><td>Location</td><td>Multicentre study (46 US clinical centres)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in migraine /headache days
<table>
<tr><th></th><th>Topiramate 100mg</th><th>Placebo</th></tr>
<tr><td>Number of migraine days per 28 days (baseline)</td><td>mean=15.2
SD=6.4
N=153</td><td>mean=15.1
SD=5.8
N=153</td></tr>
<tr><td>Change in number of migraine days per 28 days during treatment compared with baseline</td><td>mean=-5.6
SD=6.0
N=153</td><td>mean=-4.1
SD=6.1
N=153</td></tr>
<tr><td>Number of headache days per 28 days (baseline)</td><td>mean=20.4
SD=4.8
N=153</td><td>mean=20.8
SD=4.6
N=153</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. Headache. 2007; 47(2):170-180.** **Dodick DW, Silberstein S, Saper J et al. (2007) The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache 47: 1398-408** **Silberstein S, Lipton R, Dodick D et al. (2009) Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache 49: 1153-62**

Change in number of headache days per 28 days during treatment compared with baseline	mean=-5.8 SD=5.6 N=153	mean=-4.7 SD=5.6 N=153

Change in headache severity

Severity was defined as the mean **daily** headache severity, measured on the following scale: 1 = mild headache, easily ignored, 2 = mild bothersome discomfort, 3 = moderate, painful, 4 = moderate, very painful, 5 = severe, intensely painful.

	Topiramate 100mg	**Placebo**
Baseline	Not reported	Not reported
Change in headache severity during treatment	mean=0.3 SD=0.6 N=153	mean=0.2 SD=0.4 N=153

Migraine specific quality of life (MIDAS)

	Topiramate 100mg	**Placebo**
Baseline	mean=64.4 SD=46.6 N=153	mean=62.2 SD=43.4 N=153
Change in Migraine disability assessment score from baseline during treatment (MIDAS)	mean=-31.4 SD=53.8 N=153	mean=-21.0 SD=52.2 N=153

<table>
<tr><td>Bibliographic reference</td><td>Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. Headache. 2007; 47(2):170-180.

Dodick DW, Silberstein S, Saper J et al. (2007) The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache 47: 1398-408

Silberstein S, Lipton R, Dodick D et al. (2009) Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache 49: 1153-62</td></tr>
<tr><td></td><td>Change in use of acute medication
Acute medication use defined as number of days per 28 days requiring acute medication (for all headache types).
<table>
<tr><th></th><th>Topiramate 100mg</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=11.9
SD=7.2
N=153</td><td>mean=11.4
SD=6.6
N=153</td></tr>
<tr><td>Change in use of acute medication from baseline during treatment</td><td>mean=-4.4
SD=5.8
N=153</td><td>mean=-3.4
SD=5.3
N=153</td></tr>
</table>
Serious adverse events
<table>
<tr><th>Topiramate 100mg</th><th>Placebo</th></tr>
<tr><td>0/160</td><td>0/161</td></tr>
</table>
Outcomes reported but not extracted: Number of migraine or migrainous days, Number of patients with >25%, >50% and >75% reduction in migraine days (rather than migraine frequency). 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); adverse events (treatment related, treatment emergent and specific adverse events).</td></tr>
<tr><td>Source of funding</td><td>Ortho-McNeil Neurologics</td></tr>
</table>

Bibliographic reference	**Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. Headache. 2007; 47(2):170-180.** **Dodick DW, Silberstein S, Saper J et al. (2007) The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache 47: 1398-408** **Silberstein S, Lipton R, Dodick D et al. (2009) Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache 49: 1153-62**
Comments	Computer-generated random medication code numbers were prepared and pre-printed on the study medication labels. The investigators entered the qualified patient's identifier in numerical order. The randomization was performed using permuted blocks. The study was described as 'double blind'. Only 55% of participants completed the treatment regimen (similar for each group). Dropout rate was 44.5% but similar across groups. 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.

Table 40: Silberstein 2013

Bibliographic reference	**Silberstein S, Goode-Sellers S, Twomey C et al. (2013) Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia 33: 101-11**
Study type	Randomised controlled trial
Aim	To evaluate the efficacy and safety of gabapentin enacarbil (GEn) for migraine prophylaxis.
Patient characteristics	**Inclusion criteria:** - Males and females >=18 years old - International Headache Society (IHS) criteria-defined migraine headache with or without aura for at least one year with an onset before the age of 50 years. - >= 3 migraine headache attacks and >= 4migraine headache days (defined as calendar days with any occurrence of migraine headache pain of at least 30 minutes in duration) per month during each of the three months before screening and during the baseline period. - <15 migraine or non-migraine headache days per month during each of the three months before screening and during the baseline period. - Females were eligible if they were unable to bear children or, if able to bear children, if they were not pregnant and using adequate contraception. **Exclusion criteria:** - Unable to discontinue prohibited medications (beta-blockers, tricyclic antidepressants, calcium channel blockers,

Bibliographic reference	Silberstein S, Goode-Sellers S, Twomey C et al. (2013) Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia 33: 101-11

antiepileptic drugs, bupropion, serotonergic noradrenergic reuptake inhibitors) during the two-week screening period and throughout the duration of the study (fluoxetine, riboflavin, magnesium and feverfew were allowed).

- Had a history of ergotamine, triptan, opioid, or combination medication intake for >=10 days per month or simple analgesic intake for >=15 days per month for >= 3 months
- Had previously taken gabapentin or pregabalin for migraine headache prophylaxis.
- The patient reported experiencing lack of efficacy of two or more >= 8-week trials of prophylaxis of migraine headache.
- Uncontrolled hypertension (i.e. sitting systolic blood pressure >160mmHg or sitting diastolic blood pressure >90 mmHg) at the screening visit or at randomization.

Baseline characteristics (ITT population)

	Gabapentin 1200mg/d	Gabapentin 1800mg/d	Gabapentin 2400mg/d	Gabapentin 3000mg/d	Placebo
Sex (M/F)	14/52	19/115	28/105	16/46	17/111
Age (mean, SD)	39.4 (9.74)	37.7 (11.75)	39.0 (12.04)	39.1 (11.78)	41.1 (11.72)

Number of Patients

	Gabapentin 1200mg/d	Gabapentin 1800mg/d	Gabapentin 2400mg/d	Gabapentin 3000mg/d	Placebo
N	67	134	134	62	129
N (ITT analysis)	66	134	133	62	128
Drop outs	18 Adverse event (4) Withdrew consent (4) Protocol deviation (5) Lost to follow-up (4) Lack of efficacy (1)	46 Adverse event (17) Withdrew consent (14) Protocol deviation (4) Lost to follow-up (5) Lack of efficacy (1) Investigator discretion (5)	37 Adverse event (16) Withdrew consent (7) Protocol deviation (5) Lost to follow-up (5) Lack of efficacy (3) Investigator discretion (1)	25 Adverse event (13) Withdrew consent (4) Protocol deviation (3) Lost to follow-up (3) Lack of efficacy (1) Investigator discretion (1)	34 Adverse event (11) Withdrew consent (8) Protocol deviation (6) Lost to follow-up (3) Lack of efficacy (6) Investigator discretion (0)

Bibliographic reference	**Silberstein S, Goode-Sellers S, Twomey C et al. (2013) Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia 33: 101-11**
	<table><tr><td></td><td>Investigator discretion (0)</td><td></td><td></td><td></td><td></td></tr></table>
Intervention 1	Gabapentin enacarbil 1200mg/d (actual mean dose achieved = 1078mg/d)
Intervention 2	Gabapentin enacarbil 1800mg/d (actual mean dose achieved= 1702mg/d)
Intervention 3	Gabapentin enacarbil 2400mg/d (actual mean dose achieved= 2204mg/d)
Intervention 4	Gabapentin enacarbil 3000mg/d (actual mean dose achieved= 2776mg/d)
Comparison	Placebo
Methods	The trial included a 2-week screening period to determine eligibility, a 6-week baseline period to establish baseline measures, and a 20 week period which consisted of 5 weeks flexible titration to the target dose or maximum tolerated dose, 12 weeks at that dose, and 3 weeks tapered discontinuation. There was also a two week period after the end of treatment to monitor adverse events. Use of acute migraine treatment was permitted. Patients recorded information about the presence of migraine and non-migraine headache and associated symptoms daily in the baseline and treatment period in an electronic diary.
Length of follow up	Outcomes measured at end of 12-week maintenance period at titrated dose.
Location	USA and Canada (Multicentre trial)
Outcomes measures and effect size	**Change in migraine days** Post-treatment measure was the number of migraine headache days in the last four weeks of the maintenance period, where a migraine headache day was a day with any occurrence of migraine headache pain of more than 30 minutes.

	Gabapentin 1200mg/d	**Gabapentin 1800mg/d**	**Gabapentin 2400mg/d**	**Gabapentin 3000mg/d**	**Placebo**
Baseline	Not reported	Not reported	Not reported	Not reported	Not reported
Change in migraine headache days	Not reported	Not reported	Not reported	Not reported	Not reported
Change in migraine headache days **relative to placebo**	mean=0.6 95%CI=-1.0 to 2.2 N=63	mean=0.0 95%CI=-1.3 to 1.3 SE= 0.663* N=131	mean=0.5 95%CI=-0.8 to 1.8 N=130	mean=0.3 95%CI=-1.4 to 1.9 N=62	-

***Calculated by reviewer for purpose of network meta-analysis**

Bibliographic reference	Silberstein S, Goode-Sellers S, Twomey C et al. (2013) Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia 33: 101-11

****Only 1800mg/d dose used in network meta-analysis, as not possible to account for correlation between multiple arms when only mean difference data is reported**

50% responder

Number of participants with 50% reduction in migraine attack frequency where migraine attack was defined as a migraine headache of at least 30 minutes. Per protocol analysis (dropouts not included)

Gabapentin					
1200mg/d	**1800mg/d**	**2400mg/d**	**3000mg/d**	**Combined doses***	**Placebo**
31/59 (53%)	67/113 (59%)	67/123 (54%)	39/58 (67%)	165/295 (55.9%)	64/120 (53%)

***Calculated by reviewer for purpose of analysis (3000mg/d not included as dose outside recommended range)**

Change in migraine severity

Peak severity was recorded by the patient as 0=none, 1=mild, 2=moderate, 3=severe. Peak severity was maximum severity of all headache events in a single attack. Post-treatment measure was the mean peak severity in the last four weeks of the maintenance period

	Gabapentin				
	1200mg/d	**1800mg/d**	**2400mg/d**	**3000mg/d**	**Placebo**
Baseline	Not reported	Not reported	Not reported	Not reported	Not reported
Change in migraine severity	median=0.0 95%CI=-0.3 to 0.0	median=0.0 95%CI=-0.2 to 0.0	median=0.0 95%CI=-0.1 to 0.0	median=0.0 95%CI=-0.3 to 0.0	median=0.0 95%CI=-0.2 to 0.0

Not possible to calculate overall estimate of effect from these data.

Change in migraine frequency

Post-treatment measure was the number of migraine attacks in the last four weeks of the maintenance period, where a migraine attack was defined as a migraine headache of at least 30 minutes in duration.

	Gabapentin					
	1200mg/d	**1800mg/d**	**2400mg/d**	**3000mg/d**	**Combined doses****	**Placebo**
Baseline	Not reported	Not reported	Not reported	Not reported		Not reported

Bibliographic reference	**Silberstein S, Goode-Sellers S, Twomey C et al. (2013) Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia 33: 101-11**

Change in migraine frequency	Adjusted mean=-2.2 95% CI= -2.7 to -1.8 SD=1.87* N=66	Adjusted mean=-2.3 95% CI= -2.6 to -2.0 SD=1.77* N=134	Adjusted mean=-2.1 95% CI= -2.4 to -1.8 SD=1.77* N=133	Adjusted mean=-2.2 95% CI= -2.7 to -1.8 SD=1.81* N=62	mean=-2.2 SD=1.787** N=333	Adjusted mean=-2.2 95% CI= -2.5 to -1.8 SD=2.02* N=128

***calculated by reviewer from reported 95% CIs**

****calculated by reviewer for purpose of analysis (3000mg/d not included as dose outside recommended range)**

Acute medication use

Post-treatment measure was the number of days with acute medication use in the last four weeks of the maintenance period

	Gabapentin					
	1200mg/d	**1800mg/d**	**2400mg/d**	**3000mg/d**	**Combined dose****	**Placebo**
Baseline	Not reported	Not reported	Not reported	Not reported		Not reported
Change in migraine frequency	Adjusted mean=-2.3 95% CI= -3.1 to -1.5 SD=3.32* N=66	Adjusted mean=-2.7 95% CI= -3.3 to -2.2 SD=3.25* N=134	Adjusted mean=-2.2 95% CI= -2.8 to -1.7 SD=3.24* N=133	Adjusted mean=-2.1 95% CI= -2.9 to –1.3 SD=3.21* N=62	mean=-2.42 SD=3.26* N=333	Adjusted mean=--2.0 95% CI= -2.5 to -1.4 SD=3.15 N=128

***calculated by reviewer from reported 95% CIs**

****calculated by reviewer for purpose of analysis (3000mg/d not included as dose outside recommended range)**

Outcomes reported but not extracted: Plasma gabapentin concentration, other adverse events (non-serious), Number of patients with >50% reduction in migraine headache days, change in number of attacks with aura, change in number of attacks with nausea, change in number of attacks with vomiting, change in number of attacks with photophobia, change in number of attacks with phonophobia, adverse events (serious adverse events not reported separately for each group).

Source of funding	GlaxoSmithKline
Comments	ITT analysis for presented data used imputation. Quality of life measures are described the methods section but the data are not reported. Serious adverse events were not reported separately for each group. Baseline measures for outcomes not reported. Blocks of randomisation code were allocated to each centre. Randomisation was in ratio of 2:1:2:2:1 for

Bibliographic reference	**Silberstein S, Goode-Sellers S, Twomey C et al. (2013) Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia 33: 101-11**
	placebo and 1200, 1800, 2400 and 3000 mg/d groups, respectively (further randomisation details not provided). Allocation was conducted via an interactive voice recognition system at the time of randomisation. Trial described as 'double blind'.

Table 41: Stewart 1980

Bibliographic reference	**Stewart DJ, Gelston A, Hakim A (1988) Effect of prophylactic administration of nimodipine in patients with migraine. Headache 28: 260-2**
Study type	Randomised controlled trial
Aim	To assess the prophylactic effect of nimodipine for migraine prophylaxis.
Patient characteristics	**Inclusion criteria:** - Aged 18-65. - Between 2 and 10 migraine attacks per month (judged by a neurologist). - Use no hypertensive agents or prophylactic agents for migraine. - Female participants must have a negative pregnancy test. **Exclusion criteria:** - No further criteria specified. **Baseline characteristics**

	Nimodipine	**Placebo**
Sex (M/F)	Not reported	Not reported
Age (mean, SD)	Not reported	Not reported

Number of Patients

	Nimodipine	**Placebo**
N	15*	18*
N (analysis)	13	13
Drop outs	2 Reasons for dropout not reported separately for each group	5 Reasons for dropout not reported separately for each group

*12 participants also dropped out in the placebo-controlled baseline phase (not reported separately for each group

Intervention	Nimodipine 120mg/d (3 doses of 40mg)
Comparison	Placebo

<table>
<tr><td>Bibliographic reference</td><td>Stewart DJ, Gelston A, Hakim A (1988) Effect of prophylactic administration of nimodipine in patients with migraine. Headache 28: 260-2</td></tr>
<tr><td>Methods</td><td>Participants were randomised to two groups. The study began with a 4 week placebo controlled baseline period for both groups. After the baseline period, one group received nimodipine (120mg/d) and the other continued to receive placebo for a further 12 weeks.</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>Canada, setting not explicitly reported (patients referred to the study from neurologists, emergency room physicians, general internists and family practitioners).</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in headache frequency
Headache frequency defined as number of headaches per month.
<table>
<tr><th></th><th>Nimodipine 120mg/d</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=6.15
SD=3.62
N=13</td><td>mean=6.46
SD=4.21
N=13</td></tr>
<tr><td>Last month of treatment</td><td>mean=3.46
SD=2.96
N=13</td><td>mean=6.30
SD=3.17
N=13</td></tr>
<tr><td>Change in headache frequency</td><td>mean=-2.69*
SD=3.34*
N=13</td><td>mean=-0.16*
SD=3.80*
N=13</td></tr>
</table>
*data imputed by reviewer from baseline and endpoint data

Outcomes reported but not extracted: Headache index</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Randomisation was by a table of random numbers. It is unclear how concealment of allocation was maintained and blinding is not described (study described as ‘double blind’ but details not provided). Per protocol analysis.</td></tr>
</table>

Table 42: Van de Ven 1997

Bibliographic reference	**van de Ven LL, Franke CL, Koehler PJ (1997) Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. Cephalalgia 17: 596-9**
Study type	Randomised controlled trial
Aim	To assess the efficacy of bisoprolol in migraine prophylaxis.
Patient characteristics	**Inclusion criteria**:

<table>
<tr><td>Bibliographic reference</td><td>van de Ven LL, Franke CL, Koehler PJ (1997) Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. Cephalalgia 17: 596-9</td></tr>
<tr><td></td><td>- 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.
Baseline characteristics:
<table>
<tr><th></th><th>Bisoprolol 5mg</th><th>Bisoprolol 10mg</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>16/58</td><td>13/64</td><td>11/64</td></tr>
<tr><td>Age (mean)</td><td>38.3</td><td>38.9</td><td>38.8</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Bisoprolol 5mg</th><th>Bisoprolol 10mg</th><th>Placebo</th></tr>
<tr><td>N</td><td>74</td><td>77</td><td>75</td></tr>
<tr><td>N (ITT analysis)</td><td>74</td><td>77</td><td>75</td></tr>
<tr><td>Dropouts</td><td>11</td><td>9</td><td>11</td></tr>
</table></td></tr>
<tr><td>Intervention 1</td><td>Bisoprolol 5 mg/d</td></tr>
<tr><td>Intervention 2</td><td>Bisoprolol 10mg/d</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Methods</td><td>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</td></tr>
<tr><td>Length of follow up</td><td>12 week treatment period</td></tr>
<tr><td>Location</td><td>14 centres in France, the Netherlands, Belgium and Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in Migraine frequency
Migraine frequency was defined as the number of attacks per 4 weeks.
<table>
<tr><th></th><th>Bisoprolol 5 mg</th><th>Bisoprolol 10mg</th><th>Combine dose**</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=4.4</td><td>mean=4.2</td><td></td><td>mean=4.0</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**van de Ven LL, Franke CL, Koehler PJ (1997) Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. Cephalalgia 17: 596-9**

	SD=1.6 N=74	SD=1.9 N=77		SD=1.8 N=75
Last 4 weeks of treatment	mean=2.7 SD=1.7 N=74	mean=2.6 SD=1.9 N=77		mean=3.2 SD=1.8 N=75
Change in migraine frequency	mean=-1.7* SD=1.65* N=74	mean=-1.6* SD=1.9* N=77	mean=-1.65 SD=1.78 N=151	mean=-0.8* SD=1.8* N=75

***data imputed by reviewer from baseline and endpoint data**

****calculated by reviewer for purpose of analysis**

Outcomes reported but not extracted: Attack duration, adverse events (serious adverse events not reported separately).

Source of funding	Merck KgaA, Darmstadt, Germany
Comments	Randomisation method and timing unclear Allocation concealment unclear. The study was described as 'double blind', but details of blinding are not given. ITT analysis (last observation carried forward) – the authors reported that a per protocol analysis let to the same conclusions). Previous use of prophylactic medication not reported.

Table 43: Verma 2013

Bibliographic reference	**Verma A, Srivastava D, Kumar A et al. (2013) Levetiracetam in migraine prophylaxis: a randomized placebo-controlled study in a rural medical institute in northern India. Clinical Neuropharmacology 36: 193-7**
Study type	Randomised controlled trial
Aim	To assess the efficacy and tolerability of levetiracetam in adult migraine prophylaxis.
Patient characteristics	**Inclusion criteria:** - Diagnosis of migraine with or without aura according to the criteria of the International Headache Society. - 4 or more attacks per month for at least 3 months. - Previous prophylactic treatment had failed or was discontinued due to adverse effects. **Exclusion criteria:** - More than 15 days of headache per month. - Affected by headaches other than migraine. - Systemic or organic disease.

<table>
<tr><td>Bibliographic reference</td><td>Verma A, Srivastava D, Kumar A et al. (2013) Levetiracetam in migraine prophylaxis: a randomized placebo-controlled study in a rural medical institute in northern India. Clinical Neuropharmacology 36: 193-7</td></tr>
<tr><td></td><td>- Pregnant or at risk of pregnancy.

Baseline characteristics
<table>
<tr><th></th><th>Levetiracetam</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>5/20</td><td>9/18</td></tr>
<tr><td>Age (mean, SD)</td><td>31.84 (9.57)</td><td>30.44 (9.03)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Levetiracetam</th><th>Placebo</th></tr>
<tr><td>N</td><td>32</td><td>33</td></tr>
<tr><td>N (analysis)</td><td>25</td><td>27</td></tr>
<tr><td>Drop outs</td><td>7
Lost to follow up (4)
Withdrew consent (3)</td><td>6
Lost to follow up (4)
Withdrew consent (2)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Levetiracetam 1000mg/d</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Methods</td><td>A 14-day washout period preceded the trial, during which migraine prophylaxis was tapered down. The trial started with a 4 week baseline period where baseline measures were taken and inclusion and exclusion criteria re-evaluated. This was followed by randomisation to treatment or placebo and then a dose increase period were levetiracetam (or matching placebo) was started at a dose of 250mg/d and increased at a rate of 250mg/d to 1000mg/d. This was followed by a 3 month maintenance period at the target dose. Acute medication for migraine was permitted as required.</td></tr>
<tr><td>Length of follow up</td><td>3 month treatment period at maintenance dose</td></tr>
<tr><td>Location</td><td>India, Outpatient neurology department</td></tr>
<tr><td>Outcomes measures and effect size</td><td>50% responder
50% responder was defined as the number of participants with a 50% reduction in monthly migraine frequency in the last 4 weeks of treatment compared with baseline.
<table>
<tr><th>Levetiracetam 1000mg/d</th><th>Placebo</th></tr>
<tr><td>16/25*(64%)</td><td>6/27*(22%)</td></tr>
</table>
*Calculated by reviewer from reported percentages

Change in headache severity
Headache severity was rated as 0 (no pain), 1 (mild), 2 (moderate), 3 (severe).</td></tr>
</table>

Bibliographic reference	Verma A, Srivastava D, Kumar A et al. (2013) Levetiracetam in migraine prophylaxis: a randomized placebo-controlled study in a rural medical institute in northern India. Clinical Neuropharmacology 36: 193-7

	Levetiracetam 1000mg/d	Placebo
Baseline	mean=2.75 SD=0.44 N=25	mean=2.65 SD=0.48 N=27
Last 4 weeks of treatment	mean=1.29 SD=0.75 N=25	mean=2.07 SD=0.89 N=27
Change in headache severity	mean=-1.46* SD=0.65* N=25	mean=-0.58* SD=0.77* N=27

***data imputed by reviewer from baseline and endpoint data**

Change in headache frequency

Migraine frequency was defined as the number of attacks per month.

	Levetiracetam 1000mg/d	Placebo
Baseline	mean=5.17 SD=1.19 N=25	mean=5.11 SD=1.27 N=27
Last 4 weeks of treatment	mean=2.21 SD=1.47 N=25	mean=4.40 SD=1.64 N=27
Change in headache frequency	mean=-2.96* SD=1.35* N=25	mean=-0.71* SD=1.49* N=27

***data imputed by reviewer from baseline and endpoint data**

Use of acute medication

Acute medication use measured as number of tablets taken per month for acute treatment of migraine.

	Levetiracetam 1000mg/d	Placebo
Baseline	mean=5.85 SD=1.55	mean=6.15 SD=1.28

Bibliographic reference	**Verma A, Srivastava D, Kumar A et al. (2013) Levetiracetam in migraine prophylaxis: a randomized placebo-controlled study in a rural medical institute in northern India. Clinical Neuropharmacology 36: 193-7**
	<table><tr><td></td><td>N=25</td><td>N=27</td></tr><tr><td>Last 4 weeks of treatment</td><td>mean=1.87 SD=1.39 N=25</td><td>mean=5.80 SD=1.62 N=27</td></tr><tr><td>Change in acute medication use</td><td>mean=-3.98* SD=1.48* N=25</td><td>mean=-0.35* SD=1.48* N=27</td></tr></table> ***data imputed by reviewer from baseline and endpoint data** **Outcomes reported but not extracted:** Clinical disability, Headache index
Source of funding	Not reported
Comments	Randomisation was via computer-generated random number sequence. Measures to ensure allocation concealment are not described, and it is not stated whether the investigator responsible for randomisation was blinded (different members were responsible for randomisation and data collection). Blinding is not explicitly described, although it is stated that the tablets were identical across groups, implying that the trial was at least single blind. Per protocol analysis (only those completing trial were included).

Table 44: Winner 2005

Bibliographic reference	**Winner P, Pearlman EM, Linder SL et al. (2005) Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache 45: 1304-12**
Study type	Randomised controlled trial.
Aim	To assess the efficacy and safety of topiramate for the prevention of paediatric migraine with or without aura.
Patient characteristics	**Inclusion criteria:** - Age 6 to 15 years - Met the proposed International Headache Society (IHS) classification of paediatric migraine with or without aura. - Weighed more than 20 kg. - Average of 3 to 10 migraine days/month for the 3 months (84 days) prior to screening and 3 to 10 migraine days during the 4-week (28-day) prospective baseline phase. - Female subjects had to be pre-menarchal or otherwise incapable of pregnancy, or practicing a medically acceptable method of birth control for ≥1 month before study enrolment. **Exclusion criteria:**

<table>
<tr><td>Bibliographic reference</td><td>Winner P, Pearlman EM, Linder SL et al. (2005) Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache 45: 1304-12</td></tr>
<tr><td></td><td>- Cluster headache or chronic (transformed) migraine
- Exclusively migraine aura without headache.
- More than 15 headache days during the prospective baseline phase. Although the
- Overuse of analgesics or acute migraine treatments (>12 days/month of analgesics or >8 days/month of ergot or triptans)
- Previous failure of ≥2 adequately dosed migraine preventive medications.
- Previous failure of topiramate therapy for migraine.
- Use of topiramate or any other migraine preventive medication within 14 days of the prospective baseline phase.
- History of nephrolithiasis.

Baseline characteristics
<table>
<tr><th></th><th>Topiramate</th><th>Placebo</th></tr>
<tr><td>Sex (M/F)</td><td>55/53</td><td>26/23</td></tr>
<tr><td>Age (mean, SD)</td><td>11.3 (2.5)</td><td>10.7 (2.6)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Topiramate</th><th>Placebo</th></tr>
<tr><td>N</td><td>112</td><td>50</td></tr>
<tr><td>N (ITT Analysis)</td><td>108</td><td>49</td></tr>
<tr><td>Drop outs</td><td>23 (20.5%)
Lack of efficacy (2)
Limiting adverse event (7)
Subject choice (6)
Significant protocol violation (1)
Lost to follow-up (5)
Other* (2)</td><td>8 (16%)
Lack of efficacy (2)
Limiting adverse event (2)
Subject choice (1)
Significant protocol violation (0)
Lost to follow-up (2)
Other* (1)</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Topiramate 2 to 3 mg/kg/d or maximum tolerated dose, with maximum dose of 200 mg/day</td></tr>
<tr><td>Comparison</td><td>Placebo</td></tr>
<tr><td>Methods</td><td>The study started with a 56-day pre-randomisation phase which included a screening/washout period and 28-day baseline where baseline measures were recorded. Outcomes were measured using a headache diary which was completed by the parent/guardian with input from the child if appropriate. Subsequently, participants were randomised in a 2:1 ratio to receive topiramate or placebo. The baseline phase was followed by an 8 week titration phase and then a 12 week maintenance</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Winner P, Pearlman EM, Linder SL et al. (2005) Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache 45: 1304-12</td></tr>
<tr><td></td><td>period. Use of acute medication was permitted.</td></tr>
<tr><td>Length of follow up</td><td>12 week treatment period at maintenance dose</td></tr>
<tr><td>Location</td><td>US outpatient setting (multi-centre)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Change in migraine days
Migraine days defined as the number of days with migraine per 28 days.
<table>
<tr><th></th><th>Topiramate 2 to 3 mg/kg/d</th><th>Placebo</th></tr>
<tr><td>Baseline</td><td>mean=5.4
SD=1.7
N=108</td><td>mean=5.5
SD=2.0
N=49</td></tr>
<tr><td>Change in migraine days (Last 28 days of treatment compared to baseline)</td><td>mean=-3.1
SD=3.0
SE=0.289*
N=108</td><td>mean=-2.4
SD=2.8
SE=0.4*
N=49</td></tr>
</table>
*calculated by reviewer from reported standard deviations for purpose of network meta-analysis

50% responder
‘Responder’ defined as participants with >50% reduction in migraine frequency in last 28 days of treatment compared with baseline
<table>
<tr><th>Topiramate 2 to 3 mg/kg/d</th><th>Placebo</th></tr>
<tr><td>75/108* (69.4%)</td><td>26/49* (53.0%)</td></tr>
</table>
*Calculated by reviewer from reported percentages

Outcomes reported but not extracted: Change in headache days and 50%, 75% and 100% responder also reported for the whole treatment period (as well as last 28 days), Adverse events (non-serious), body weight</td></tr>
<tr><td>Source of funding</td><td>Ortho-McNeil Pharmaceutical, Raritan, NJ.</td></tr>
<tr><td>Comments</td><td>Method of randomisation is not described. Allocation concealment was ensured by packaging drugs according to according to a medication code schedule generated before the trial and providing physicians with a drug assignment inventory. Participants were assigned to the inventory numerically and received the corresponding medication. Participants, investigators, clinical staff and study monitors were blind to treatment allocation until the study was complete and the database finalised. Intention to treat analysis is presented here. Per protocol analysis was also presented and leads to the</td></tr>
</table>

Bibliographic reference	Winner P, Pearlman EM, Linder SL et al. (2005) Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache 45: 1304-12
	same conclusions.

Appendix H: GRADE profiles

Table 45: Network meta-analysis (change in migraine days)

Quality assessment							Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
11[1]	RCT	serious risk of bias[2]	no serious inconsistency[3]	no serious indirectness	serious imprecision[4]	none	Low

[1] *Diener 2009, Apostol 2008, Brandes 2004, Lewis 2009, Lipton 2011, Silberstein 2004, Winner 2005, Diener 2004, Holroyd 2010, Silberstein 2013, Dodick 2009*
[2] *All included studies were double-blind randomised controlled trials. Methods for randomisation and allocation concealment were often not reported. Many of the trials had high dropout rates (up to 40% of participants). Most trials used an intention to treat analysis to mitigate potential bias, but with dropout rates so high, potential for bias caused by different reasons for attrition across groups and studies is possible.*
[3] *It was not possible to assess inconsistency between direct and indirect effect estimates as there were no loops in the network that were not formed by 3-arm trials.*
[4] *There is substantial variability in the treatment estimates for some interventions compared with placebo (divalproex sodium, amitriptyline, telmisartan) with confidence intervals incorporating clinically important benefits and harms. However, for other interventions (for example topiramate), the uncertainty in the effect estimate is much less. However, the large uncertainty associated with the effect estimates for some treatments leads to substantial uncertainty in the ranking of treatments. Many nodes in the network are only connected by a single trial.*

Table 46: Telmisartan vs Placebo

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Telmisartan	Placebo	Relative (95% CI)	Absolute	
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	44	-	MD -0.06 (-1.85 to 1.73)	Moderate

[1] *Diener 2009*
[2] *There was a difference between telmisartan and placebo groups in the number of headache days at baseline that occurred by chance and was discovered after randomisation. The baseline acute medication use was not reported.*

Table 47: Trazodone vs Placebo

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trazodone	Placebo	Relative (95% CI)	Absolute	
Change in migraine/headache frequency (Better indicated by lower values)											
1[1]	RCT	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	18	18	-	MD -0.1 (-0.59 to 0.39)	Very low

[1] *Battistella 1993*
[2] *Some participants were outside of the age range of the review (<12 years).*
[3] *Confidence intervals encompass both clinically important benefit and harm.*

Table 48: Gabapentin vs Placebo

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute	Quality
50% responder											
1[1]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	165/295 (55.9%)	64/120 (53.3%)	RR 1.05 (0.86 to 1.28)	27 more per 1000 (from 75 fewer to 149 more)	Moderate
Change in migraine/headache frequency (Better indicated by lower values)											
2[3]	RCT	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	355	159	-	MD -0.06 (-0.44 to 0.32)	Moderate

[1] *Silberstein 2013*
[2] *Confidence intervals encompasses clinically important benefit and no clinically important difference.*
[3] *Feuerstein 1990, Silberstein 2013*
[4] *One study (Feuerstein 1990) used a retrospective baseline period, which may be susceptible to recall bias. In addition, there were 2 outliers with very high baseline values in the placebo group of this study which led to substantially larger standard deviations in the placebo group, and potentially data that was not normally distributed.*

Table 49: Levetiracetam vs Placebo

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Placebo	Relative (95% CI)	Absolute	Quality
50% responder											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Placebo	Relative (95% CI)	Absolute	Quality
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/25 (64%)	6/27 (22.2%)	RR 2.88 (1.34 to 6.19)	418 more per 1000 (from 76 more to 1000 more)	Moderate
Change in migraine/headache severity (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	27	-	MD -0.88 (-1.27 to -0.49)	Moderate
Change in migraine/headache frequency (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	27	-	MD -2.26 (-3.03 to -1.49)	Moderate
Change in use of acute treatment (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	27	-	MD -3.63 (-4.44 to -2.82)	Moderate

[1] *Verma 2013*
[2] *Per-protocol analysis and moderate dropout rate (approximately 20%). Unclear whether all investigators were blind to treatment allocation.*

Table 50: Divalproex sodium vs Placebo

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Divalproex sodium	Placebo	Relative (95% CI)	Absolute	Quality
50% responder - All ages											
3[1]	RCT	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	187/425 (44%)	47/149 (31.5%)	RR 1.75 (0.75 to 4.07)	237 more per 1000 (from 79 fewer to 968 more)	Low
50% responder - Mean age under 18											
1[4]	RCT	no serious	no serious	no serious	no serious	none	97/227	33/71	RR 0.92 (0.69 to	37 fewer per 1000 (from	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Divalproex sodium	Placebo	Relative (95% CI)	Absolute	Quality
		risk of bias	inconsistency	indirectness	imprecision		(42.7%)	(46.5%)	1.23)	144 fewer to 107 more)	High
50% responder - Mean age over 18											
2[5]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	90/198 (45.5%)	14/78 (17.9%)	RR 2.46 (1.5 to 4.03)	262 more per 1000 (from 90 more to 544 more)	High
Change in migraine/headache frequency – All ages (Better indicated by lower values)											
2[6]	RCT	no serious risk of bias	serious[2]	no serious indirectness	very serious[7]	none	288	103	-	MD -1.11 (-3.43 to 1.22)	Very Low
Change in migraine/headache frequency - Mean age under 18 (Better indicated by lower values)											
1[4]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	228	71	-	MD 0.07 (-0.49 to 0.63)	High
Change in migraine/headache frequency - Mean age over 18 (Better indicated by lower values)											
1[8]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	60	32	-	MD -2.3 (-2.99 to -1.61)	Moderate
Serious adverse events											
1[10]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	2/122 (1.6%)	4/115 (3.5%)	RR 0.47 (0.09 to 2.52)	18 fewer per 1000 (from 32 fewer to 53 more)	Low

[1] *Apostol 2008, Klapper 1997, Mathew 1995*
[2] *Confidence intervals are non-overlapping and test for heterogeneity is statistically significant. Inconsistency is potentially clinically important (no difference vs clinically important benefit of Divalproex sodium).*
[3] *Confidence intervals encompass clinically important benefit of Divalproex and no clinically important difference.*
[4] *Apostol 2008*
[5] *Klapper 1997, Mathew 1995*
[6] *Apostol 2008, Mathew 1995*
[7] *Confidence intervals encompass both clinically important benefit and harm.*

[8] *Mathew 1995*
[9] *Standard errors estimated by reviewer from figure.*
[10] *Freitag 2002*

Table 51: Topiramate vs Placebo

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topiramate**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**
Change in migraine/headache days (Better indicated by lower values)											
2[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	185	180	-	MD -2.27 (-4.2 to -0.35)	Low
50% responder											
8[4]	RCT	serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	618/1362 (45.4%)	159/585 (27.2%)	RR 1.66 (1.37 to 1.99)	179 more per 1000 (from 101 more to 269 more)	Moderate
Change in migraine/headache severity (Better indicated by lower values)											
2[5]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	504	267	-	SMD 0.06 (-0.21 to 0.32)	Moderate
Quality of life (Better indicated by lower values)											
4[6]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	365	372	-	SMD -0.3 (-0.51 to -0.09)	Low
Change in use of acute treatment (Better indicated by lower values)											
6[7]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1208	719	-	MD -0.8 (-1.13 to -0.48)	Moderate
Serious adverse events											
2[8]	RCT	serious[2]	no serious inconsistency	no serious indirectness	very serious[9]	none	4/208 (1.9%)	6/212 (2.8%)	RR 0.67 (0.19 to 2.35)	9 fewer per 1000 (from 23 fewer to 38 more)	Very Low

[1] *Diener 2007, Silberstein 2007*
[2] *High dropout rates across studies (1/3 to 1/2 of participants). Although this was potentially mitigated by using intention to treat analyses, this was only possible when at least one post-baseline efficacy measurement was available.*
[3] *Confidence intervals encompass clinically important benefit and no clinically important difference.*
[4] *Brandes 2004, Diener 2004, Lakshmi 2007, Lewis 2009, Mei 2004, Silberstein 2004, Silberstein 2006, Winner 2005*
[5] *Brandes 2004, Silberstein 2007*
[6] *Diener 2007, Lakshmi 2007, Lipton 2011, Silberstein 2007*

[7] *Brandes 2004, Diener 2004, Diener 2007, Lipton 2011, Silberstein 2004, Silberstein 2007*
[8] *Diener 2007, Lipton 2011*
[9] *Confidence intervals encompass both clinically important benefit and harm.*

Table 52: Bisoprolol vs Placebo

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bisoprolol	Placebo	Relative (95% CI)	Absolute	Quality
Change in migraine/headache frequency (Better indicated by lower values)											
1[1]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	151	75	-	MD -0.85 (-1.35 to -0.35)	Moderate

[1] *Van de Ven 1997*
[2] *Confidence intervals encompass clinically important benefit and no clinically important difference.*

Table 53: Nadolol vs Placebo

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nadolol	Placebo	Relative (95% CI)	Absolute	Quality
50% responder											
1[1,2]	RCT	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/22 (27.3%)	0/8 (0%)	RR 5.09 (0.32 to 81.29)	-	Very Low

[1] *Freitag 1984*
[2] *Confidence intervals encompass both clinically important benefit and harm.*
[3] *No reporting of dropouts from study. No exclusion criteria reported or indication of baseline headache frequency or severity.*

Table 54: Propranolol vs Placebo

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Placebo	Relative (95% CI)	Absolute	Quality

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Placebo	Relative (95% CI)	Absolute	Quality
50% responder											
2[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	76/221 (34.4%)	39/198 (19.7%)	RR 1.64 (1.16 to 2.33)	126 more per 1000 (from 32 more to 262 more)	Low
Change in migraine/headache frequency (Better indicated by lower values)											
2[4]	RCT	serious[2]	serious[5]	no serious indirectness	very serious[6]	none	165	162	-	MD -2.07 (-4.59 to 0.45)	Very Low
Change in use of acute treatment (Better indicated by lower values)											
1[7]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	143	143	-	MD -0.8 (-1.4 to -0.2)	Low
Change in use of acute treatment (Better indicated by lower values)											
1[8]	RCT	serious[9]	no serious inconsistency	serious[10]	very serious[11]	none	27	24	-	MD 0.56 (-0.64 to 1.76)	Very Low

[1] *Diener 1996, Diener 2004*
[2] *Moderate to high dropout rates (15-35%) - only partially migated by intention to treat analysis.*
[3] *Confidence intervals encompass both clinically important benefit and no clinically important difference.*
[4] *Diener 2004, Pradalier 1989*
[5] *Test for heterogeneity is statistically significant and confidence intervals are non-overlapping.*
[6] *Confidence intervals encompass both clinically important benefit and harm.*
[7] *Diener 2004*
[8] *Nadelmann 1986*
[9] *Investigator responsible for dose titration was not blind to treatment allocation.*
[10] *Outcome measure may not be applicable to current practice (types of analgesic given a score and 'rescue medication unit index' calculated by multiplying score by amount of medication used).*
[11] *Confidence intervals encompass both clinically important harm and no clinically important difference.*

Table 55: Propranolol/nadolol vs Placebo

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol/nadolol	Placebo	Relative (95% CI)	Absolute	
Change in migraine/headache days - 10 months (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	53	55	-	MD -0.5 (-1 to 0 higher)	Low
50% responder											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	18/35 (51.4%)	22/40 (55%)	RR 0.94 (0.61 to 1.43)	33 fewer per 1000 (from 214 fewer to 236 more)	Very Low
Change in migraine/headache frequency - 5 months (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	55	-	MD 0 (-0.21 to 0.21)	Moderate
Change in migraine/headache frequency - 10 months (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	55	-	MD 0 (-0.33 to 0.33)	Moderate
Change in Quality of life - 5 months (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	55	-	MD 0 (-0.93 to 0.93)	Moderate
Change in Quality of life - 10 months (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	55	-	MD 0.3 (-0.84 to 1.44)	Moderate

[1] *Holroyd 2010*
[2] *High dropout rates (30-55%) only partly mitigated by intention to treat analysis.*
[3] *Confidence intervals encompass both clinically important benefit and no clinically important difference.*
[4] *Confidence intervals encompass both clinically important benefit and harm.*

Table 56: Nimodipine vs Placebo

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nimodipine	Placebo	Relative (95% CI)	Absolute	
Change in migraine/headache frequency (Better indicated by lower values)											
2[1]	RCT	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	28	28	-	MD -0.9 (-3.27 to 1.48)	Very Low

[1] *Batistella 1990, Stewart 1980*
[2] *Moderate dropout rates in both studies (>20%) and analysis was per protocol.*
[3] *One of the two studies included participants with age outside of the study population (<12 years).*
[4] *Confidence intervals encompass both clinically important benefit and no clinically important difference.*

Table 57: Topiramate vs Amitriptyline

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Topiramate**	**Amitriptyline**	**Relative (95% CI)**	**Absolute**	**Quality**
Change in migraine/headache frequency (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious	none	152	143	-	MD -0.1 (-0.9 to 0.7)	Moderate
Quality of life (Better indicated by lower values)											
1[1]	RCT	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	152	143	-	MD 1.9 (-3.13 to 6.93)	Moderate
Serious adverse events											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	very serious imprecision[5]	none	4/177 (2.3%)	8/169 (4.7%)	RR 0.48 (0.15 to 1.56)	25 fewer per 1000 (from 40 fewer to 27 more)	Very low

[1] *Dodick 2009*
[2] *High dropout rates (around 40%) for both study arms, only partly mitigated by intention to treat analysis.*
[4] *High dropout rates (around 40%) and intention to treat analysis was not possible for quality of life outcome*
[5] *Confidence intervals encompass clinically important effects favouring both Topiramate and Amitriptyline.*

Table 58: Topiramate vs Sodium Valproate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Sodium valproate	Relative (95% CI)	Absolute	
Change in migraine/headache severity (Better indicated by lower values)											
2[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	63	63	-	SMD -0.13 (-1.1 to 0.83)	Very Low
Change in migraine/headache frequency (Better indicated by lower values)											
2[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63	63	-	MD -0.04 (-0.71 to 0.63)	Moderate
Change in use of acute treatment (Better indicated by lower values)											
1[4]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	28	28	-	MD -0.44 (-1.21 to 0.33)	Low

[1] *Afshari 2012, Bavrasad 2010*
[2] *Dropout rates were moderate to high (20-30%) in Ashrafi study, but were not considered in the analysis.*
[3] *Confidence intervals encompass both clinically important differences favouring topiramate and sodium valproate.*
[4] *Afshari 2012*
[5] *Confidence intervals encompass both clinically important difference favouring topiramate and no clinically important difference.*

Table 59: Topiramate vs Propranolol

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Propranolol	Relative (95% CI)	Absolute	
50% responder											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	72/282 (25.5%)	43/143 (30.1%)	RR 0.85 (0.62 to 1.17)	45 fewer per 1000 (from 114 fewer to 51 more)	Low
Change in migraine/headache frequency (Better indicated by lower values)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	Propranolol	Relative (95% CI)	Absolute	
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	282	143	-	MD 0.25 (-0.26 to 0.76)	Moderate
Change in use of acute treatment (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	282	143	-	MD 0.4 (-0.11 to 0.91)	Moderate

[1] *Diener 2004*
[2] *High dropout rates (>40% across study), which were substantially higher in the group taking 200mg/d of topiramate compared with propranolol.*
[3] *Confidence intervals encompass both clinically important favouring propranolol and no clinically important difference.*

Table 60: Propranolol vs Sodium Valproate

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol	Sodium valproate	Relative (95% CI)	Absolute	
50% responder											
1[1]	RCT	serious	no serious inconsistency	serious[2]	serious[3]	none	25/30 (83.3%)	19/30 (63.3%)	RR 1.32 (0.96 to 1.8)	203 more per 1000 (from 25 fewer to 507 more)	Very Low
Change in migraine/headache frequency (Better indicated by lower values)											
1[1]	RCT	serious[4]	no serious inconsistency	serious[2]	serious[3]	none	30	30	-	MD -2.23 (-3.85 to -0.61)	Very Low

[1] *Bidabadi 2010*
[2] *Population for the trial including participants outside of the population for the review (<12 years).*
[3] *Confidence intervals encompass both clinically important difference favouring propranolol and no clinically important difference.*
[4] *Baseline and outcome data was collected using retrospective questionnaires - potentially less accurate and more susceptible to recall bias than prospective headache diary as for other studies.*

Table 61: Metoprolol vs Nebivolol

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metoprolol	Nebivolol	Relative (95% CI)	Absolute	
50% responder											
1[1]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/14 (57.1%)	8/16 (50%)	RR 1.14 (0.59 to 2.23)	70 more per 1000 (from 205 fewer to 615 more)	Low
Change in migraine/headache frequency (Better indicated by lower values)											
1[1]	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	14	16	-	MD -0.4 (-1.23 to 0.43)	Moderate

[1] *Schellenberg 2007*
[2] *Confidence intervals encompass both clinically important differences favouring metoprolol and nebivolol.*
[3] *Confidence intervals encompass both clinically important difference favouring metoprolol and no clinically important difference.*

Table 62: Cinnarizine vs Divalproex Sodium

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cinnarizine	Sodium Valproate	Relative (95% CI)	Absolute	
50% responder											
1[1]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/67 (20.9%)	37/58 (63.8%)	RR 0.33 (0.2 to 0.54)	427 fewer per 1000 (from 293 fewer to 510 fewer)	Low

[1] *Mansoureh 2008*
[2] *Dropout rate was high (around 40%), but analysis was per protocol and so did not take this into account. Tablets were not identical in appearance, leading to the possibility of unblinding.*

Table 63: Cinnarizine vs Sodium Valproate

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cinnarizine	Sodium Valproate	Relative (95% CI)	Absolute	
50% responder											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/50 (20.9%)	36/54 (63.8%)	RR 0.48 (0.31 to 0.75)	347 fewer per 1000 (from 167 fewer to 460 fewer)	Moderate
Change in migraine/headache severity (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	50	54	-	MD 1.02 (0.41 to 1.63)	Low
Change in migraine/headache frequency (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	50	54	-	MD 1.78 (0.02 to 3.54)	Low
Change in Quality of life (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	50	54	-	MD 1.14 (-2.55 to 4.83)	Low
Change in use of acute treatment (Better indicated by lower values)											
1[1]	RCT	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	54	-	MD 0.27 (-2.67 to 3.21)	Moderate

[1] *Bostani 2013*
[2] *Moderate dropout rate (>20%) and per protocol analysis. Not details of baseline data collected provided.*
[3] *Confidence intervals encompass both clinically important difference favouring sodium valproate and no clinically important difference.*

Table 64: Cinnarizine vs Topiramate

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cinnarizine**	**Topiramate**	**Relative (95% CI)**	**Absolute**	**Quality**
50% responder											
1[1]	RCT	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	17/20 (85%)	13/20 (65%)	RR 1.31 (0.9 to 1.89)	201 more per 1000 (from 65 fewer to 578 more)	Low
Change in migraine/headache severity (Better indicated by lower values)											
1[1]	RCT	no serious	no serious inconsistency	serious[2]	serious[3]	none	20	20	-	MD -1.7 (-3.28 to -0.12)	Low

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cinnarizine	Topiramate	Relative (95% CI)	Absolute	Quality
		risk of bias									
Change in migraine/headache frequency (Better indicated by lower values)											
1[1]	RCT	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	20	20	-	MD -1.2 (-5.08 to 2.68)	Very Low

[1] *Ashrafi 2014*
[2] *Included participants outside of the population for the review (<12 years).*
[3] *Confidence intervals encompass both clinically important difference favouring cinnarizine and no clinically important difference.*

Appendix I: Forest plots

Figure 1: Telmisartan vs Placebo – Change in acute medication use

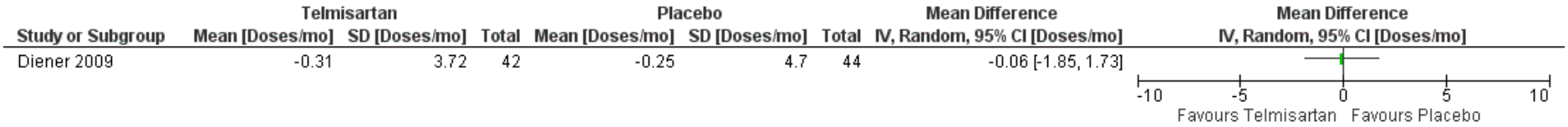


Figure 2: Trazodone vs Placebo – Change in migraine/headache frequency

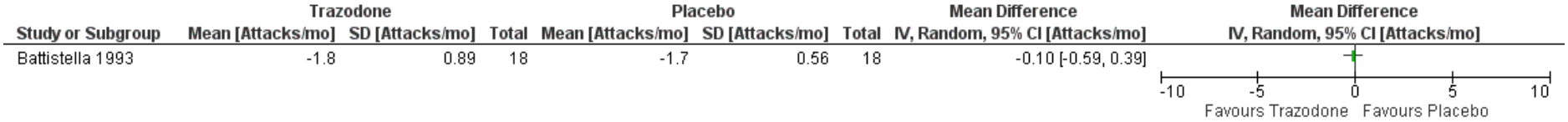


Figure 3: Gabapentin vs Placebo – 50% responder

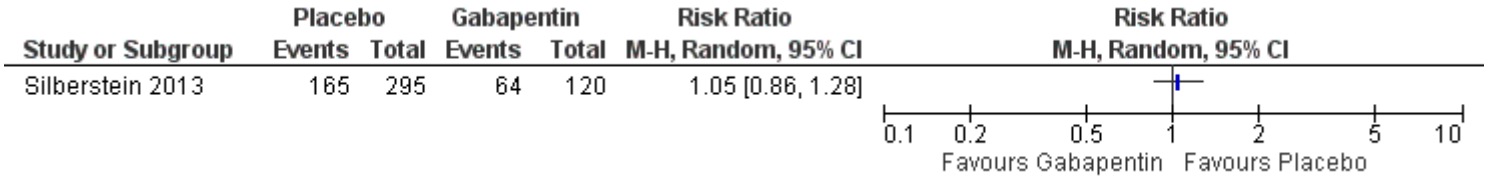


Figure 4: Gabapentin vs Placebo – Change in migraine/headache frequency

Study or Subgroup	Gabapentin Mean [Attacks/mo]	Gabapentin SD [Attacks/mo]	Gabapentin Total	Placebo Mean [Attacks/mo]	Placebo SD [Attacks/mo]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [Attacks/mo]
Feuerstein 1990	-1.4	2.6	22	-0.7	2.1	31	8.5%	-0.70 [-2.01, 0.61]
Silberstein 2013	-2.2	1.79	333	-2.2	2.02	128	91.5%	0.00 [-0.40, 0.40]
Total (95% CI)			**355**			**159**	**100.0%**	**-0.06 [-0.44, 0.32]**

Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.76)

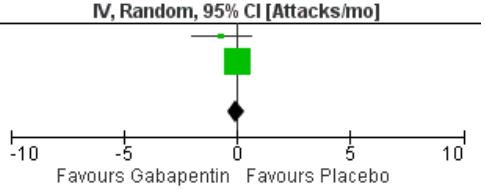


Figure 5: Levetiracetam vs Placebo - 50% responder

Study or Subgroup	Levetiracetam Events	Levetiracetam Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Verma 2013	16	25	6	27	2.88 [1.34, 6.19]

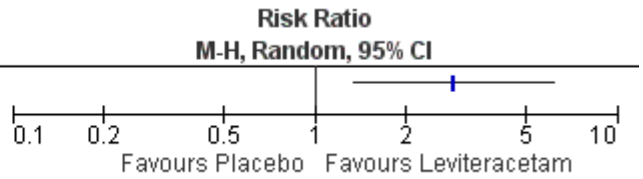


Figure 6: Levetiracetam vs Placebo - Change in migraine/headache intensity

Study or Subgroup	Levetiracetam Mean [0-3 scale]	Levetiracetam SD [0-3 scale]	Levetiracetam Total	Placebo Mean [0-3 scale]	Placebo SD [0-3 scale]	Placebo Total	Mean Difference IV, Random, 95% CI [0-3 scale]
Verma 2013	-1.46	0.65	25	-0.58	0.77	27	-0.88 [-1.27, -0.49]

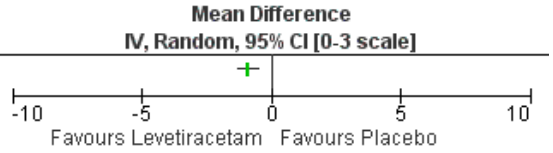


Figure 7: Levetiracetam vs Placebo - Change in migraine/headache frequency

Study or Subgroup	Levetiracetam Mean [Attacks/mo]	Levetiracetam SD [Attacks/mo]	Levetiracetam Total	Placebo Mean [Attacks/mo]	Placebo SD [Attacks/mo]	Placebo Total	Mean Difference IV, Random, 95% CI [Attacks/mo]
Verma 2013	-2.96	1.35	25	-0.7	1.49	27	-2.26 [-3.03, -1.49]

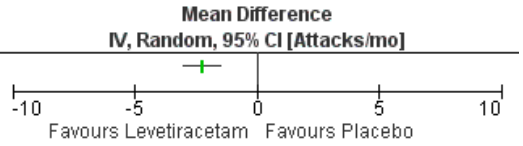


Figure 8: Levetiracetam vs Placebo - Change in acute medication use

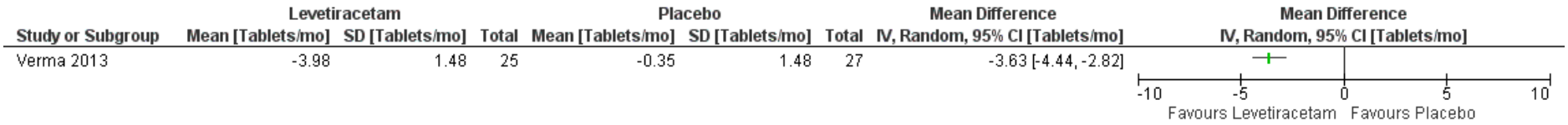


Figure 9:Divalproex sodium vs Placebo – 50% responder

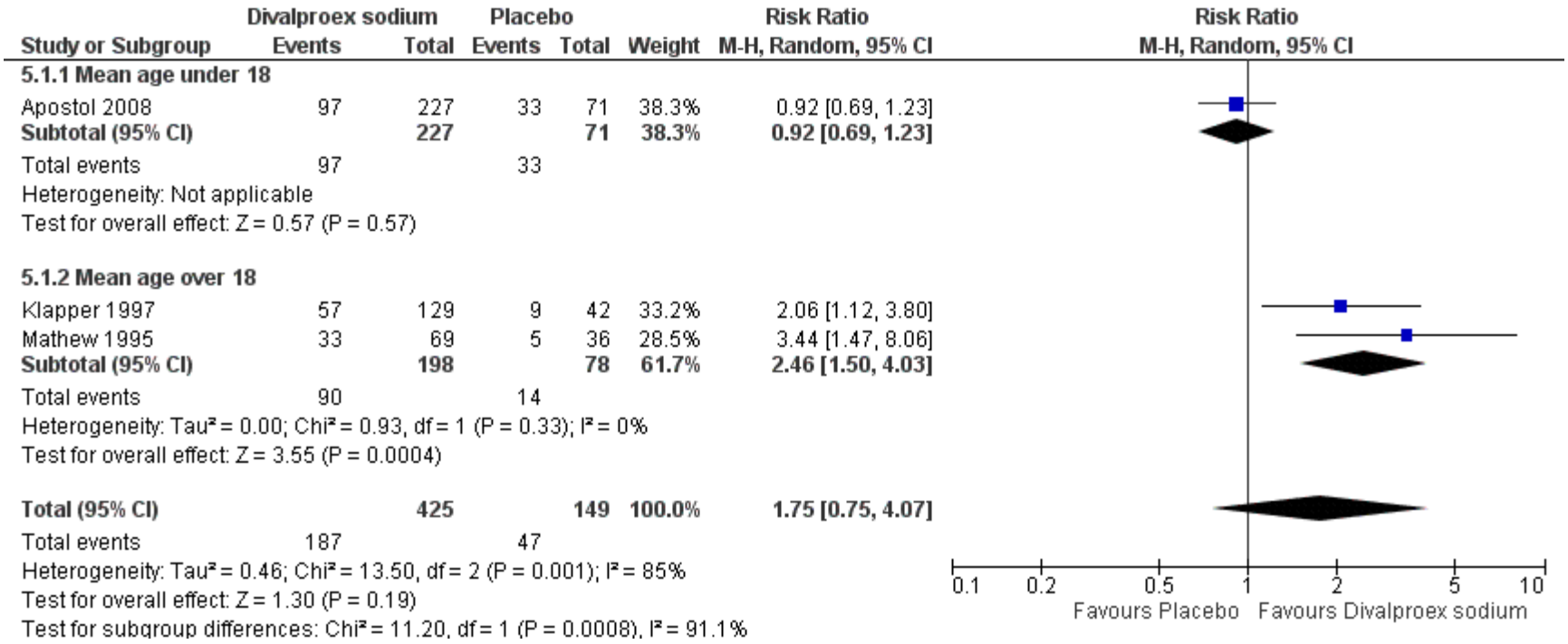


Figure 10:Divalproex sodium vs Placebo – Change in migraine/headache frequency

Study or Subgroup	Divalproex sodium Mean [Attacks/mo]	SD [Attacks/mo]	Total	Placebo Mean [Attacks/mo]	SD [Attacks/mo]	Total	Weight	Mean Difference IV, Random, 95% CI [Attacks/mo]
5.2.1 Mean age under 18								
Apostol 2008	-1.83	1.81	228	-1.9	2.18	71	50.4%	0.07 [-0.49, 0.63]
Subtotal (95% CI)			**228**			**71**	**50.4%**	**0.07 [-0.49, 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.81)								
5.2.2 Mean age over 18								
Mathew 1995	-3	1.87	60	-0.7	1.46	32	49.6%	-2.30 [-2.99, -1.61]
Subtotal (95% CI)			**60**			**32**	**49.6%**	**-2.30 [-2.99, -1.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.51 (P < 0.00001)								
Total (95% CI)			**288**			**103**	**100.0%**	**-1.11 [-3.43, 1.22]**
Heterogeneity: Tau² = 2.71; Chi² = 27.24, df = 1 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 0.93 (P = 0.35)								
Test for subgroup differences: Chi² = 27.24, df = 1 (P < 0.00001), I² = 96.3%								

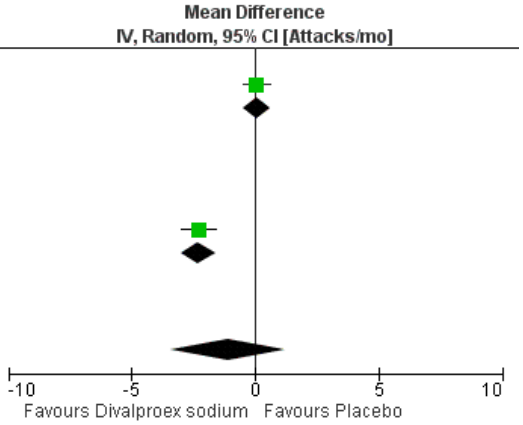


Figure 11:Divalproex sodium vs Placebo – Serious adverse events

Study or Subgroup	Divalproex Sodium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Freitag 2002	2	122	4	115	100.0%	0.47 [0.09, 2.52]
Total (95% CI)		**122**		**115**	**100.0%**	**0.47 [0.09, 2.52]**
Total events	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						

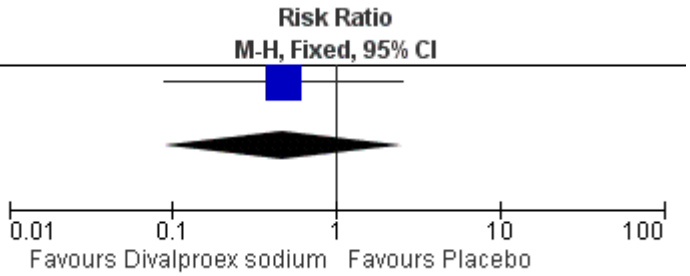


Figure 12:Topiramate vs Placebo – Change in migraine days (chronic migraine only –see network meta-analysis for other subgroups)

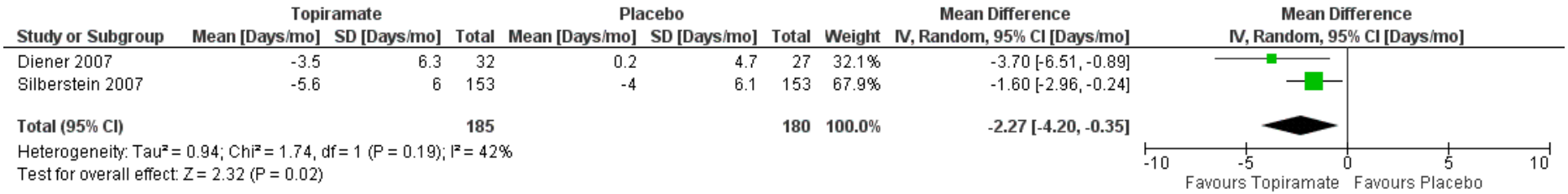


Figure 13:Topiramate vs Placebo – 50% responder

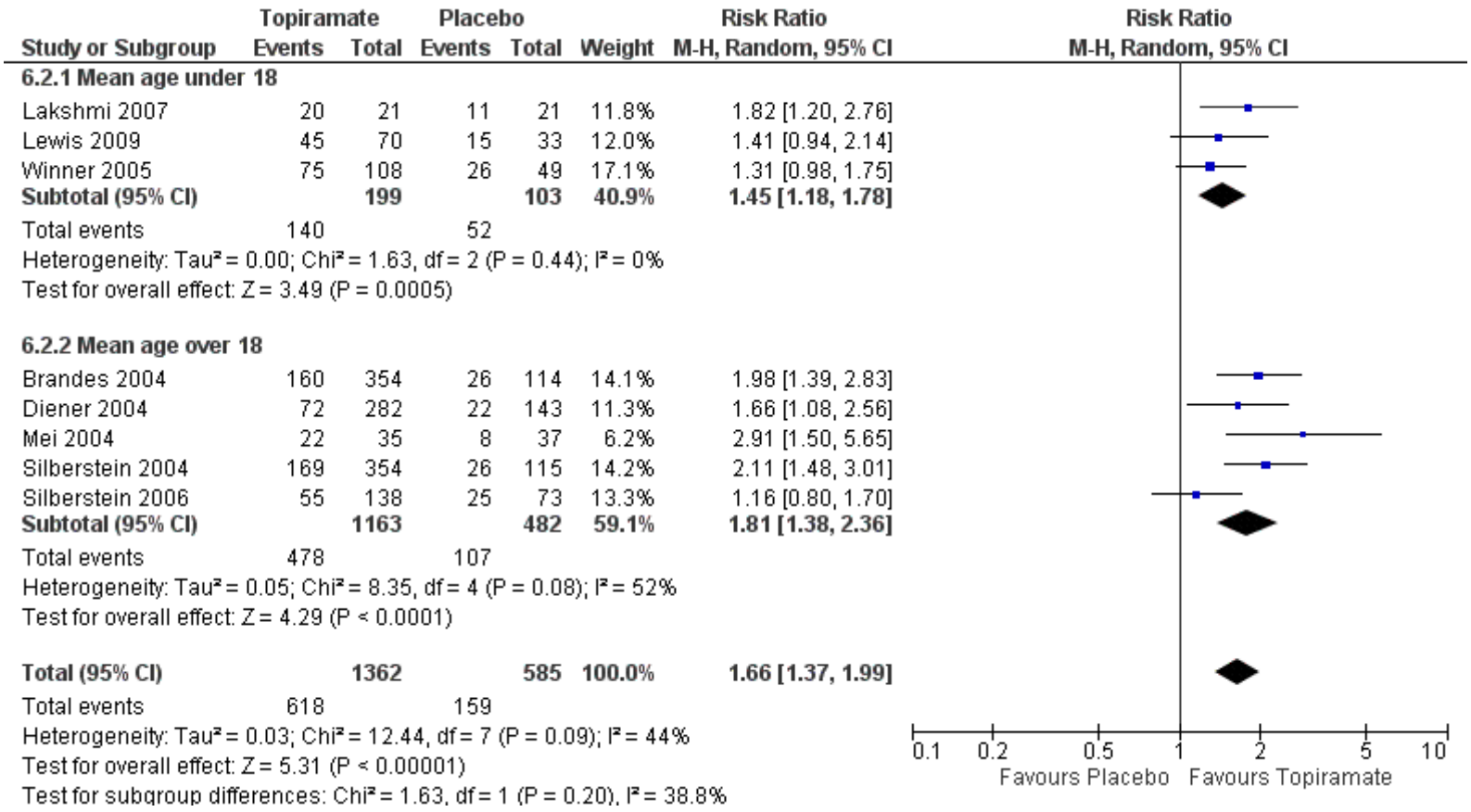


Figure 14:Topiramate vs Placebo – Change in migraine/headache intensity

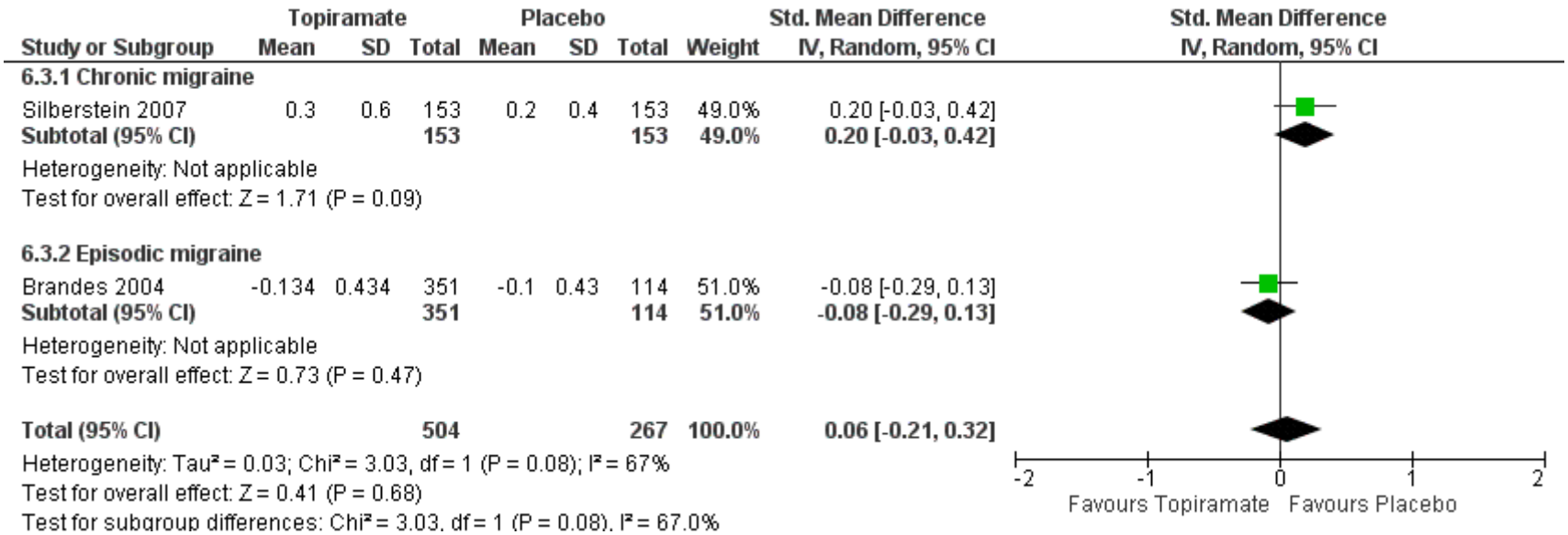


Figure 15:Topiramate vs Placebo – Quality of life

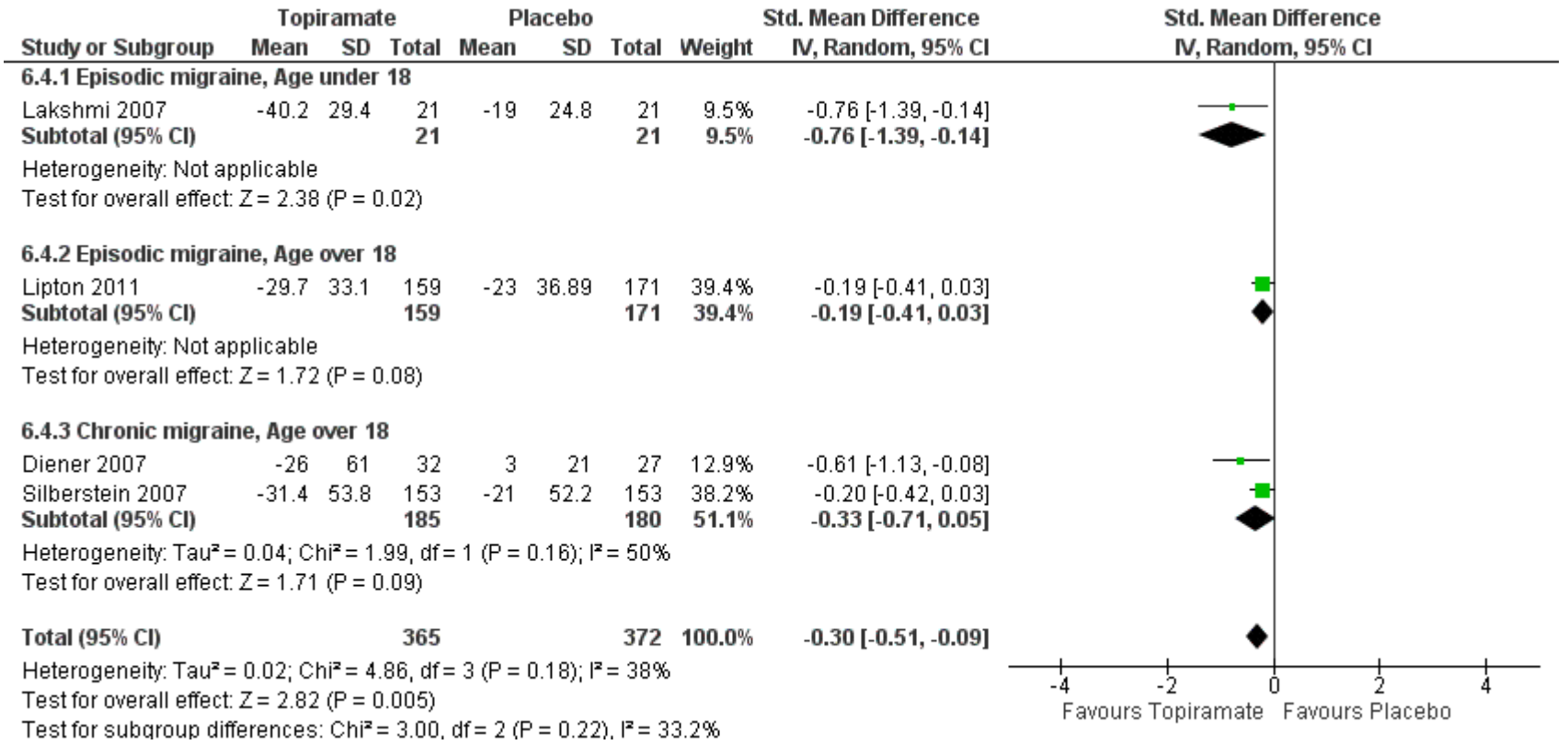


Figure 16:Topiramate vs Placebo – Change in acute medication use

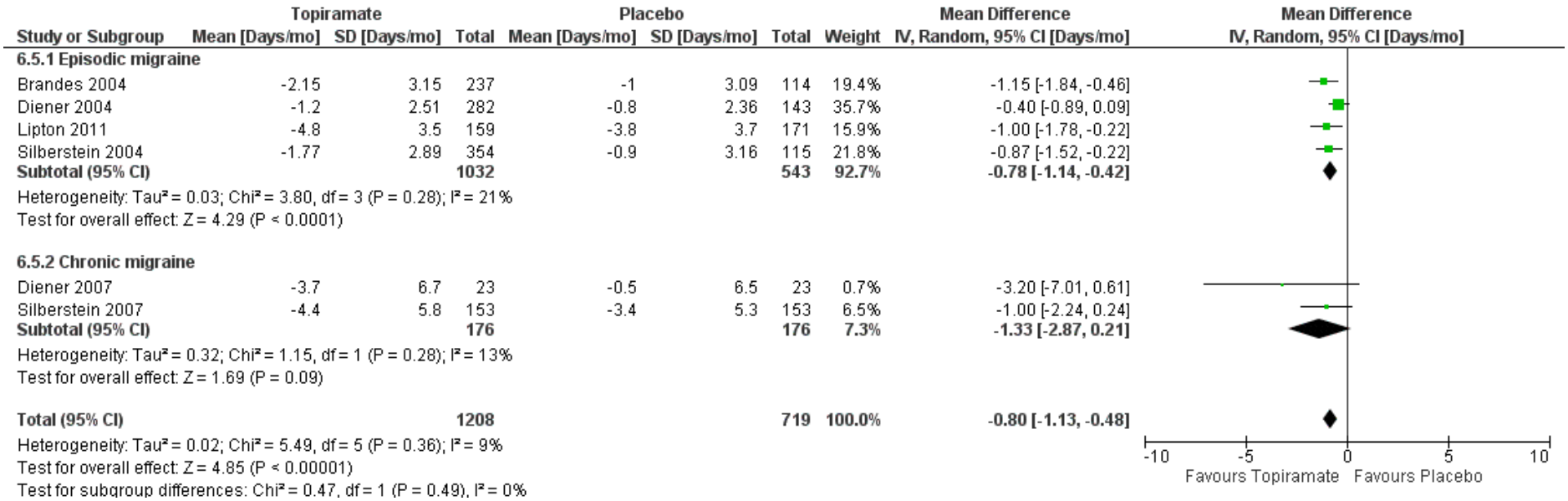


Figure 17:Topiramate vs Placebo – Serious adverse events

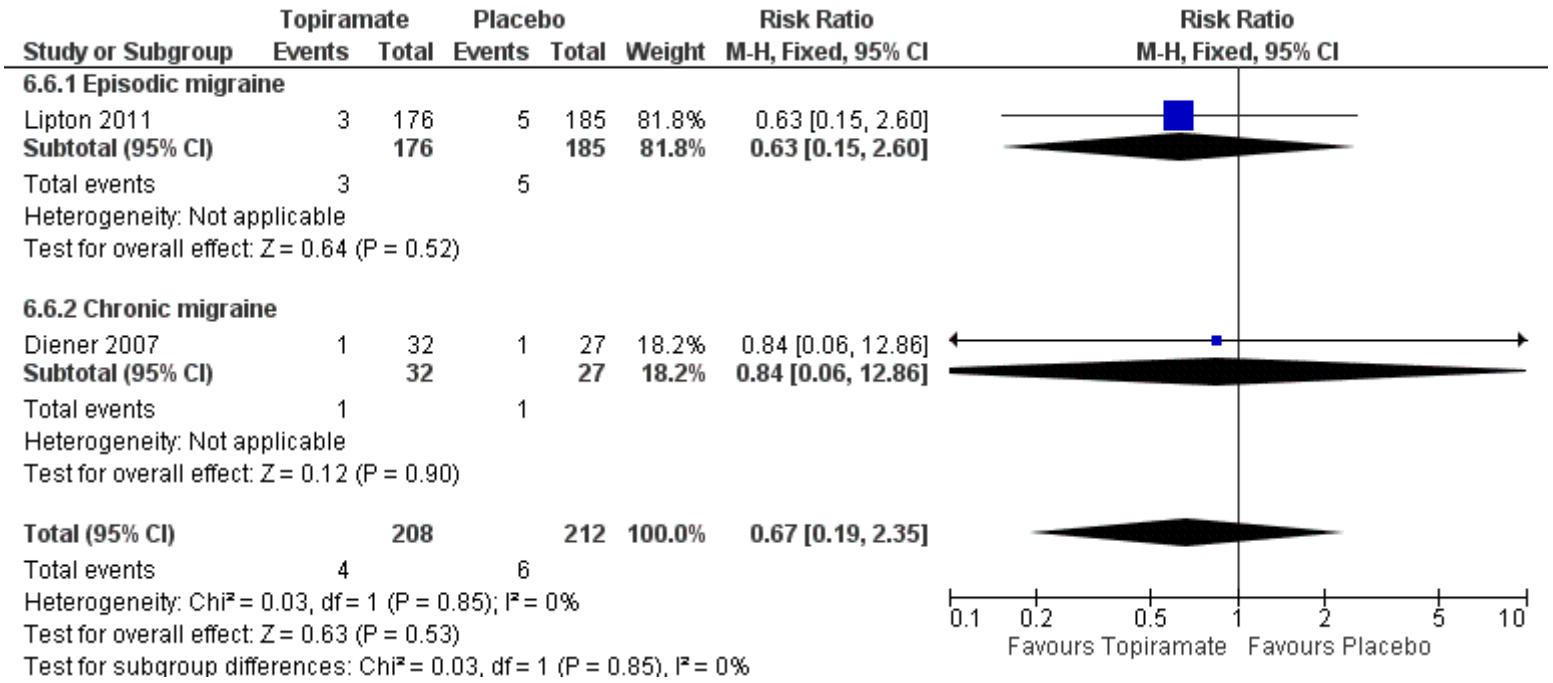


Figure 18: Bisoprolol vs Placebo – Change in migraine/headache frequency

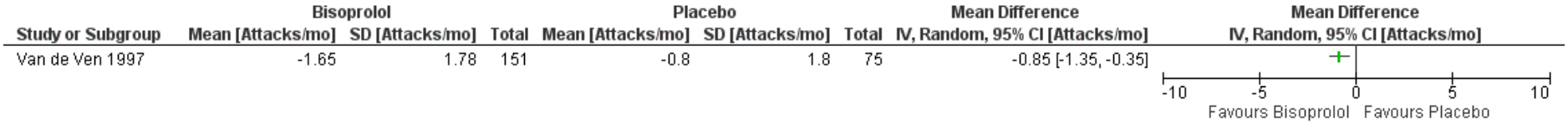


Figure 19: Nadolol vs Placebo – 50% responder

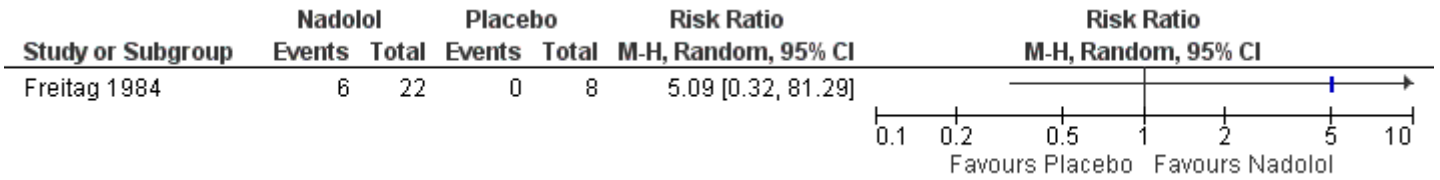


Figure 20: Propranolol vs Placebo – 50% responder

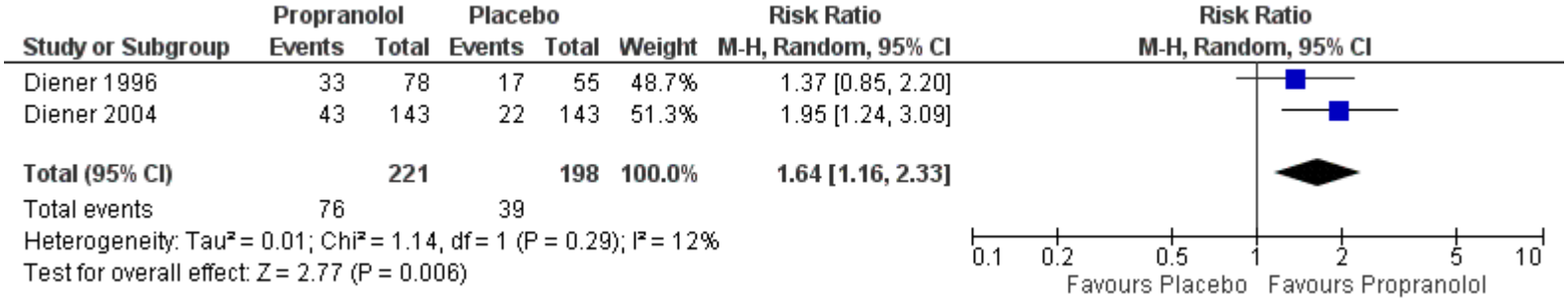


Figure 21: Propranolol vs Placebo – Change in headache/migraine frequency

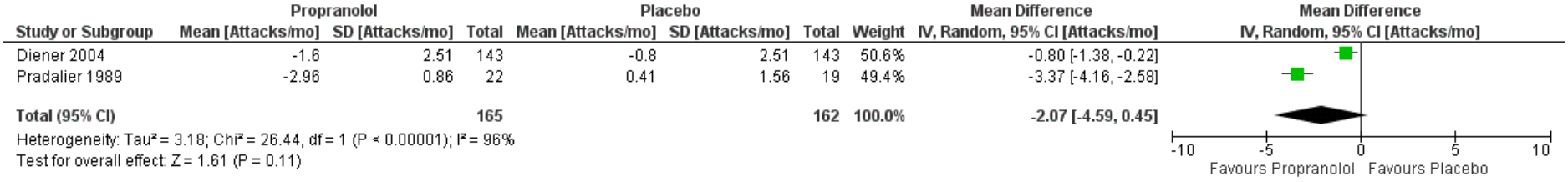


Figure 22: Propranolol vs Placebo – Change in acute medication use

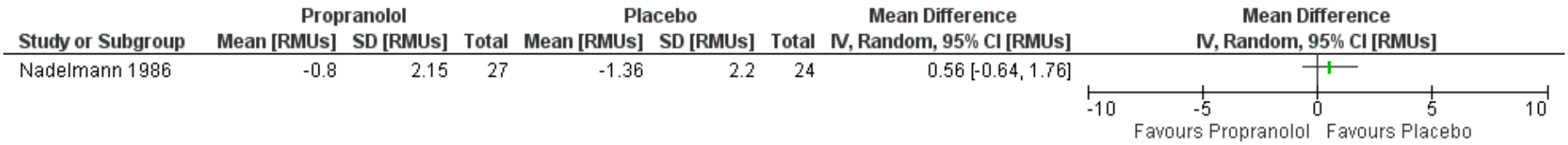


Figure 23: Propranolol/nadolol vs Placebo – Change in migraine days (10 months follow up)

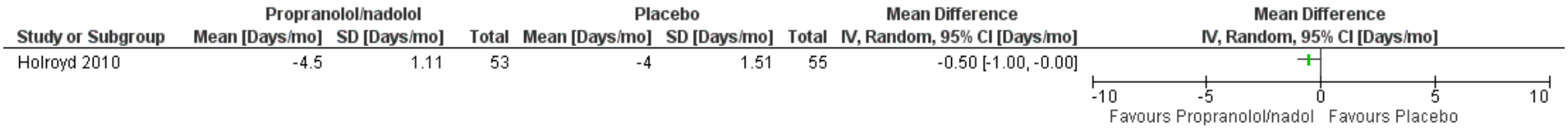


Figure 24: Propranolol/nadolol vs Placebo – 50% responder

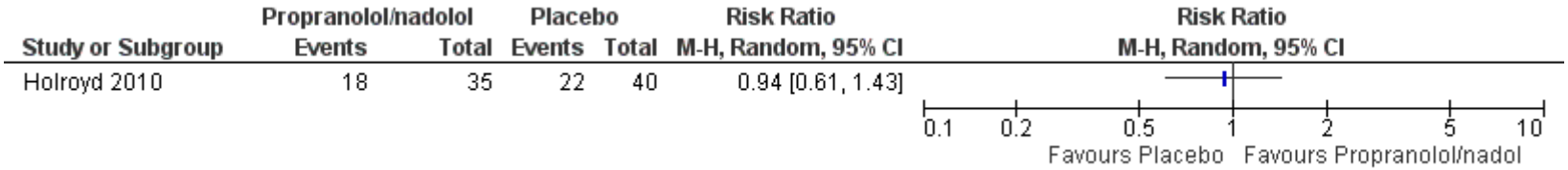


Figure 25: Propranolol/nadolol vs Placebo – Change in migraine/headache frequency (5 months follow up)

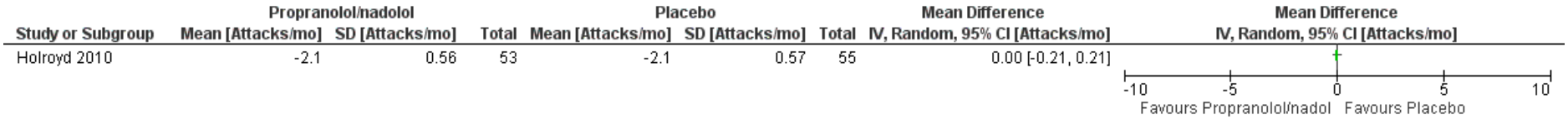


Figure 26: Propranolol/nadolol vs Placebo – Change in migraine/headache frequency (10 months follow up)

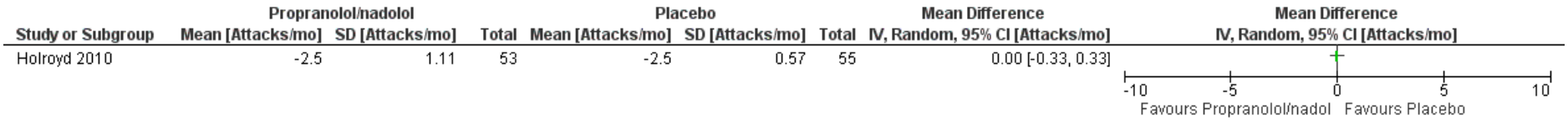


Figure 27: Propranolol/nadolol vs Placebo – Quality of life (5 months follow up)

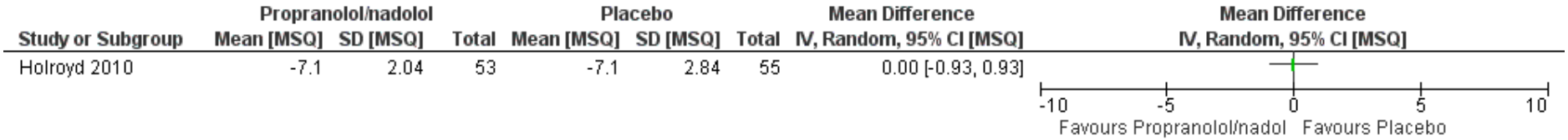


Figure 28: Propranolol/nadolol vs Placebo – Quality of life (10 months follow up)

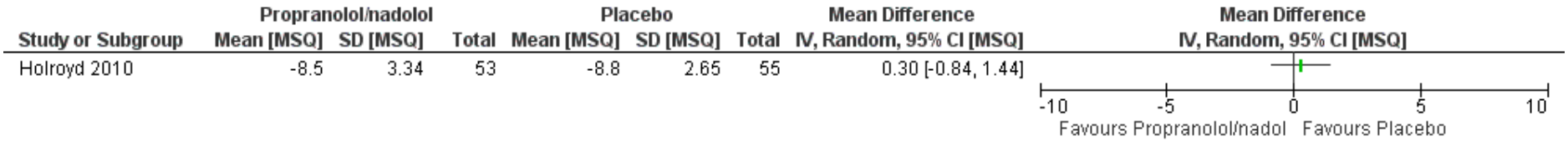


Figure 29: Nimodipine vs Placebo – Change in migraine/headache frequency

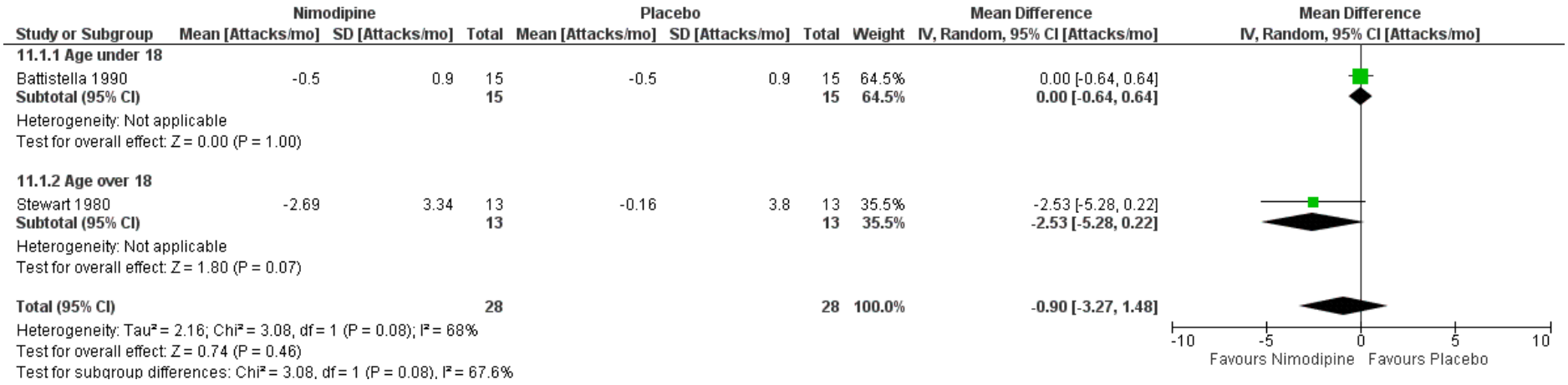


Figure 30: Topiramate vs Amitriptyline – Change in migraine/headache frequency

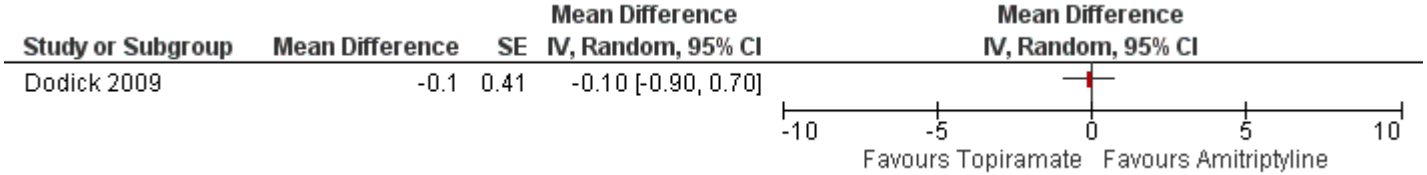


Figure 31: Topiramate vs Amitriptyline – Quality of life

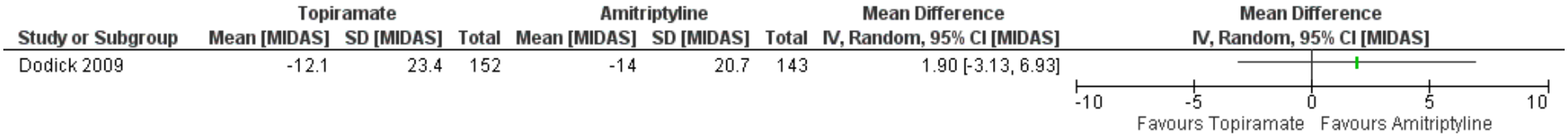


Figure 32: Topiramate vs Amitriptyline – Serious adverse events

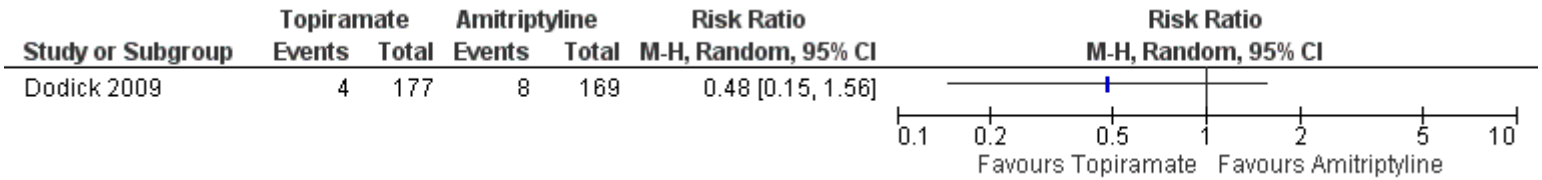


Figure 33: Topiramate vs Sodium Valproate – Change in migraine/headache intensity

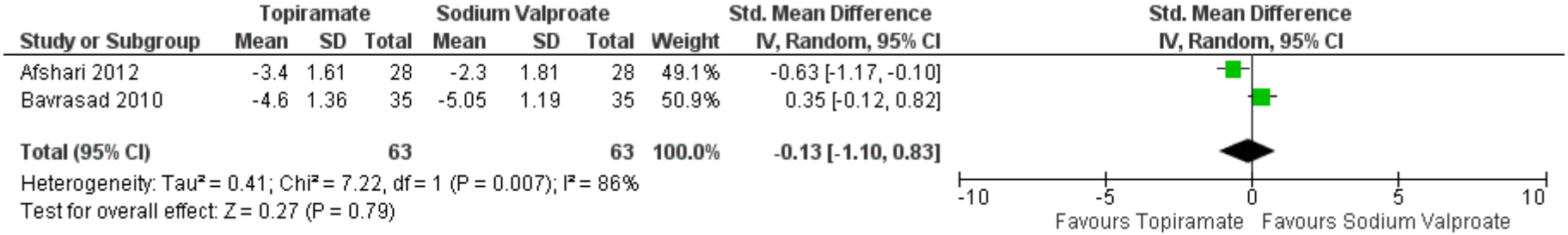


Figure 34: Topiramate vs Sodium Valproate – Change in migraine/headache frequency

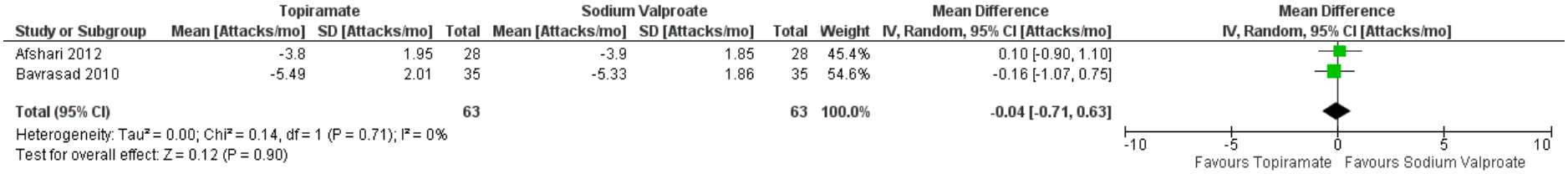


Figure 35: Topiramate vs Sodium Valproate – Change in acute medication use

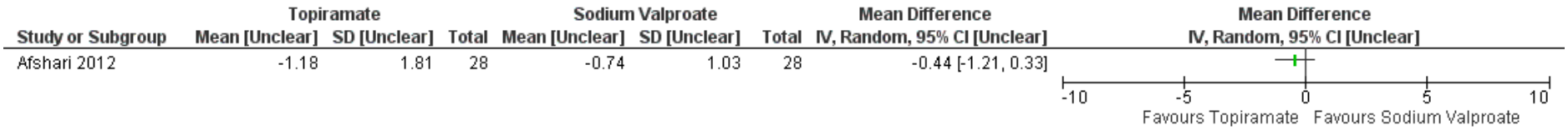


Figure 36: Topiramate vs Propranolol – 50% responder

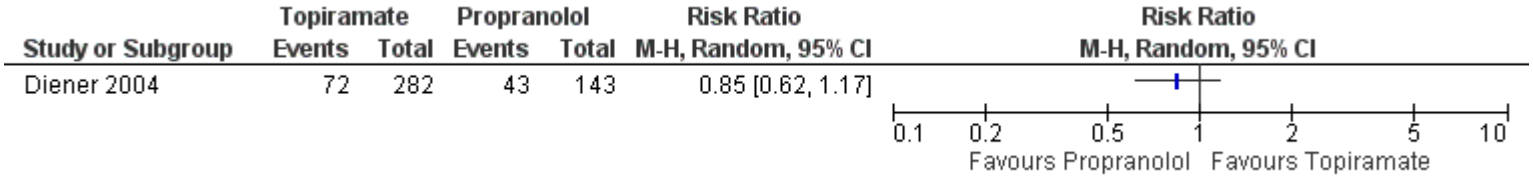


Figure 37: Topiramate vs Propranolol – Change in migraine/headache frequency

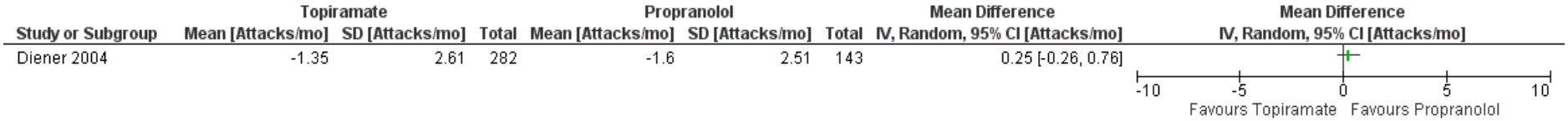


Figure 38: Topiramate vs Propranolol – Change in acute medication use

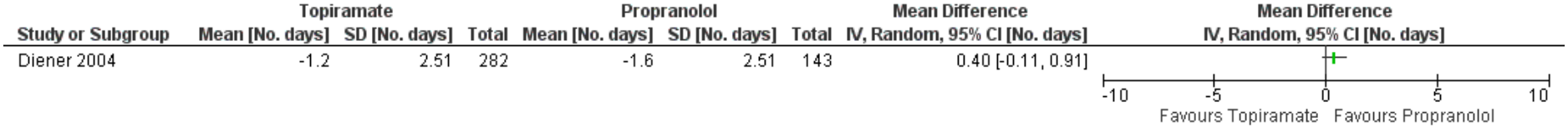


Figure 39: Propranolol vs Sodium Valproate – 50% responder

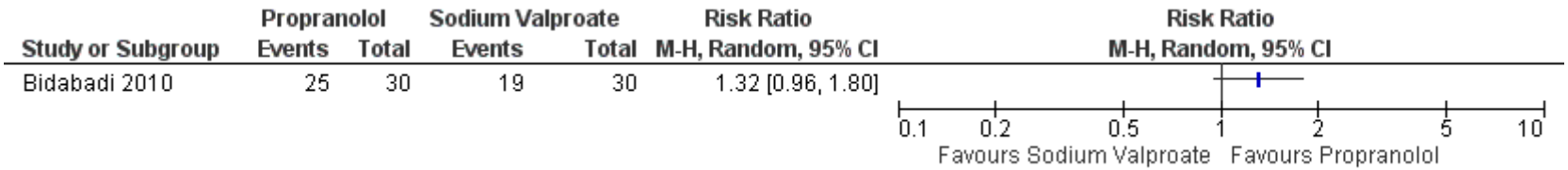


Figure 40: Propranolol vs Sodium Valproate – Change in migraine/headache frequency

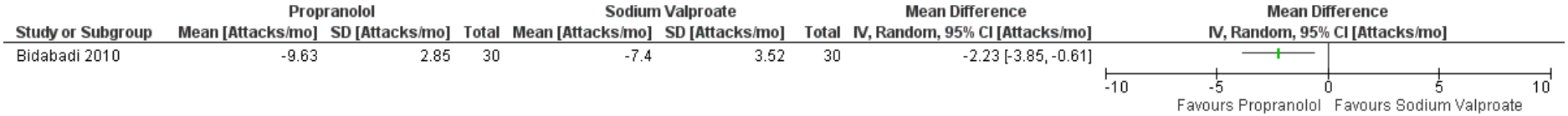


Figure 41: Metoprolol vs Nebivolol – 50% responder

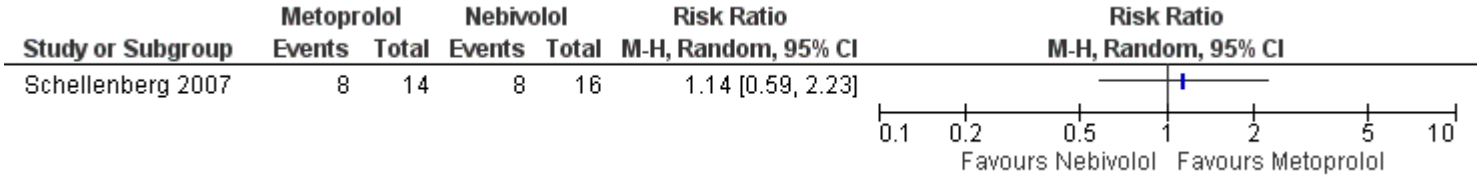


Figure 42: Metoprolol vs Nebivolol – Change in migraine/headache frequency

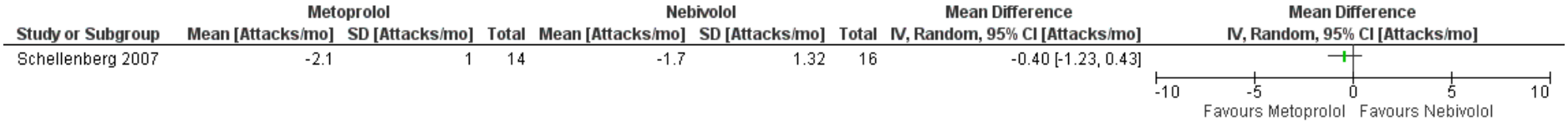


Figure 43: Cinnarizine vs Divalproex Sodium – 50% responder

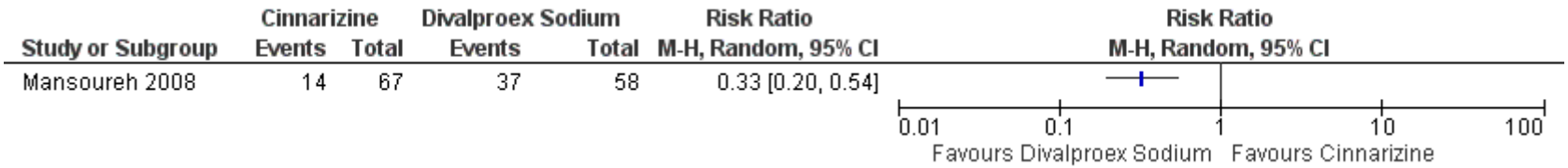


Figure 44: Cinnarizine vs Sodium Valproate – 50% responder

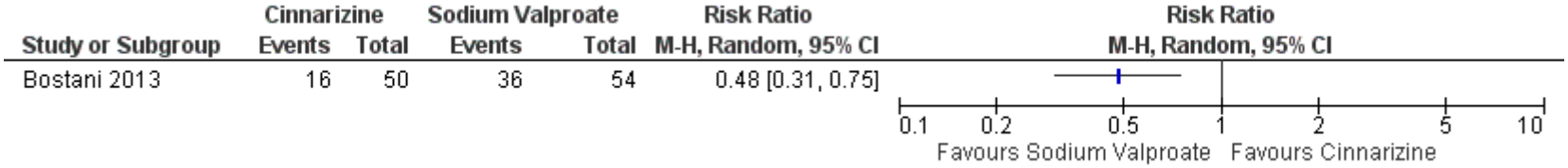


Figure 45: Cinnarizine vs Sodium Valproate – Change in migraine/headache intensity

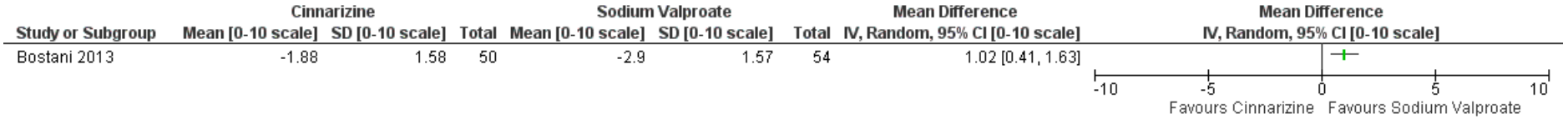


Figure 46: Cinnarizine vs Sodium Valproate – Change in migraine/headache frequency

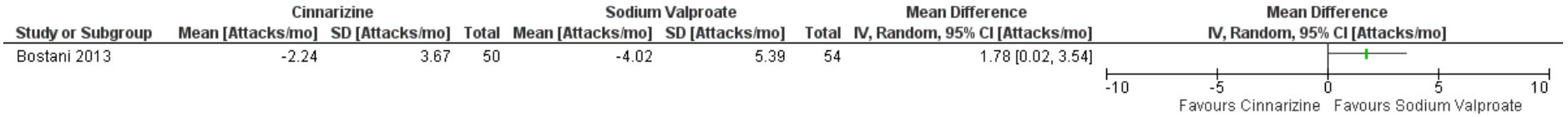


Figure 47: Cinnarizine vs Sodium Valproate – Quality of life

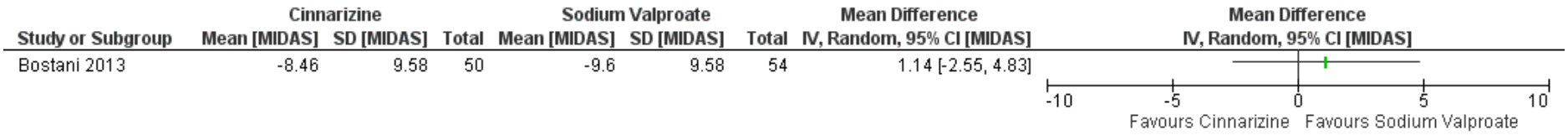


Figure 48: Cinnarizine vs Sodium Valproate – Acute medication use

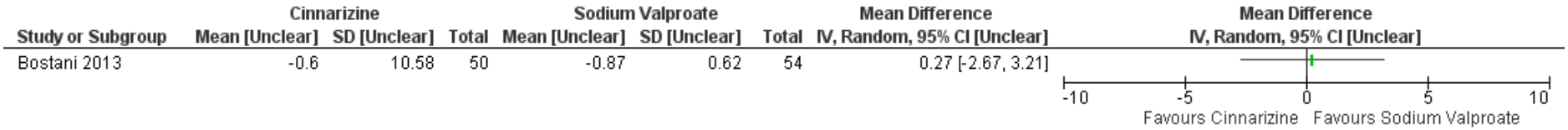


Figure 49: Cinnarizine vs Topiramate – 50% responder

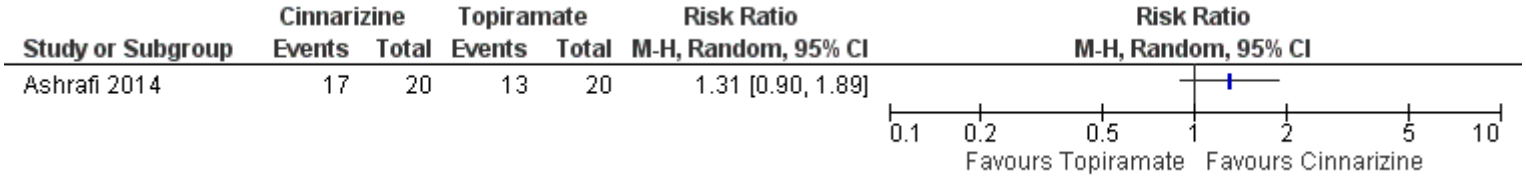


Figure 50: Cinnarizine vs Topiramate – Change in migraine/headache intensity

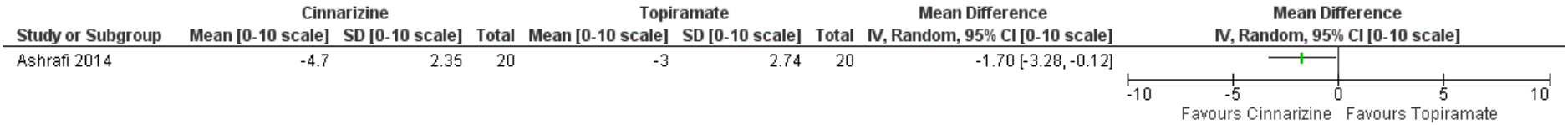
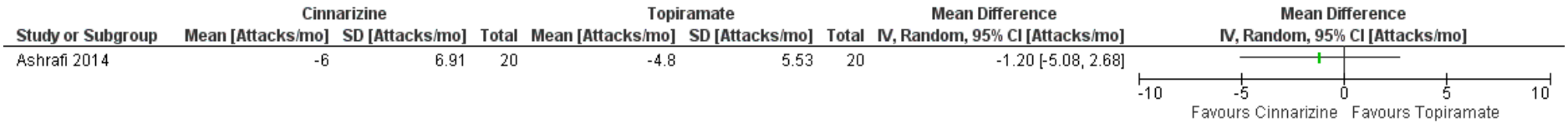


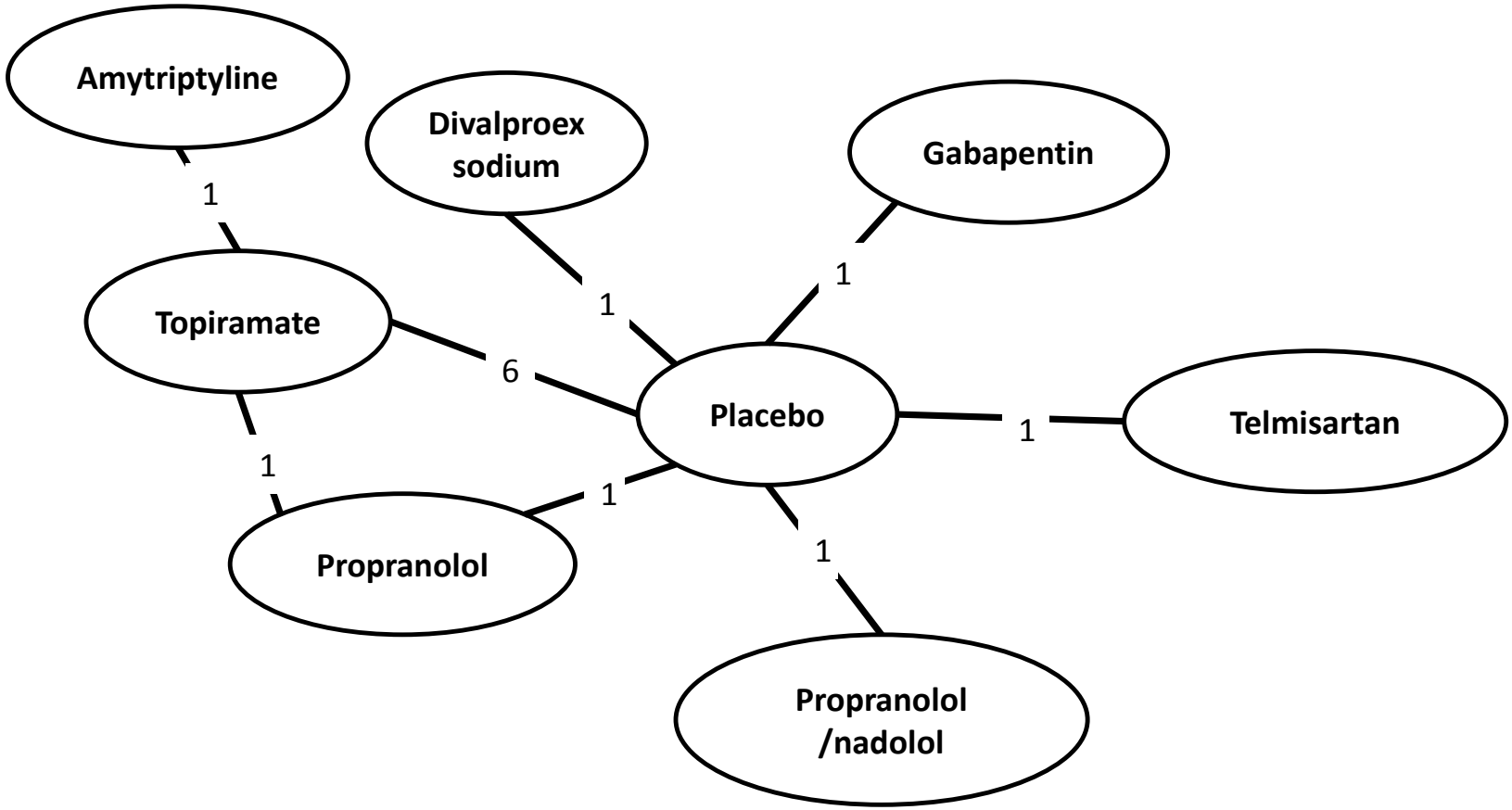
Figure 51: Cinnarizine vs Topiramate – Change in migraine/headache frequency



Appendix J: Network meta-analysis

A network meta-analysis was conducted for the outcome ‘change in migraine/headache days’ to allow the evidence across comparisons to be combined into a single internally consistent model. All of the studies that reported a change in migraine/headache days from baseline were included with the exception of 2 studies (Diener et al. 2007; Silberstein et al. 2007), which included only participants with chronic migraine. The other studies that were included in the review that reported this outcome were on populations with episodic migraine, and so the Committee considered that the inclusion of these two studies may introduce substantial unwanted heterogeneity. The studies were combined in a separate conventional pair-wise meta-analysis, which is reported in Section 2.3.1. The network diagram is shown in Figure 52.

Figure 52: Network diagram. Lines indicate trials comparing treatments. The numbers on each line indicate the number of trials to make that comparison.



J.1 Implementation

We undertook hierarchical Bayesian network meta-analysis using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk/). We used the WinBUGS code provided in the appendices of TSD 2 without substantive alteration to specify synthesis models. We used a normal likelihood with correction for multi-arm trials. Non-informative prior distributions were used for all parameters. Priors were normally distributed with a mean of 0 and variance of 10,000, except for the standard deviation between trials for the random effects meta-analyses which had a uniform prior distribution ranging from 0 to 5. Placebo was used as the reference treatment as this treatment had the most links with other nodes in the network.

We report results summarising 50,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations. Three separate chains with different initial values were used.

J.2 WinBUGS code

The network meta-analysis formed part of the economic analysis reported in Appendix O. The model used and the data input to the model is shown together with the code for the economic analysis in Appendix P.

J.3 Validation

The data were fitted and random effects models, and the goodness of fit evaluated by calculating the total residual deviance (a calculation of the model's ability to predict the individual data points underlying it – a well-fitting model will have a total residual deviance approximately equal to the number of data points) and the deviance information criteria (an estimate of deviance that is 'penalised' according to the number of parameters in the model, and is useful for comparing models), The total residual deviance and deviance information criteria for the fixed and random effects models are shown in Table 65.

Table 65: Measures of goodness of fit of fixed- and random-effects models

Measure of goodness of fit	Fixed effect model	Random effects model
Total Residual deviance*	38.9	30.4
Deviance information criterion (DIC)	44.4	42.4
Between trial standard deviation (95% credible intervals)	-	0.40 (0.05 to 0.88)
*Compared to 28 data points		

A random effects model was preferred because the treatment effects were unlikely to be identical across studies due to differences in baseline migraine frequency and age. The total residual deviance for the random effects model was closer to the number of unconstrained data points, and the deviance information criterion was lower. Subsequent results present data from the random effects model only.

One possible concern was that the age of populations across studies was variable, with some studies in children, some in adults, and some with a mixed population of young people and adults. In order to assess whether data from children and young people should be included in the analysis, a sensitivity analysis was performed with studies that only included participants under the age of 18 removed. The results of the sensitivity analysis (with results of the main analysis for comparison) are shown in Table 66. The results of the main analysis and sensitivity analysis were broadly similar (with the exception that there was no treatment estimate for divalproex sodium in the sensitivity analysis, as the only trial for this treatment was on under 18s). The between trial standard deviations were also similar for both analyses, indicating that age did not add substantial heterogeneity. Therefore we concluded that studies with populations of all ages should be included.

Table 66: Sensitivity analysis

	Mean difference re Placebo (95% CrI)	
Treatment	**Main analysis**	**Sensitivity analysis**
Telmisartan	-0.51 (-2.30 to 1.28)	-0.51 (-2.39 to 1.37)
Amitriptyline	-0.93 (-2.27 to 0.38)	-0.93 (-2.40 to 0.53)
Divalproex Sodium	0.11 (-1.00 to 1.23)	-
Gabapentin	0.00 (-1.58 to 1.58)	-0.01 (-1.71 to 1.72)
Topiramate	-1.03 (-1.52 to -0.58)	-1.02 (-1.62 to -0.46)
Propranolol	-1.19(-2.20 to -0.19)	-1.17 (-2.31 to -0.07)
Propranolol/nadolol	-0.60 (-1.65 to 0.47)	-0.60 (-1.80 to 0.59)
	Between trial standard deviation (95% CrI)	
	Main analysis	**Sensitivity analysis**
sd	0.40 (0.05 to 0.88)	0.43 (0.03 to 1.09)

The quality of evidence from the network meta-analysis was assessed using a modified version of the GRADE approach to quality rating. Each GRADE domain was rated as ‘no serious’, ‘serious’ or ‘very serious’ and an overall quality rating was derived for the evidence from the network meta-analysis as whole. The GRADE profile for the network meta-analysis can be found in Appendix H. For a description of how the GRADE criteria were applied to the network meta-analysis, see Section 2.3.1

J.4 Results

Table 67: Relative effectiveness showing all pair-wise combinations

	Placebo	Telmisartan	Amitriptyline	Divalproex Sodium	Gabapentin	Topiramate	Propranolol	Propranolol /nadolol
Placebo		-0.51 (-2.06 to 1.04)		0.10 (-0.72 to 0.92)	0.00 (-1.30 to 1.30)	-1.01 (-1.37 to -0.65)	-0.80 (-1.48 to -0.12)	-0.60 (-1.06 to -0.14)
Telmisartan	-0.51 (-2.30 to 1.28)							
Amitriptyline	-0.93 (-2.27 to 0.38)	-0.42 (-2.64 to 1.79)				-0.10 (-0.90 to 0.70)		
Divalproex Sodium	0.11 (-1.00 to 1.23)	0.63 (-1.48 to 2.72)	1.03 (-0.67 to 2.79)					
Gabapentin	0.00 (-1.58 to 1.58)	0.52 (-1.90 to 2.89)	0.93 (-1.13 to 3.00)	-0.11 (-2.06 to 1.80)				-
Topiramate	-1.03 (-1.52 to -0.58)	-0.52 (-2.39 to 1.32)	-0.10 (-1.34 to 2.05)	-1.14 (-2.37 to 0.05)	-1.03 (-2.70 to 0.61)		-0.35 (-1.05 to 0.35)	-
Propranolol	-1.19 (-2.20 to -0.19)	-0.68 (-2.74 to 1.38)	-0.26 (-1.83 to 1.32)	-1.30 (-2.81 to 0.19)	-1.19 (-3.07 to 0.69)	-0.16 (-1.11 to 0.82)		-
Propranolol/nadolol	-0.60 (-1.65 to 0.47)	-0.09 (-2.16 to 2.00)	0.33 (-1.34 to 1.13)	-0.71 (-2.24 to 0.83)	-0.60 (-2.48 to 1.31)	0.43 (–0.69 to 1.62)	0.59 (-0.85 to 2.07)	-

The values given are mean differences. The segment below the shaded cells is derived from the network meta-analysis and shows the mean difference as the row treatment minus the column treatment. Values in parentheses are 95% credible intervals. The segment above the shaded cells shows pooled direct evidence (random effects pairwise meta-analysis), where available, and shows the mean difference as the column treatment minus the row treatment. Numbers in parentheses are 95 confidence intervals.

Table 68: Probability that each treatment is the best, together with median rankings with 95% credible intervals.

	Probability best	Median rank (95% CrI)
Placebo	0.00	6 (5 to 8)
Telmisartan	0.17	5 (5 to 8)
Amitriptyline	0.23	3 (1 to 7)
Divalproex Sodium	0.06	7 (3 to 8)
Gabapentin	0.04	6 (1 to 8)
Topiramate	0.11	3 (1 to 5)
Propranolol	0.38	2 (1 to 6)
Propranolol/nadolol	0.06	4 (1 to 8)

Figure 53: Change in migraine/headache days. Relative effect of all treatments compared with placebo. Squares indicate the median of the posterior distribution for each effect, and lines indicate 95% Credible intervals.

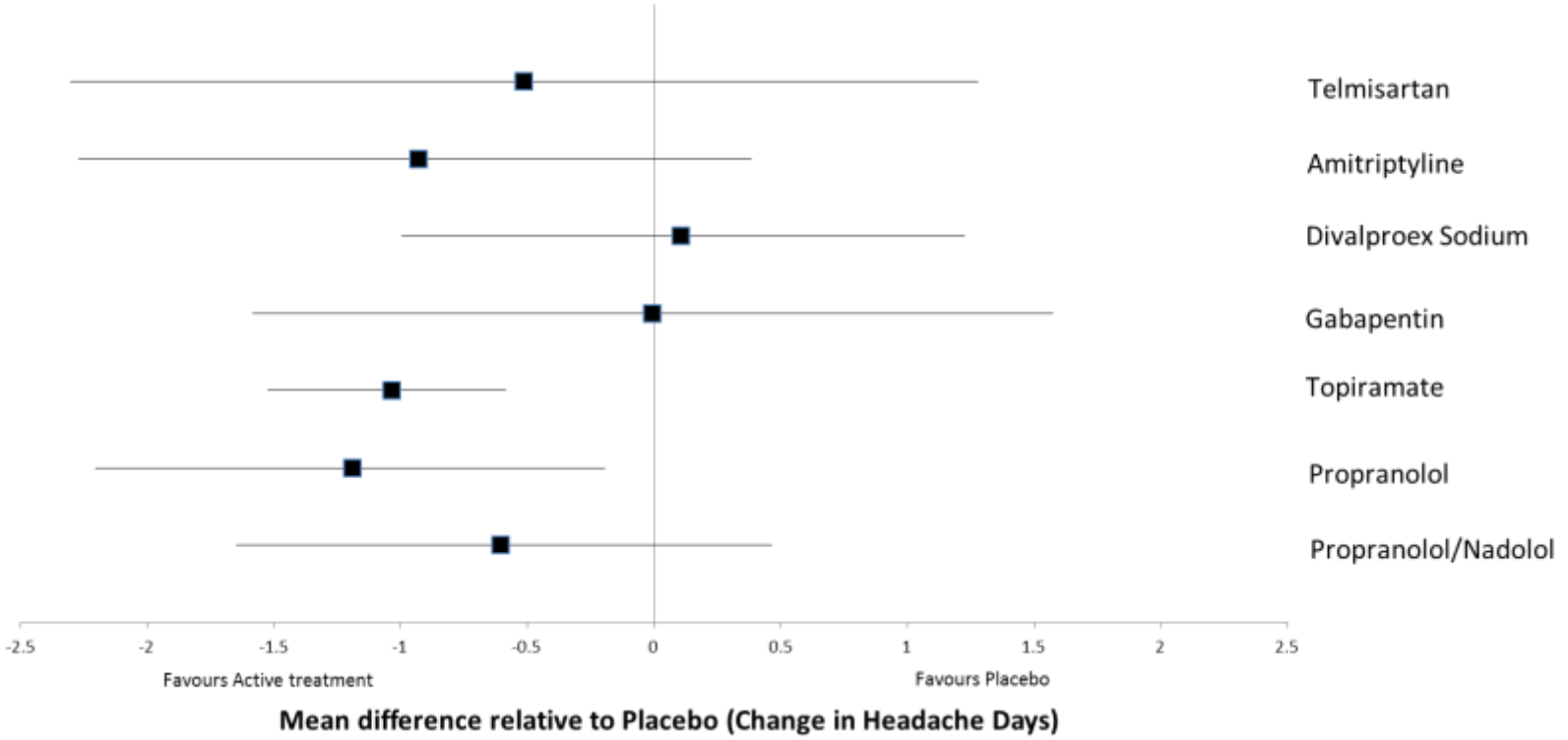
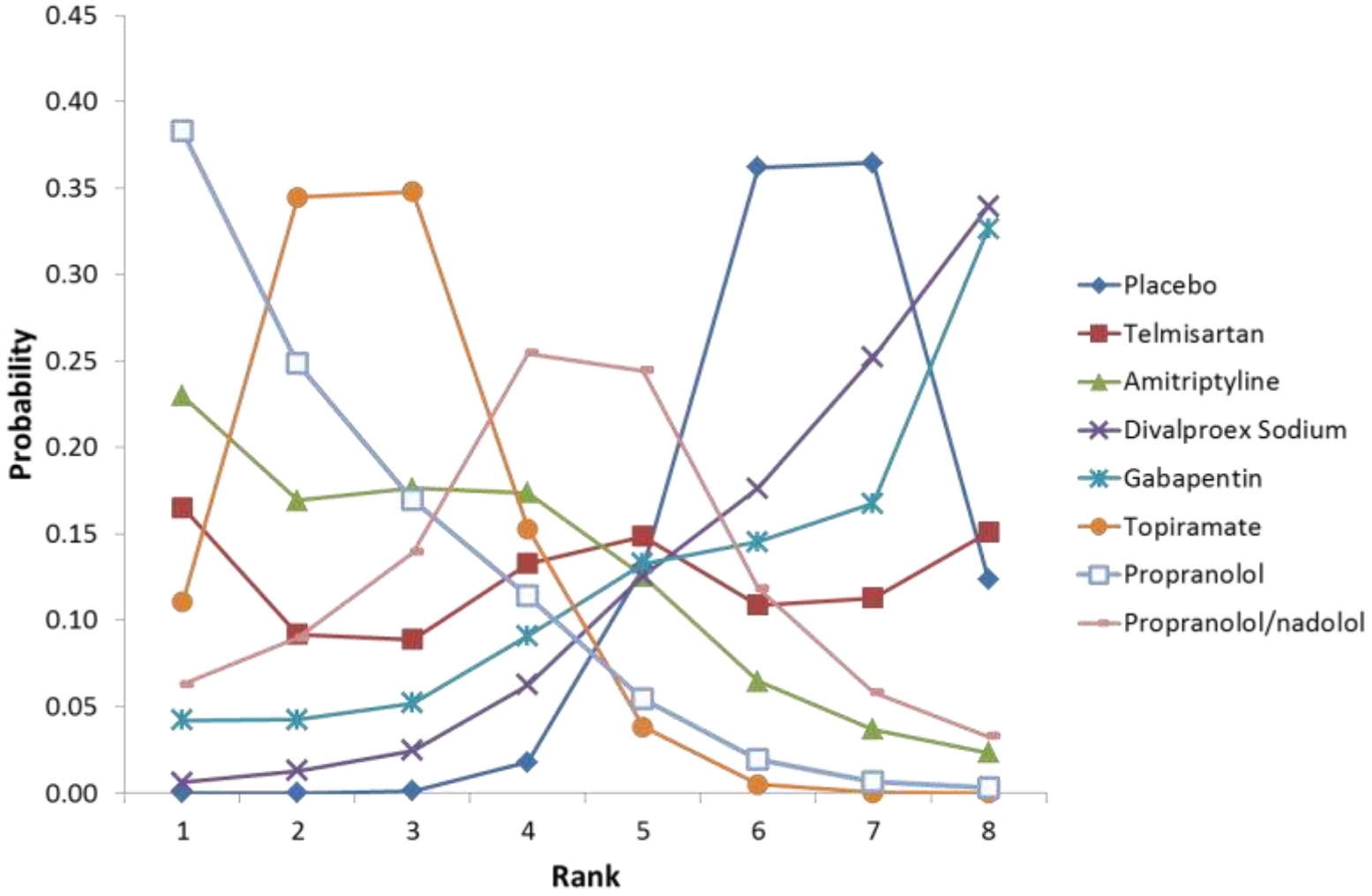


Figure 54: Rank probability plots. The probability of each treatment assuming each rank (1 to 8) is plotted. Different treatments are shown by each line.



J.5 Quality assessment

A modified version of the approach recommended by the GRADE working group was adopted:

- A starting quality rating was assigned, based on the study design. All studies in the network were randomised controlled trials; therefore the initial quality rating was 'high'.
- The rating was then downgraded for risk of bias, inconsistency, imprecision and indirectness using the criteria detailed below. Each quality element considered to have 'serious' or 'very serious' limitations, and resulting in downgrading of 1 or 2 levels respectively.

Risk of bias

The overall quality of evidence for each outcome was considered for risk of bias and assessed conventionally for each included trial. These were then compiled as an overall assessment for the entire group of included studies within the network for the following criteria:

- Appropriateness of randomisation method
- Adequacy of concealment methods (blinding)
- Other sources of bias. For example, failure to adequately account for attrition.

The seriousness of imprecision (no serious, serious or very serious) was considered in relation to the impact on decision making.

Inconsistency

Within a network meta-analysis two forms of inconsistency can exist: inconsistency between direct and indirect treatment effects and inconsistency (heterogeneity) between trials within a single comparison. In order to assess consistency between direct and indirect evidence, there must be 'loops' in the network in order for direct and indirect evidence to be combined into a coherent model. In the current network, the only loop is formed by a 3-arm trial, and therefore it is not possible to assess inconsistency between direct and indirect evidence. Between trial inconsistency (or heterogeneity) was considered by examining the within trial standard deviation.

Indirectness

Evidence was downgraded in quality based on indirectness in population, intervention, comparator or outcome for the majority of studies in the network, as in conventional pairwise comparisons for GRADE.

Imprecision

Evidence was downgraded if there was uncertainty around the indirect estimates and the probability ranking of relative treatments. This was judged for the following variables:

- The number of direct head-to-head trials
- Assessment of the degree of overlap in credible intervals
- Uncertainty in treatment rankings

The seriousness of imprecision (no serious, serious or very serious) was considered in relation to the impact on decision making.

Appendix K: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 69. The economic search strategy is shown in Table 70. The same strategy was translated for the other databases listed.

Table 69: Economic search summary

Databases	Version/files	No. retrieved
HTA database (Wiley)*	October 2014	3
MEDLINE (Ovid)	19456 to January wk 2 2015	257
MEDLINE In-Process (Ovid)	January 19 2015	23
EMBASE (Ovid)	1974 to 2015 January 19	1403
NHS Economic Evaluation Database - NHS EED (Wiley)	October 2014	16

Table 70: Economic search strategy

Medline Database
Strategy used: 1 exp migraine disorders/ 21729 2 (migrain* or hemicran*).tw. 24636 3 "alice in wonderland syndrome".tw. 63 4 1 or 2 or 3 28380 5 exp Angiotensin-Converting Enzyme Inhibitors/ 38615 6 exp Angiotensin Receptor Antagonists/ 17477 7 ((angiotensin receptor adj4 block*) or arb or arbs).tw. 6357 8 ((ACE or angiotensin or kininase or dipeptid* or peptidyl) adj4 (inhibit* or enzyme* or antagonist*)).tw. 49322 9 Losartan/ 5774 10 (candesartan or eprosartan or epratenz or tevesten or teveten or tevetan or irbesartan or approvel or aprovel or "arbez lr" or avapro or ifirmasta or irban or irbetan or iretensa or irovel or irvell or karvera or sabervel or losartan or acetensa or angiobloq or angioten or avastar or azarten or convertal or cormac or co?aar* or insaar or lifezar or lozaar or losacar or losacor or lozaprex or oscaar or satoren or tensartan or tozaar or olmesartan or alteis or benevas or benicar or olmec or olmetec or votum or telmisartan or "kinzal mono" or kinzalmono or micardis or predxal or pritor* or semintra or tolura or actelsar).tw. 11299 11 exp Antidepressive Agents/ 121001 12 exp Serotonin Uptake Inhibitors/ 31280 13 (antidepress* or anti depress* or thymoleptic* or thymoanaleptic* or neurothymoleptic* or psychoenergi?er* or thymolytic* SNRI* or SSRI*).tw. 49574 14 ((serotonin or 5-ht or 5 ht or hydroxytryptamine) adj4 (uptake or reuptake) adj4 inhibitor*).tw. 12891 15 Paroxetine/ 3500 16 (paroxetine or seroxat or paxil or aropax or aroxat or brisdelle or deroxat or dexorat or divarius or motivan or paroxet or paroxetine or paxan or paxtine or paxxet or pexeva or setine or tagonis).tw. 4291 17 citalopram/ 3699 18 (citalopram or cytalopram or celexa or cipram or citopram or elopram or futuril or humorap or kitapram or lupram or nitalapram or psiconor or recital or sepram or seralgan or serital or seropram or talam or zentius or cipramil).tw. 3707 19 (escitalopram or lexapro or cipralex or seroplex or sipralexa).tw. 1216 20 fluoxetine/ 7603

Medline Database

21 (fluoxetin* or pro?ac or sarafem or actan or adofen or andep or ansilan or auroken or auscap or captaton or daforin or depren or deprexin or deprizac or deproxin or elizac or floxet or fluctin* or fludac or flufran or fluketin or flunil or flunirin or fluohexal or fluox or fluoxac or fluxeren or fluoxifar or fluoxil or fluronin or flusac or flutin* or fluxen or fluxet* or fontex or foxetin* or fropine or fuloren or lanclic or lorien or lovan or magrilan or margrilan or modipran or nopres or nuzac or oxedep or plinzene or pragmaten or prizma or proctin or prodep or prozamin or qualisac or rapiflux or rowexetina or salipax or sanzur or sarafem or selfemra or sinzac or zactin or zepax).tw. 9206

22 Fluvoxamine/ 1703

23 (fluvoxamin* or favarin or faverin or floxyfral or luvox or dumirox).tw. 2169

24 Sertraline/ 2429

25 (sertraline or lustral or sealdin or besitran or altruline or gladem or aremis or zolof* or dominum or doxime or fatral or fridep or lesefer or nudep or seltra or serad or sercerin or serlain or serlift or sertranex or sertranquil or sosser or tresleen or zosert or atruline).tw. 2990

26 (mirtazapine or avanza or norset or remergil or remergon or remeron or zispin).tw.

27 (venlafaxine or efexor or effexor or trevilor or efectin or elafax or trewilor or vaxor or "venix-xr" or venla or venlax or viepax).tw. 2618

28 amitriptyline/ 6005

29 (amitryptylin* or lentizol or endep or tryptizol or domical or amitrip or anapsique or amineurin or sarotex or dam?len or saroten or tryptine or larox?l or apo-amitriptyline or triptafen or elavil or novoprotect or syneudon or tryptanol or adepress or adepril or ambivalon or amilit or amiplin or amiprin or amitid or amitril or amyline or amytril or antalin or antitryptyline or alatrol* or anafron or enovil or etafon or euplit or lanton or lentizol or miketorin or pinsaun or proheptadien or qualtriptene or redomex or "sarboten retard 75" or saroten* or stelminal or sylvemid or teperin or terepin or trepiline or tridep or tripta or triptanol or triptizol or triptyl or triptyline or trynol or tryptizol or trytomer or uxen or vanatrip or amitryptylene or amitriptylinumhydrochloride or amitryptilline or amitryptine or damilene or damylene or elatrol or elatrolet or enafon or laroxal or laroxyl or sarotard or sarotex).tw. 234

30 imipramine/ 9268

31 (imipramin* or pryleugan or melipramin* or janimine or tofranil or norchlorimipramine or imidobenzyle or imizin* or berkomin or chrytemin or daypress or deprinol or depsol or ethipramine or fronil or "ia pram" or imavate or imidol or imipramide or norpramine or novopramine or pramine or presamine or primonil or psychoforin* or sermonil or serviapramine or talpramin or trofanil or venefon or antidep or antideprin or apo-imipramine or depsonil or imizin*).tw. 8858

32 nortriptyline/ 2006

33 (nortriptylin* or nortrilen* or norfenazin or allegron or paxtibi or desmethylamtriptyline or desitriptyline or av?ntyl or pamelor or acetexa or altilev or ateben or martimil or noramitriptyline or noritren or norline or norpress or nortrix or nortryptilin* or nortyline or norventyl or ortrip or psychostyl or sens?val or vividyl).tw. 2049

34 desipramine/ 5372

35 (desipramin* or pertofran* or demethylimipramine or petylyl or petrofan* or norpramin or desmethylimipramine or deprexan or "desmethyl imipram*" or despiramine or nebril or noripramin* or norpramin* or pentrofane or pertofrin* or sertofren or nortimil).tw. 5996

36 Dothiepin/ 270

37 (dosulepin* or dothiepin or prothiaden* or altapin or depresym or dothapax or idom or prepadine or prothiadiene or prothiadine or protiaden).tw. 332

38 (duloxetine or cymbalta or ariclaim or duzela or xeristar or yentreve).tw. 1353

39 exp Adrenergic beta-Antagonists/ 76902

40 ((beta adj4 (block* or antagonist* or adrenergic or sympathicolytic* or adrenolytic* or antiadrenergic*)) or (betasympatholytic* or "beta sympatholytic*")).tw. 71753

41 propanolol/ 30819

42 (propanolol or ob?idan or dexpropanolol or inderal or propranolol or anaprilin* or avlocardyl or rexigen or obzid?n or betadren or dociton* or acifol or adrexan or alperol or anapryline or angilol or apsolol or arcablock or artensol or authus or becardin or bedranol or beprane or ber?olol or "beta neg" or betaneg or "beta tablinen*" or "beta-timelet" or "beta timelet" or betabloc or betadripresan or betaprol or betares or betaryl or blocard or blocaryl or cardinol or ciplar or corbeta or deralin or dibubinate or dideral or durabeton or duranol or efektolol or elbrol or emforal or farmadral or

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farprolol or frekven or frina or hemang?ol or hopranolol or ikopal or impral or inderalici or inderex or indicardin or indobloc or innopran or lederpronol or levopropranolol or napriline or noloten or obsin or oposim or phanerol or prandol or "prano puren" or pranopuren or prestoral or prolol or pronovan or propabloc or propal or propalong or propayerst or propercuten or prophylux or "propra ratiopharm" or propral or propanur or proprasylyt* or reducor or sagittol or stapranolol or sumial or tensiflex or waucoton or anaprilinium or inderal or inpanol or ipran).tw. 30454

43 metoprolol/ 4830

44 (metoprolol or beloc* or betaloc* or betalok or belok or seloken or spesi?or or lopressor).tw. 5667

45 nadolol/ 763

46 (nadolol or solgol or corgard or "apo-nadol" or "apo-nadolol" or betadol or farmagard or nadic).tw. 1034

47 Timolol/ 3265

48 (timolol or timoptol or timacar or optimol or timoptic or blocadren or timol or apotimol or apotimolol or apotimop or betimol or timoptol or istatol or ofal or ofan or timolo or titol or "apo timol*" or "apo-timol*" or moducren or nyolol).tw. 3600

49 atenolol/ 4809

50 (atenolol or tenormin* or ablok or adoll or alonet or altol or anolene or anolpin or anselol or arandin or asten or atarox or atcardil or atecard or atehexal or atelol or atenblock or atendol or atenet or ateni or atenil or ateno or atenogamma or atenol or atereal or aterol or atestad or atinol or atolmin or "b-vasc" or betablok or betacar or betarol or "betatop ge" or beten or bloket or blokium or blotex or cardioten or catenol or coratol or corotenol or durabeta or esatenolol or evitocor or farnormin or "felo-bits" or hypernol or internolol or "lo-ten" or loten or lotenal or martenol or mirobect or myocord or neotenol or nolol or normalol or norm?ten or nortelol or noten or oraday or ormidol or paesumex or plenacor or preloc or premorine or prenolol or prenormine or ranlol or rozamin or serten or stermin or temoret or tenblock or tenidon or tenoblock or tenocor or tenol or tenolin or tenolol or tenopress or tenoprin or tenostat or tensig or tensinor or ternolol or therabloc or tredol or velorin or vericordin or wesipin or hypoten).tw. 6189

51 exp adrenergic alpha-agonists/ 147359

52 ((adrenergic or adrenoceptor or noradren*) adj4 (agonist* or agent* or stimulat*)).tw. 33362

53 (alpha adj4 (agonist* or sympathicomimetic*)).tw. 13254

54 Clonidine/ 12583

55 (clonidine or clofelin or klofelin or clopheline or clofenil or catapres* or klofenil or hemiton or clophazolin or isoglaucon or gemilon or dixarit or adesipress or arkamin or atensina or catasan or chlofazolin or clofelin* or clophelin* or clinidine or clomidine or clondine or clonicel or clonidin* or clonipresan or clonistada or clonnirit or daipres or dcai or dichlorophenylam or inomidazoline or duraclon or haemiton or hemiton or hypodine or jenloga or kapvay or melzin or normopres?n or paracefan or sulmidine or taitecin or "tenso timelets" or caprysin or chlofazolin* or chlophelin).tw. 13371

56 exp Calcium Channel Blockers/ 71759

57 (calcium adj4 (block* or inhibit* or antagonist*)).tw. 42313

58 Nimodipine/2447

59 (nimodipin* or modus or nymalize or remontal or kenesil or brainal or admon or calnit or eugerial or grifonimod or kenzolol or nidip or nimodilat or nimotop or nisom or periplum or tropocer or vasoflex or vasotop).tw. 4014

60 Diltiazem/ 5927

61 (diltiazem or dilacor or aldizem or cardil or tiazac or dilzem or cardizem or dilren* or acalix or adizem* or altiazem or anginyl or angiotrof?n or angiozem or angizem or angoral or anoheal or anzem or auscard or balcor or beatizem or "bi-tildiem" or bloclacin or britiazim or bruzem or calcicard or calnurs or cardcal or cardiazem or cardiben or cardiem or cardiosta or cardium or carex or cartia or cascor or cirilen or coras or cordizem or dazil or deltazen or diacor or diatal or diladel or dilatam* or dilcard* or dilem or dilfar or dilgard or diloc or dilso or "dilt-cd" or diltahexal or diltam or diltan or diltelan or diltia or diltiamax or diltiasyn or diltime or diltzac or diltzanton or dilzem or dilzene or dilzereal or dilzicardin or dinisor or dodexen or dyalac or entrydil or filazem or gadoserin or grifodilzem or hagen or helsibon or herbess?r or hesor or incoril or kaizem or lacerol or levodex or levozem or lytelsen or masdil or miocardie or "mono-tildiem* or monotildiem" or myonil or pazeadin or presoken or surazem or tazem or taztia or tiadil or tiamate or tilazem or tildiem or vasmulax or vasocardol or wentizem or "apo-diltiazem" or "apo diltiazem" or herben or tiazac or ziruvate or

Medline Database

zandil or zemtrial or zildem).tw. 8526

62 Verapamil/ 15902

63 (verapamil or i?optin* or finoptin or lekoptin or dexverapamil or calan or falicard or cordilox or iproveratril or "aop-verap" or apoacor or arpamyl or azupamil or berkatens or calaptin or cardiagutt or cardibeltin or cardiolen or cardiover or caveril or cintsu or civicor or coraver or cordilat or corpamil or covera or dignover or dilacor?n or durasoptin or flamon or geangin or hexasoptin or ika?or or ikapress or "iso-card sr" or manidon or napamil or novapamyl or veramil or novopressan or phynoptin or quasar or ravamil or securon or univer or vasolan or vasomil or vasopten or verabeta or veracaps or veracor or verahaxal or veraloc or veramex or verapamil or verapin or verapress or veratad or verdilac or verelan or verexamil or veroptin or verpamil or vetrimil or vortac or zolvera).tw. 20499

64 Flunarizine/ 1138 Advanced

65 (flunarizin* or sibelium or sibelum or flunagen or flunarin or flunarl or fluxarten).tw. 1482

66 exp Anticonvulsants/ 118240

67 (antiepileptic* or anticonvuls* or antiepileptiform or (anti adj2 (convuls* or epileptic*))).tw. 35211

68 Valproic Acid/ 10304

69 (((acid or acetate or sodium) adj4 (proylacetic or dipropyl* or propylpentanoate or proplyvalenrate or propyl)) or dipropylacetate).tw. 1571

70 (valproate adj4 (sodium or semisodium or calcium or magnesium)).tw. 2579

71 (acid adj4 (valproic or propylisopylacetic or propylpentanoic)).tw. 5705

72 (depakin* or vupral or ergenyl or depakene or depakote or "sodium divalproex" or "alpha propylval" or apilepsin or atemperator or convulex or depacon or depalept or deprakine or diprosin or epil?m or epilex or everiden or goilim or labazene or leptilan* or myloproin or "myproic acid" or orfil or orfiril or orlept or petilin or propymal or stavzor or valcote or valeptol or valerin or valoin or valpakine or valparin or valporal or valprax or valpro or valprosid or valsup).tw. 293

73 (topiramate or top?max or epitomax or qudexy or trokendi).tw. 2982

74 (gabapentin or neurontin or fanatrex or gabarone or gralise or nupentin or neogab or dineurin or gabatin or gantin or kaptin or neurotonin).tw. 3762

75 exp Receptors, Serotonin/ 21062

76 ((serotonin or serotonergic or serotoninergic) adj4 (modulat* or receptor*)).tw. 13154

77 ((5-ht or 5 ht or tryptamine or hydroxytryptamine) adj4 receptor*).tw. 12887

78 Methysergide/ 2813

79 (meth?sergid* or desernil or sandoz or dimethylergomertin or methylmethylgonovine or desril or deseril or sansert).tw. 4173

80 ((methyl adj4 (lysergic or sergid*)) or (methyllsergic adj4 butanolamide)).tw. 48

81 Pizotyline/ 247

82 (pizot?fen* or pizotylin* or sandom?gran or polomigran or litec).tw. 310

83 Ergotamine/ 2086

84 (ergotamin* or ergomar or ergo sanol or ergokranit or ergo-kranit or (ergo adj1 kranit) or gynergen or ergostat or cornutamine or ergodryl or "mono ergodryl" or "mono-ergodryl").tw. 1503

85 Cyproheptadine/ 2061

86 (cyproheptadine or peritol or antergan or dihexazin or periactin or viternum or lingraine or adekin or antisemin or cip?actin or ciproeptadine or ciproral or crypoheptadin* or cyheptine or cylat or cyprahept?dine or cyproatin or cyprogin or cyprohaptadin or cyproheptadiene or cyproheptadin* or cypromin or cyprono or cyprosian or cytadine or ennamax or glocyp or heptasan or ifrasal or "istam-far" or klavivitina or kulinet or nuran or periactinol or petina or pilian or pronicy or sinapdin or trimetabol or peritol).tw. 2136

87 exp Receptors, N-Methyl-D-Aspartate/ 22969

88 ((receptor* or antagonist* or block*) adj4 (nmda or n-methyl or n methyl or methylaspartate)).tw. 33794

89 Memantine/ 1636

90 (memantin* or axura or namenda or ebix* or akatinol or maruxa or nemdatine).tw. 1971

91 or/5-90 714034

92 4 and 91 5255

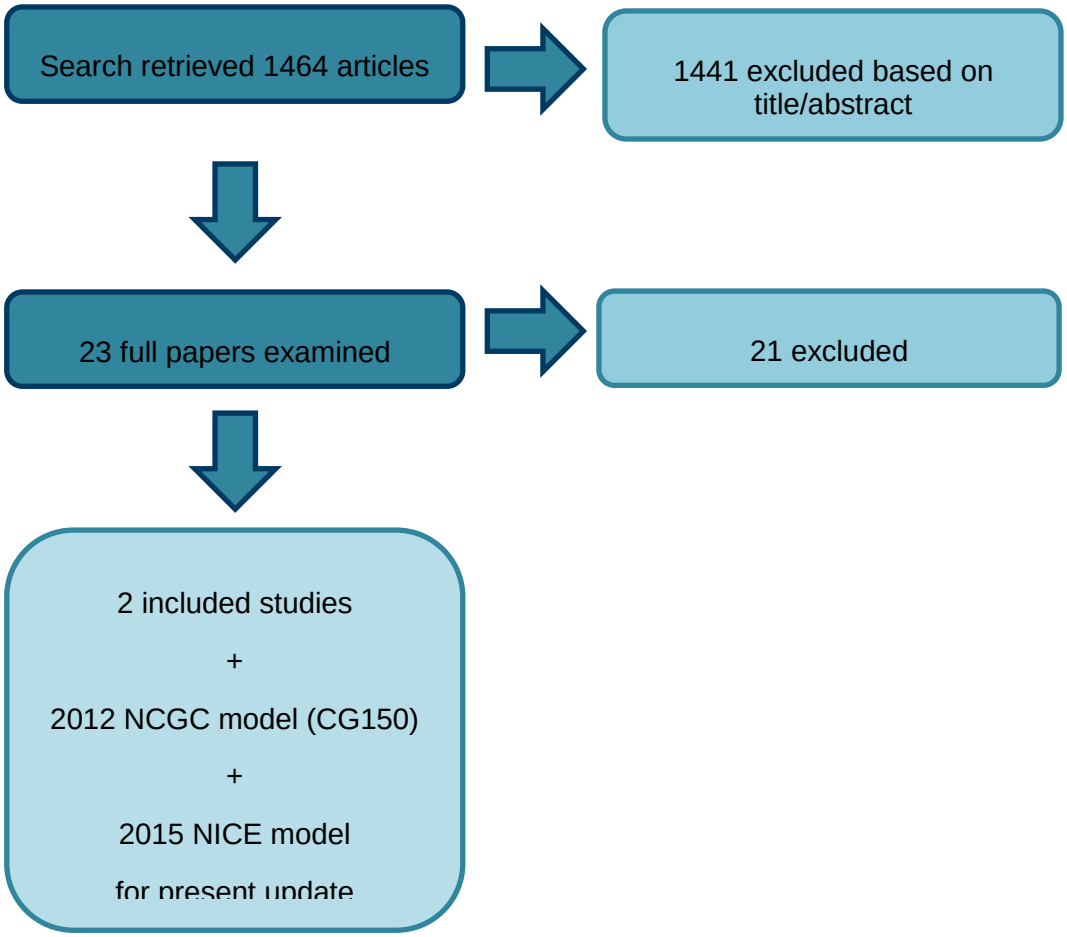
93 Economics/ 26539

Medline Database

94 exp "Costs and Cost Analysis"/ 183530
95 Economics, Dental/ 1855
96 exp Economics, Hospital/ 19774
97 exp Economics, Medical/ 13480
98 Economics, Nursing/ 3911
99 Economics, Pharmaceutical/ 2535
100 Budgets/ 9849
101 exp Models, Economic/ 10352
102 Markov Chains/ 10008
103 Monte Carlo Method/ 20368
104 Decision Trees/ 8897
105 econom$.tw. 157780
106 cba.tw. 8719
107 cea.tw. 16258
108 cua.tw. 793
109 markov$.tw. 11670
110 (monte adj carlo).tw. 21024
111 (decision adj3 (tree$ or analys$)).tw. 8384
112 (cost or costs or costing$ or costly or costed).tw. 308740
113 (price$ or pricing$).tw. 23213
114 budget$.tw. 17432
115 expenditure$.tw. 35007
116 (value adj3 (money or monetary)).tw. 1353
117 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 2846
118 or/93-117 658075
119 "Quality of Life"/ 121111
120 quality of life.tw. 139951
121 "Value of Life"/ 5406
122 Quality-Adjusted Life Years/7177
123 quality adjusted life.tw. 5987
124 (qaly$ or qald$ or qale$ or qtime$).tw. 4935
125 disability adjusted life.tw. 1206
126 daly$.tw. 1185
127 Health Status Indicators/ 20075
128 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 15425
129 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 999
130 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 2677
131 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 21
132 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 332
133 (euroqol or euro qol or eq5d or eq 5d).tw. 3947
134 (qol or hql or hqol or hrqol).tw. 24989
135 (hye or hyes).tw. 53
136 health$ year$ equivalent$.tw. 38
137 utilit$.tw. 111824
138 (hui or hui1 or hui2 or hui3).tw. 852
139 disutili$.tw. 209
140 rosser.tw. 71

Medline Database
141 quality of wellbeing.tw. 5
142 quality of well-being.tw. 324
143 qwb.tw. 168
144 willingness to pay.tw. 2212
145 standard gamble$.tw. 642
146 time trade off.tw. 740
147 time tradeoff.tw. 201
148 tto.tw. 592
149 or/119-148 320995
150 118 or 149 935513
151 92 and 150 304
152 animals/ not humans/ 3876726
153 151 not 152 300
154 limit 153 to english language 257

Appendix L:Economic review flowchart



Appendix M: Excluded economic studies

Table 71: Excluded economic studies

Reference	Reason for exclusion
Adelman JU, Adelman LC, Von SR (2002) Cost-effectiveness of antiepileptic drugs in migraine prophylaxis. Headache 42: 978-83.	Selectively excluded - cost-effectiveness analysis that was superseded by more applicable included cost-utility analyses
Brown JS, Papadopoulos G, Neumann PJ et al. (2005) Cost-effectiveness of topiramate in migraine prevention: results from a pharmacoeconomic model of topiramate treatment. Headache 45: 1012-22.	Selectively excluded – another article was included that reported an adaption of this model to the UK setting by the same authors
Brown JS, Rupnow MF, Neumann P et al. (2006) Cost effectiveness of topiramate in the prevention of migraines in the United States: an update. Managed Care Interface 19: 31-8.	Selectively excluded – another article was included that reported an adaption of this model to the UK setting by the same authors
Ergun H, Gulmez SE, Tulunay FC (2007) Cost-minimization analysis comparing topiramate with standard treatments in migraine prophylaxis. European Neurology 58: 215-7.	Selectively excluded - cost-minimisation analysis that was superseded by more applicable included cost-utility analyses.
Evans KW, Boan JA, Evans JL et al. (1997) Economic evaluation of oral sumatriptan compared with oral caffeine/ergotamine for migraine. Pharmacoeconomics 12: 565-77.	No prophylaxis
Knoth RL, Stang PE, Chen KS et al. (2004) Cost and savings associated with treating migraine headache with zolmitriptan or an analgesic-sedative combination in a managed care organization. Journal of Pharmaceutical Finance, Economics and Policy 13: 19-32.	No prophylaxis
Lainez MJ (2009) The effect of migraine prophylaxis on migraine-related resource use and productivity. CNS Drugs 23: 727-38.	Narrative review only
Linde M, Chisholm D, Steiner T (2013) A generalized cost-effectiveness analysis of interventions against migraine using WHO-CHOICE methodology. Cephalalgia 33: 135-6.	Conference abstract
Lofland JH, Nash DB (2005) Oral serotonin receptor agonists: a review of their cost effectiveness in migraine. [Review] [52 refs]. Pharmacoeconomics 23: 259-74.	Narrative review of acute treatments
Maizels M, Saenz V, Wirjo J (2003) Impact of a group-based model of disease management for headache. Headache 43: 621-7.	Not an economic evaluation of prophylactic medicines
Mennini FS, Gitto L, Martelletti P (2008) Improving care through health economics analyses: Cost of illness and headache. Journal of Headache and Pain 9: 199-206.	Narrative review only
Moja L, Cusi C, Sterzi R et al. (2009) Selective Serotonin Re-uptake Inhibitors (SSRIs) for preventing migraine and tension-type headaches. Cochrane Database of Systematic Reviews	No economic evaluations included
Sandrini G, Perrotta A, Tassorelli C et al. (2009) Eletriptan. Expert Opinion On Drug Metabolism & Toxicology 5: 1587-98.	No prophylaxis
Sandrini G, Perrotta A, Nappi G (2006) Eletriptan: a review and	No prophylaxis

Reference	Reason for exclusion
new perspectives. Expert Review of Neurotherapeutics 6: 1413-21.	
Shamliyan TA, Kane RL, Ramakrishnan R et al. (2013) Migraine in children: preventive pharmacologic treatments (Structured abstract). Health Technology Assessment Database	No economic evaluations included
Silberstein SD, Feliu AL, Rupnow MF et al. (2007) Topiramate in migraine prophylaxis: long-term impact on resource utilization and cost. Headache 47: 500-10.	Selectively excluded - cost-minimisation analysis that was superseded by more applicable included cost-utility analyses
Takiya L, Piccininni LC, Kamath V (2006) Safety and efficacy of eletriptan in the treatment of acute migraine. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy 26: 115-28.	Narrative review only
Thompson M, Gawel M, Desjardins B et al. (2005) An economic evaluation of rizatriptan in the treatment of migraine. Pharmacoeconomics 23: 837-50.	No prophylaxis
Wertz DA, Quimbo RM, Yaldo AZ et al. (2009) Resource utilization impact of topiramate for migraine prevention in the managed-care setting. Current Medical Research & Opinion 25: 499-503.	Selectively excluded - cost-minimisation analysis that was superseded by more applicable included cost-utility analyses
Wu J, Hughes MD, Hudson MF et al. (2012) Antimigraine medication use and associated health care costs in employed patients. Journal of Headache and Pain 13: 121-7.	Not an economic evaluation of prophylactic medicines
Yu J, Goodman MJ, Oderda GM (2009) Economic evaluation of pharmacotherapy of migraine pain: A review of the literature. Journal of Pain and Palliative Care Pharmacotherapy 23: 396-408.	Systematic review only (checked for anything additional to the present review)

Appendix N: Economic evidence tables

A full economic evidence table has not been provided for the de novo modelling undertaken for this update. Please refer to appendix O for the full details of this analysis.

Table 72: Full economic evidence tables

Bibliographic reference	**Brown JS, Papadopoulos G, Neumann PJ et al. (2006) Cost-effectiveness of migraine prevention: the case of topiramate in the UK. Cephalalgia 26: 1473-82.**
Evaluation design	

Interventions	Topiramate 100mg per day
Comparators	No prophylaxis
Base-line cohort characteristics	• People with moderate to high frequency of migraine • 6 migraines per month
Type of Analysis	Cost-utility analysis
Structure	Decision tree
Cycle length	Not applicable
Time horizon	1 month
Perspective	NHS
Country	UK
Currency unit	£
Cost year	2005
Discounting	Not applicable
Other comments	Key assumptions: • No adverse effects included

Results

Comparison	Topiramate vs. no prophylaxis
Incremental cost	£220 (per year)
Incremental effects	0.0384 QALYs

Bibliographic reference	**Brown JS, Papadopoulos G, Neumann PJ et al. (2006) Cost-effectiveness of migraine prevention: the case of topiramate in the UK. Cephalalgia 26: 1473-82.**	
	Incremental cost effectiveness ratio	£5,728 per QALY (2005) or £7,209 (2015) [1]
	Conclusion	"This analysis suggests topiramate is a cost-effective treatment for migraine prevention compared with no preventive treatment."
Data sources		
	Base-line data	• Monthly migraine frequency from 3 topiramate clinical trials: 6 per month
	Effectiveness data	• Probability of reduction in migraine frequency from 3 topiramate clinical trials: 0.279 for ≥75%, 0.209 for 50-75%, 0.512 for <50% reduction in migraine frequency • Reduction in migraine rate by response category from simulation based on clinical trial data: 86.5% for ≥75% category, 61.8% for 50-75% category, 26% for <50% category
	Cost data	• Cost of topiramate from BNF September 2005: £34.36 per month • Additional physician visits for topiramate treatment assumed: 1.5 per year at a cost of £18.65 • Cost of acute medical services from published literature per migraine attack ○ Physician visit for migraine: £18.65 ○ Hospitalisation for migraine: £1,059 ○ Emergency service visit for migraine: £41.96 ○ Usual care: £0.69 • Probability of resource use per migraine attack: ○ Hospitalisation: 0.000243 for triptan users and 0.000698 for usual care ○ Emergency service visit: 0.001271 for triptan users and 0.003663 for usual care ○ Physician visit: 0.003537 for triptan users and 0.009985 for usual care • Cost of triptan from BNF September 2005 assuming 1.5 tablets per attack: £6.85
	Utility data	• SF-36 from 3 topiramate clinical trials
Uncertainty		
	One-way sensitivity analysis	• Untreated number of migraines per month varied from 3 to 12 resulting in ICERs ranging from £6,644 to £3,897 per QALY respectively • Rate of triptan use per attack varied from 0% to 100% resulting in ICERs ranging from £6,481 to £3,466 per QALY respectively • Treatment discontinuation rate varied from 0% to 50% resulting in ICERs ranging from £5,317 to £6,100 per QALY respectively • Utility gain varied from -60% to +60% resulting in ICERs ranging from £14,320 to £3,580

Bibliographic reference	**Brown JS, Papadopoulos G, Neumann PJ et al. (2006) Cost-effectiveness of migraine prevention: the case of topiramate in the UK. Cephalalgia 26: 1473-82.**
	<table><tr><td></td><td>per QALY respectively</td></tr><tr><td>**Probabilistic sensitivity analysis**</td><td>Not done</td></tr></table>
Applicability	**Partially Applicable** • This analysis compared only one antiepileptic medicine against no prophylaxis. • The utilities were based on the SF-36 quality of life measure.
Limitations	**Potentially serious limitations** • Adverse effects not included • The cost of topiramate is now substantially reduced compared with what was used in this analysis (£1.60 per month in 2015 down from £34.36 per month used in the 2006 analysis).[2] • The cost of triptan is now substantially reduced compared with what was used in this analysis (for example, sumatriptan costs £0.28 per tablet compared with £4.57 per tablet used in the 2006 analysis). The specific triptan medicine used for this analysis was not specified. • No probabilistic sensitivity analysis
Conflicts	Funding for the study provided by Johnson & Johnson

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; NHS: National Health Service; UK: United Kingdom
[1] *ICER converted to 2015 £ using the CCEMG – EPPI-Centre Cost Converter, http://eppi.ioe.ac.uk/costconversion/default.aspx, accessed 18.03.2015*
[2] *£1.60 per month derived by the present update author as follows: 60 pack of 100mg topiramate tablets £3.16 from the NHS Electronic Drug Tariff March 2015 (3.16/60*365/12). £34.36 per month derived by Brown et al. based on the British National Formulary September 2005.*

Bibliographic reference	**Yu J, Smith KJ, Brixner DI (2010) Cost effectiveness of pharmacotherapy for the prevention of migraine: a Markov model application. CNS Drugs 24: 695-712.**
Evaluation design	

Bibliographic reference	Yu J, Smith KJ, Brixner DI (2010) Cost effectiveness of pharmacotherapy for the prevention of migraine: a Markov model application. CNS Drugs 24: 695-712.	
	Interventions	1. Amitriptyline 75 mg/day 2. Topiramate 100 mg/day 3. Topiramate 200 mg/day 4. Timolol 20 mg/day 5. Divalproex sodium 1000 mg/day 6. Propranolol 160 mg/day 7. No prophylaxis
	Comparators	No treatment
	Base-line cohort characteristics	6 migraines per month
	Type of Analysis	Cost-utility analysis
	Structure	Markov model
	Cycle length	1 day
	Time horizon	365 days
	Perspective	Societal
	Country	United States
	Currency unit	US$
	Cost year	2009
	Discounting	Not applicable
	Other comments	Key assumptions • Clinical efficacy measure was the percentage reduction in migraine frequency (converted to QALYs) • No discontinuation considered • Maximum doses of preventive medicines used in clinical trials • Both triptan and usual care used as possible acute treatments • Some patients received a second dose of triptan for acute treatment • Patients that used usual care for acute treatment could not switch to a triptan • Adverse effects were included. A disutility of 20% was applied of the symptom. No cost was associated with adverse effects.

Bibliographic reference	**Yu J, Smith KJ, Brixner DI (2010) Cost effectiveness of pharmacotherapy for the prevention of migraine: a Markov model application. CNS Drugs 24: 695-712.**
Results	The results reported by this study were reanalysed to calculate direct costs only, to more closely represent an NHS perspective, and conduct incremental analysis (as opposed to the average cost-effectiveness analysis presented in the article. Dominated by topiramate 200: • Amitriptyline • Topiramate 100 • No prophylaxis Dominated by timolol: • Propranolol • Divalproex sodium

Comparison	Topiramate 200 mg/day vs. no treatment
Incremental cost	£1399 (2015)
Incremental effects	0.456 QALYs
Incremental cost effectiveness ratio	£3,067 (2015) [1]
Conclusion	The study concluded that “use of any of the five drugs for migraine prevention in combination with abortive medications dominated abortive medication use alone.” Incremental analysis based on direct costs only for the present paper showed that topiramate 200 mg/day and timolol 20 mg/day were more cost effective than no treatment, no prophylaxis, and all other preventive medicines.

Comparison	Timolol 20 mg/day vs. topiramate 200 mg/day
Incremental cost	£130 (2015)
Incremental effects	0.032 QALYs
Incremental cost effectiveness ratio	£4,058 (2015) [1]
Conclusion	The study concluded that “use of any of the five drugs for migraine prevention in combination with abortive medications dominated abortive medication use alone.” Incremental analysis based on direct costs only for the present paper showed that topiramate 200 mg/day and timolol 20 mg/day were more cost effective than no treatment, no prophylaxis, and all other preventive medicines.

Bibliographic reference	**Yu J, Smith KJ, Brixner DI (2010) Cost effectiveness of pharmacotherapy for the prevention of migraine: a Markov model application. CNS Drugs 24: 695-712.**
Data sources	

Base-line data	Cohort of people who experience 6 migraines per month
Effectiveness data	Efficacy of prophylactic medicines and adverse events from minimum two randomised controlled trials each from the literature: • Reduction in monthly migraine frequency (figures in parentheses are the ranges used in sensitivity analyses): ○ Amitriptyline 75 mg/day: 49.24% (24.70 to 70.11%) ○ Propranolol 160 mg/day: 38.83% (31.37 to 45.17%) ○ Timolol 20 mg/day: 40.33% (36.76 to 43.89%) ○ Divalproex sodium 1000 mg/day: (34.91% (27.27 to 42.55%) ○ Topiramate 200 mg/day: 41.12% (28.26 to 52.38%) ○ Topiramate 100 mg/day: 37.43% (22.58 to 50.00%) • Probability of adverse effects ○ Amitriptyline 75 mg/day: 59.64% (46.85 to 63.80%) ○ Propranolol 160 mg/day: 11.81% (3.47 to 17.60%) ○ Timolol 20 mg/day: 16.85% (11.70 to 22.00%) ○ Divalproex sodium 1000 mg/day: 26.10% (15.00 to 37.20%) ○ Topiramate 200 mg/day: 45.66% (43.99 to 47.32%) ○ Topiramate 100 mg/day: 46.68% (30.00 to 68.00%)
Cost data	Drug costs from US reference costs and an online store The cost of hospitalisation, emergency room and physician visits for migraine were obtained from a US cost of disease study Costs (all 2009): • Usual care: US$2.98 • All triptans: US$22.26 • Amitriptyline 75 mg/day: US$0.99 • Timolol 20 mg/day: US$0.92 • Propranolol 160 mg/day: US$2.51 • Divalproex sodium 20 mg/day: US$1.00 • Topiramate 100 mg/day: US$0.49 • Topiramate 200 mg/day: US$0.49

Bibliographic reference	**Yu J, Smith KJ, Brixner DI (2010) Cost effectiveness of pharmacotherapy for the prevention of migraine: a Markov model application. CNS Drugs 24: 695-712.**
	Utility data: Health Utility Index Mark 3 from a US survey
Uncertainty	**One-way sensitivity analysis**: • A scenario based on lowest percentage reduction in monthly frequency, highest rate of adverse events and a greater disutility due to adverse effects indicate that amitriptyline 75 mg/day and topiramate 100 mg/day could result in lower QALYs at a lower cost compared with no prophylaxis. Topiramate 200 mg/day, timolol 20,g/day and divalproex sodium 1000 mg/day dominated no prophylaxis. Propranolol had an ICER of US$4,695 (2009) compared to no prophylaxis. **Probabilistic sensitivity analysis**: • A cost-effectiveness acceptability curve of pair-wise comparisons between each preventive medicine and no prophylaxis suggested use of either topiramate 200 mg/day, timolol 20 mg/day or divalproex sodium 1000 mg/day was likely to be cost effective for any level of willingness to pay up to US$100,000 per QALY. • A comparison of the 6 preventive medicines in cost-effectiveness acceptability curves shows that amitriptyline was likely to be most cost-effective for a willingness to pay up to US$18,000 per QALY followed by timolol 20 mg/day, topiramate 200 mg/day and topiramate 100 mg/day.
Applicability	**Partially Applicable** • Utilities derived from the Health Utilities Index Mark 3 (HUI3) measure • Analysis conducted for compliant population. This may not be generalisable to the clinical practice.
Limitations	**Potentially Serious Limitations** • Cost of triptan derived from an average of all available triptans resulting in a cost of US$22.26 (2009). This contrasts with the cost of £0.28 per dose for sumatriptan in 2015 (subsequently used for the economic modelling for the present update). The higher cost of triptan would have had the effect of decreasing the relative cost effectiveness of no prophylaxis and increasing the relative cost effectiveness of prophylactic medicines than they would have been with a lower cost for triptan, other things being equal. • Probabilistic sensitivity analysis used triangular and uniform distributions. • No cost was applied to adverse events.

Bibliographic reference	**Yu J, Smith KJ, Brixner DI (2010) Cost effectiveness of pharmacotherapy for the prevention of migraine: a Markov model application. CNS Drugs 24: 695-712.**
Conflicts	The authors state that no sources of funding were used to conduct the study and they had no conflicts of interest that were relevant to the content.

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; NHS: National Health Service; UK: United Kingdom
[1] *ICER converted to 2015 £ using the CCEMG – EPPI-Centre Cost Converter, http://eppi.ioe.ac.uk/costconversion/default.aspx, accessed 18.03.2015*

Bibliographic reference	**National Clinical Guideline Centre (2012) Headaches: Diagnosis and management of headaches in young people and adults. NICE Clinical Guideline 150.**
Evaluation design	

Interventions	Prophylaxis interventions that showed a reduction in migraine days according to the meta-analysis undertaken in CG150: • Acupunture 15 sessions over 6 months • Telmisartan 80 mg/day • Propranolol 25 mg/day • Topiramate 100 mg/day
Comparators	No prophylaxis
Base-line cohort characteristics	Patients diagnosed with migraine aged 12 or over
Type of Analysis	Cost-utility analysis
Structure	Bayesian coding in WinBUGS
Cycle length	1 month
Time horizon	6 months
Perspective	NHS
Country	UK
Currency unit	£
Cost year	2011
Discounting	Not applicable
Other comments	Key assumptions: • No adverse effects from preventive medicines • Two additional GP visits over 6 months for each preventive medicine compared to no treatment and acupuncture

Bibliographic reference	**National Clinical Guideline Centre (2012) Headaches: Diagnosis and management of headaches in young people and adults. NICE Clinical Guideline 150.**
	• It takes 2 hours for acute treatment to take effect. Therefore, effective treatment was scaled at 22/24 for responsive people.
Results	

Comparison	vs. no treatment: • Propranolol • Topiramate • Telmisartan • Acupuncture
Incremental cost	vs. no treatment: • Propranolol: £90 • Topiramate: £112 • Telmisartan: £194 • Acupuncture: £228
Incremental effects	vs. no treatment: • Propranolol: 0.594 • Topiramate: 1.065 • Telmisartan: 0.510 • Acupuncture: 0.583
Incremental cost effectiveness ratio	Incremental net monetary benefit and probability that strategy is the most cost effective (based on £20,000 per QALY) • No treatment: £0; 2.2% • Propranolol: £53.63; 25.5% • Topiramate: £139.90; 45.2% (most cost-effective) • Telmisartan: -£66.53; 20.7% • Acupuncture: -£75.21; 6.4%
Conclusion	“Topiramate is the most cost effective treatment for prophylactic pharmacological treatment of migraine. However, there is some uncertainty around this conclusion and some of the other strategies have some probability of being cost-effective. Acupuncture is not cost-effective if the strategy comprises an average of 15 visits.”

Bibliographic reference	**National Clinical Guideline Centre (2012) Headaches: Diagnosis and management of headaches in young people and adults. NICE Clinical Guideline 150.**
Data sources	

Base-line data	
Effectiveness data	Effectiveness of each intervention from the NMA conducted for CG150. Average reduction in migraine days for: • Telmisartan: 0.5134 • Topiramate: 1.039 • Propranolol: 0.5175 • Acupuncture: 0.09266
Cost data	• Cost of preventive medicines from BNF 2011 per 6 month course: ○ Topiramate 100 mg/day: £43.73 (includes 1 pack of 25 mg for the first few days) ○ Propranolol 25 mg/day: £16.08 ○ Telmisartan 80mg/day: £119 ○ Acupunture: £232.56 (15 visits over 6 months based on the cost of half an hour of one community physiotherapist, £15.50) • 2 x GP visits for each of the preventive medicines: £82 from PSSRU reference costs • Cost of acute treatment: £2.23 (triptan + NSAID) source not provided
Utility data	• Following successful migraine treatment: 0.81 from literature • Decrement for experiencing a migraine attack: -0.3 from literature

Uncertainty

One-way sensitivity analysis	For acupuncture to be cost effective compared to no treatment, the number of visits needed to be reduced to 9 (from 15 base case), but it was still not cost-effective compared to topiramate or propranolol.
Probabilistic sensitivity analysis	As per results from Bayesian analysis reported.

Applicability	**Directly Applicable**

Bibliographic reference	**National Clinical Guideline Centre (2012) Headaches: Diagnosis and management of headaches in young people and adults. NICE Clinical Guideline 150.**
Limitations	**Potentially Serious Limitations** • Adverse effects of preventive medicine not included
Conflicts	Refer to NICE Clinical Guideline 150

Appendix O: Cost-effectiveness analysis of prophylactic pharmacological treatment for migraine

O.1 Introduction

An economic model was developed to investigate the cost effectiveness of pharmacological prophylaxis for migraine. It was based on a model initially created by the National Clinical Guideline Centre (NCGC) in 2012 for NICE's *Clinical Guideline 150, Headaches*.

This analysis was undertaken because the results of previous economic studies were of limited usefulness because the costs of both prophylactic medicines and acute treatments have decreased since they were conducted. In addition, the conclusions of the 2012 NCGC model were of limited value if the network meta-analysis on which it was based was superseded by the new network meta-analysis conducted for this update.

Please refer to Appendix J for details of the network meta-analysis conducted for this update.

O.2 Overview

Population

The population was people aged 12 or over who experience migraine.

Interventions

Three pharmacological interventions were compared against no prophylaxis.

- Amitriptyline
- Topiramate
- Propranolol

These medicines were selected for comparison in the economic model because they were found to be effective in the clinical network meta-analysis (Appendix J). Topiramate and propranolol were associated with clinically significant mean reductions in headache days of 1.03 and 1.19 respectively with credible intervals that were statistically significant. The credible interval for amitriptyline was quite wide and just crossed the line of no effect but was associated with a mean reduction of 0.93 headache days, well over the minimally important difference of 0.5 days.

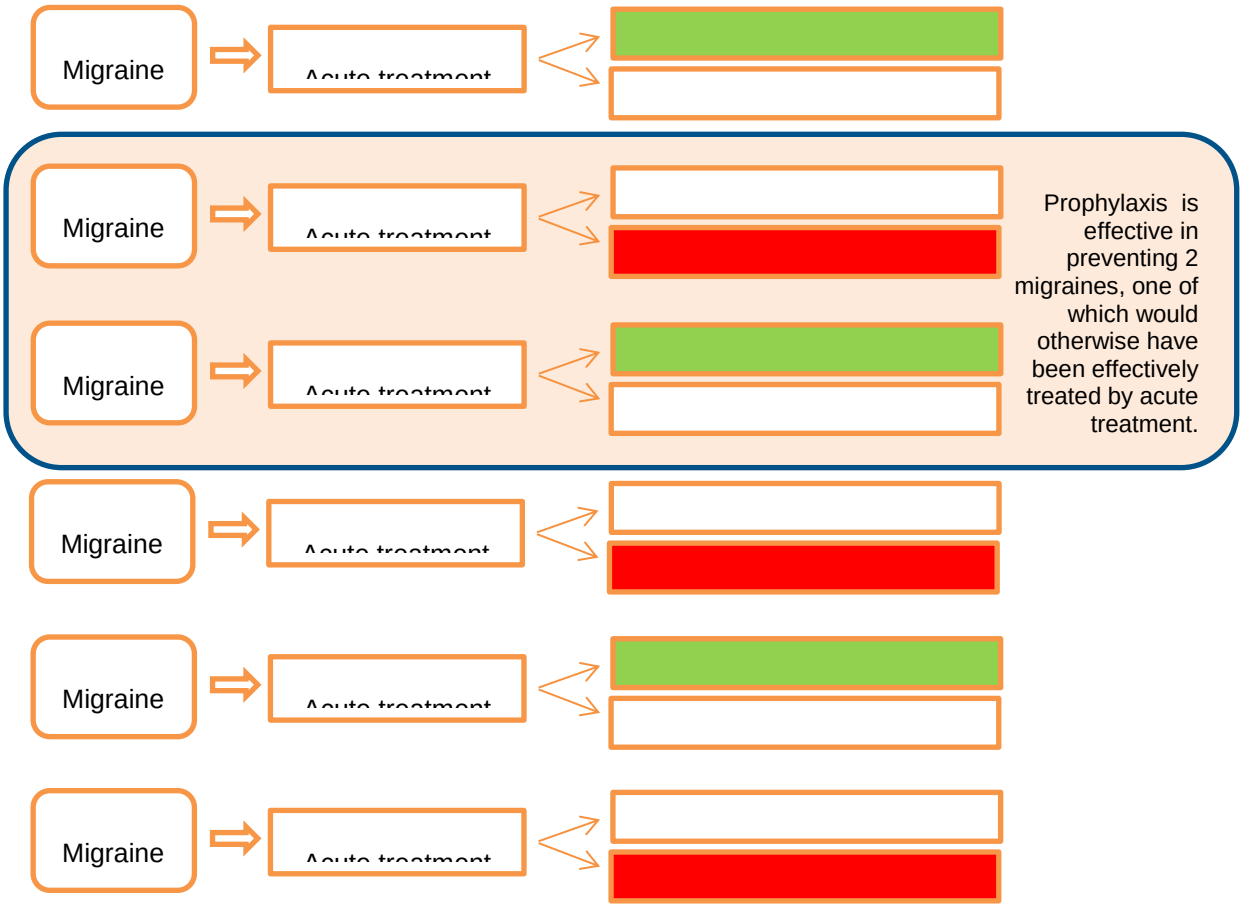
The Committee considered there was insufficient evidence of clinical effectiveness based on the results of the network meta-analysis for the following medicines to be carried forward to the economic model:

- Telmisartan
- Divalproex sodium
- Gabapentin
- Propranolol/nadolol combination

Structure

The decision analysis was based on the network meta-analysis (appendix J) and built in WinBUGS 1.4.3. The code for the base case of this model can be found in appendix P. The change in number of migraine days per month was the main measure of effectiveness and this was obtained from the network meta-analysis conducted for this update (appendix J). This was combined with the costs and quality adjusted life years (QALYs) associated with each migraine attack. Acute treatment was triptan plus a nonsteroidal anti-inflammatory drug (NSAID) in accordance with the recommendation on acute treatment in CG150. The probability of acute treatment being successful is taken from the acute treatment model in CG150. The QALY gain of an avoided attack is determined by the avoided migraine day that may or may not have been successfully treated with triptan plus NSAID. Figure 55 is a graphical representation of this process based on an example of a person who experiences 6 migraines per month and prophylaxis is successful in reducing this by 2 migraines per month.

Figure 55: Structure of the cost-effectiveness model: example of 1 simulation where two migraine days are prevented



Cost calculations

The incremental cost of a prophylactic medicine vs. no prophylaxis is calculated by taking the cost of the six month course of prophylactic medicine less the cost of the acute treatment avoided.

$$IncCost = C_{prophlyaxis} - (\delta \times C_{acute}) \times 6 \quad \textbf{(1)}$$

Where $C_{prophlyaxis}$ is the cost of a course of prophylactic medicine over 6 months, δ is the treatment effect in number of migraine days prevented per month, C_{acute} is the cost of acute treatment and 6 is the time horizon of the model in months.

The Committee considered whether to include the cost of GP consultations because it was included in the 2012 NCGC model. The cost of GP consultations has not been included in the model because the Committee could not establish whether prophylactic interventions would be associated with an increase or decrease in consultations. Prophylaxis may be associated with an increase in GP consultations for the purposes of monitoring treatment progress. Prophylaxis may be associated with a decrease in GP consultations if it is effective and people with migraine require fewer consultations with their GP. Prophylaxis may be associated with no change in GP consultations compared to no prophylaxis because people with migraine could already be in regular contact with their GP, for example, in order to obtain prescriptions for acute treatment. The Committee determined that, on average, there is unlikely to be an incremental difference in GP consultations compared with no prophylaxis and between prophylactic interventions.

QALY calculations

The incremental QALYs compared with no prophylaxis was based on the reduction in migraine days over 6 months assuming each migraine was treated with triptan plus NSAID.

The first calculation is for the utility associated with a day of migraine treated with triptan plus NSAID which may or may not be successful. When a migraine occurs, if the treatment is successful, there will be a 2 hour delay before it provides pain relief. Therefore, a person accrues 2/24 of a day of migraine-weighted utility and 22/24 of a day of normal 'well' utility. The probability of the acute treatment being successful is determined by the acute treatment model conducted for CG150. This results in the following equation for the utility of an acute migraine day.

$$U_{acute} = \frac{22}{24} \times \left(p_{acute} \times U_{well} + (1 - p_{acute}) \times U_{migraine}\right) + \frac{2}{24} \times U_{migraine} \quad \textbf{(2)}$$

Where p_{acute} is the probability of response to acute treatment, U_{well} is the utility associated with no migraine for one day and $U_{migraine}$ is the utility weight associated with migraine for one day.

Incremental QALYs gained over six months can then be calculated using the following formula. Formula 3 has a denominator of 365 because full utility values, that would apply over one year, are used in formula 2 and this needs to be converted back into days in accordance with the rest of the model.

$$incQALYs = \frac{6 \times \delta \times (U_{well} - U_{acute})}{365} \quad \textbf{(3)}$$

Cost-effectiveness calculations

Cost effectiveness is expressed in terms of incremental net monetary benefit (INMB) compared with no prophylaxis. This is calculated by multiplying the incremental QALYs by NICE's cost-effectiveness threshold, £20,000 per QALY less the incremental cost.

$$incNMB = incQALYs_x \times \lambda - incCost_x \quad \textbf{(4)}$$

Where $incQALYs_x$ and $incCost_x$ are the incremental QALYs and incremental cost for each strategy, x, compared with no prophylaxis and λ is NICE's cost-effectiveness threshold, £20,000.

The treatment with the highest INMB is the most cost-effective option at the specified threshold because it is the option that provides the highest health benefits (QALYs) compared with its relevant cost. Calculating INMB helps to identify the optimal strategy in probabilistic analyses. Results can be reported in a similar way to the results of the clinical network meta-analysis (e.g. probability that a treatment is the most cost effective).

Time horizon and discounting

The timeframe of the model is 6 months. The Committee discussed whether a longer time period would be appropriate. It was agreed that 6 months was sufficient time for a prophylactic treatment to have an impact if it was effective for that patient and clinical and cost effectiveness was unlikely to change after this date. Due to the cyclical nature of migraine, the topic experts advised it may be inappropriate to model beyond this timeframe as people stop taking prophylactic medicine for a period of time if migraines stop and then start again if migraines come back some years later. It is unlikely there would be evidence to support extending the model on this basis beyond 6 months. Discounting has not been applied.

Perspective

For costs, the perspective of the NHS was adopted to comply with the methods set out in *Developing Guidelines: The Manual October 2014*. Subsequently, the cost of lost working days and reduced productivity are outside the boundaries of this perspective and not included to the degree that they are not already accounted for in the calculation of quality adjusted life years. The perspective of people with migraine was adopted for health benefits.

O.3 Parameters

Effectiveness

The effectiveness of prophylactic medicines was taken from the network meta-analysis conducted for this update in terms of reduction in migraine days. Please see appendix J for additional detail of this analysis.

Table 73: Effectiveness of prophylactic medicines

Treatment	Mean reduction in migraine days (95% credible interval)
No prophylaxis	-
Amitriptyline	0.93 (-0.38 to 2.27)
Topiramate	1.03 (0.58 to 1.52)
Propranolol	1.19 (0.19 to 2.20)

The effectiveness of acute treatment with triptan and NSAID was a 55.36% probability (precision 63.8977) of sustained response from migraine, with a normal distribution. This was taken from the acute treatment network meta-analysis in *CG150, Headaches, Appendix I*. The acute treatment parameters were retained from the 2012 NCGC model.

Cost

The cost of medicines was obtained from the Drug Tariff April 2015. The model was based on the cost of a 6 month course at the maximum dose used in the UK for migraine prophylaxis. The costs do not account for titration. The Committee advised that practice is highly varied across the UK therefore it would be difficult to establish an accurate representative titration regimen for each medicine. Effecitvely this means the model begins 6 to 8 weeks after a person with migraine begins taking the low dose of their prophylactic medicine.

Table 74: Cost of prophylactic medicines

Treatment	Calculations	6 month cost (£)
No prophylaxis	-	0
Amitriptyline	7 packs of 28 x 50 mg tablets at £1.19 per pack	8.33
Topiramate	3 packs of 60 x 100 mg £3.13 per pack	9.39
Propranolol	4 packs of 56 x 160 mg tablets at £5.34 per pack	21.36

Table 75: Cost of acute treatment medicines

Treatment	Calculations	Cost per dose (£)
Sumatriptan and NSAID	1 x 50mg dose of sumatriptan from a pack of 6 tablets costing £1.66 per pack plus a 200mg dose of ibuprofen from a pack of 24 tablets costing £1.02 per pack	0.32

Utilities

Two utilities are used in the calculations of health benefit described above – one to represent the migraine state and one to represent the no migraine state. People not experiencing a migraine were assumed to be at full health. That is, a utility weight of 1 was applied to people when not experiencing a migraine. The utility weight used for the well state is somewhat irrelevant because the model is driven by the change in disutility due to migraines. The migraine disutility was taken from a 2011 US study that used the EQ-5D to measure the quality of life of 330 people who had 1 to 6 moderate to severe migraine attacks per month (Xu et al., 2011). The disutility applied to people experiencing a migraine in the model was -0.493 (95% CI -0.4100 to -0.5654), representing severe migraine. A beta distribution was applied based on this data with α=77.9171 and β=80.1297.

O.4 One-way sensitivity analyses

SA1 Oral solution

Topic experts advised that some adolescents are unable to consume tablets so a sensitivity analysis was conducted taking into account the increased cost of these preparations. All other parameters in the model including effectiveness are assumed identical to the base case. There is no oral solution version of topiramate. This sensitivity analysis is implemented by changing the costs of prophylactic medicines and taking out topiramate as a comparator. There is no requirement to change formulas. The oral solution form of propranolol did not

appear in the Drug Tariff so the cost was taken from the BNF. In this scenario, acute treatment would take the form of two 10 mg doses of nasal spray sumatriptan at a cost of £11.80 (Drug Tariff June 2015).

Table 76: Cost of oral solution form of prophylactic medicines

Treatment	Calculations	6 month cost (£)	Source
No prophylaxis	-	0	-
Amitriptyline	6 bottles of 50mg/5mL 150mL at £19.20 per bottle	£115.20	Drug Tariff April 2015
Topiramate	-	-	-
Propranolol	6 bottles of 50mg/5mL 150 mL at £19.98 per bottle	£119.88	BNF accessed 29 May 2015

SA2 Lower disutility for migraine

Xu et al. (2011) reported disutilities for mild, moderate and severe migraine pain. The disutility for severe migraine was used in the base case. Because disutility avoided is the key driver of health benefit in the model, a sensitivity analysis was conducted using the moderate disutility for migraine pain, -0.186 (95% CI -0.1645 to -0.2053). Parameters were adjusted in the WinBUGS code and no new formulas were required.

SA3 Adverse Events

Serious adverse events were included as an outcome in the clinical systematic review but this was rarely reported in studies and when it was it was they were very low numbers. Therefore, the Committee could not draw a conclusion on the relative occurrence of serious adverse events between prophylactic medicines and compared with no prophylaxis.

An analysis was conducted for the purposes of the economic model by extracting data on dropouts due to adverse events from studies included in the network meta-analysis. This was not included in the base case because of the unreliability of how these were reported in studies and the variability of the severity of adverse events. Table 77 contains a summary of this data.

Table 77: Number of dropouts due to adverse events

	Amitriptyline		Topiramate		Propranolol		Placebo	
Study	Drop outs	N (ITT)	Drop outs	N (ITT)	Drop outs	N (ITT)	Drop outs	N (ITT)
Apostol 2008								
Brandes 2004			32	120			14	114
Diener 2004			37	139	29	143	15	143
Diener 2009								
Dodick 2009	34	159	34	172				
Holroyd 2010								
Lewis 2009			3	35			1	33
Lipton 2011			21	177			18	175
Silberstein 2004			24	125			11	115
Silberstein 2013								
Winner 2005			7	108			2	49

This was incorporated into the model by adjusting the formulas to account for the proportion of people who dropout due to adverse events. The probability of dropout due to adverse events was incorporated probabilitistically into the model based on the data in Table 77. These are the identical figures reported in the evidence tables for the clinical review

(appendix G). Meta-analyses were conducted in WinBUGS to establish the probability of dropping out due to an adverse event for topiramate and placebo. The code used to investigate the dropouts for topiramate is provided in appendix Q. Similar code was used for placebo. Meta-analyses were not required for amitriptyline or propranolol because there is only one study reporting this outcome for each. The distributions and their parameters used in SA3 are provided in Table 78. These parameters are subsequently transformed into the probability scale in WinBUGS.

Table 78: Parameters used to represent the probability of dropping out due to an adverse event

Prophylactic medicine	Distribution	Alpha or mean	Beta or standard deviation
Placebo	Normal	-2.312	0.2651
Amitriptyline	Beta	34	125
Topiramate	Normal	-1.659	0.3362
Propranolol	Beta	29	114

People that experience an adverse event are assumed to stop taking prophylactic medicine before it has had a chance to prevent any migraines. No migraines are prevented and no health benefit accrues to the proportion of people that dropout. In addition, a disutility is applied to the proportion of people that dropout from the adverse event for one day. Yu et al. (2011) assumed a 20% utility decrement for adverse events based on expert opinion and this amount was applied here. The new formula for calculating incremental health benefits taking into account adverse events is:

$$incQALYs = \frac{p_{adverse} \times [6 \times (U_{well} - U_{acute}) + U_{adverse}] + (1 - p_{adverse}) \times [6 \times \delta \times (U_{well} - U_{acute})]}{365} \quad \textbf{(3b)}$$

Where $p_{adverse}$ is the risk of dropping out due to an adverse event and $U_{adverse}$ is the utility decrement due to experiencing the adverse event.

The cost of a course of prophylactic medicine is reduced to a single pack because it is assumed people stop taking the medicine once they experience an adverse event. The formula for incremental cost changes to account for the proportion of people who experience adverse events. There is no cost associated with experiencing an adverse event itself, only the reduced cost of the discontinued course of prophylactic medicine and the same acute treatment cost as the no prophylaxis treatment arm.

$$IncCost = p_{adverse} \times [C_{adverse} - (\delta \times C_{acute}) \times 6] + (1 - p) \times [C_{prophylaxis} - (\delta \times C_{acute}) \times 6] \quad \textbf{(1b)}$$

Where $C_{adverse}$ is the cost of 1 pack of prophylactic treatment.

Table 79: Cost of 1 pack of prophylactic medicine

Treatment	Calculations	6 month cost (£)
No prophylaxis	-	0
Amitriptyline	1 pack of 28 x 50 mg tablets	1.19
Topiramate	1 pack of 60 x 100 mg tablets	3.13
Propranolol	1 pack of 56 x 160 mg tablets	5.34

O.5 Results

Table 80 shows the results of the base case analysis compared with no prophylaxis. Propranolol was the most cost effective prophylactic medicine with the highest incremental cost-effectiveness ratio up to the £20,000 threshold, £4,359 per QALY. It also had the highest probability of being most cost effective at 47%. Topiramate and amitriptyline had positive incremental net monetary benefits. Amitriptyline had the second highest probability of being most cost effective, 31%, followed by topiramate at 22%.

Figure 56 contains a summary of the point estimates of the ICERs on the cost-effectiveness plane where the orange, solid line indicates the £20,000 cost-effectiveness threshold. This figure shows that all prophylactic medicines are to the south-east of the threshold and therefore cost-effective compared to no prophylaxis. Propranolol is preferred because it maximises health benefits at an incremental cost that is below the cost-effectiveness threshold.

Figure 57 shows the probability of a treatment achieving that rank based on its INMB using a cost-effectiveness threshold of £20,000 per QALY. Rank 1 in this figure is to the same as the probability of being best reported in table 80. Propranolol has the highest probability of ranking first, topiramate has the highest probability of ranking second and amitriptyline has the highest probability of ranking third. There is a greater than 90% probability that no prophylaxis ranks last.

Figure 58 is a cost-effectiveness acceptability curve showing the probability that a treatment is considered cost effective at different levels of the cost-effectiveness threshold.

Table 80: Probabilistic base case cost effectiveness of prophylactic medicines

Treatment	Incremental Cost (£)	Incremental Benefit (QALYs)	Incremental cost-effectiveness ratio (£/QALY)	Incremental net monetary benefit (£; £20,000/QALY threshold)	Probability best
No prophylaxis	-	-	-	-	0%
Amitriptyline (vs. no prophylaxis)	6.52	0.01688	386	331	31%
Topiramate (vs. amitriptyline)	0.883	0.00164	538	32	22%
Propranolol (vs. topiramate)	11.68	0.00268	4359	41.92	47%

Figure 56: Cost-effectiveness plane for base case analysis of prophylactic medicines compared with no prophylaxis (comparator at the origin is no prophylaxis)

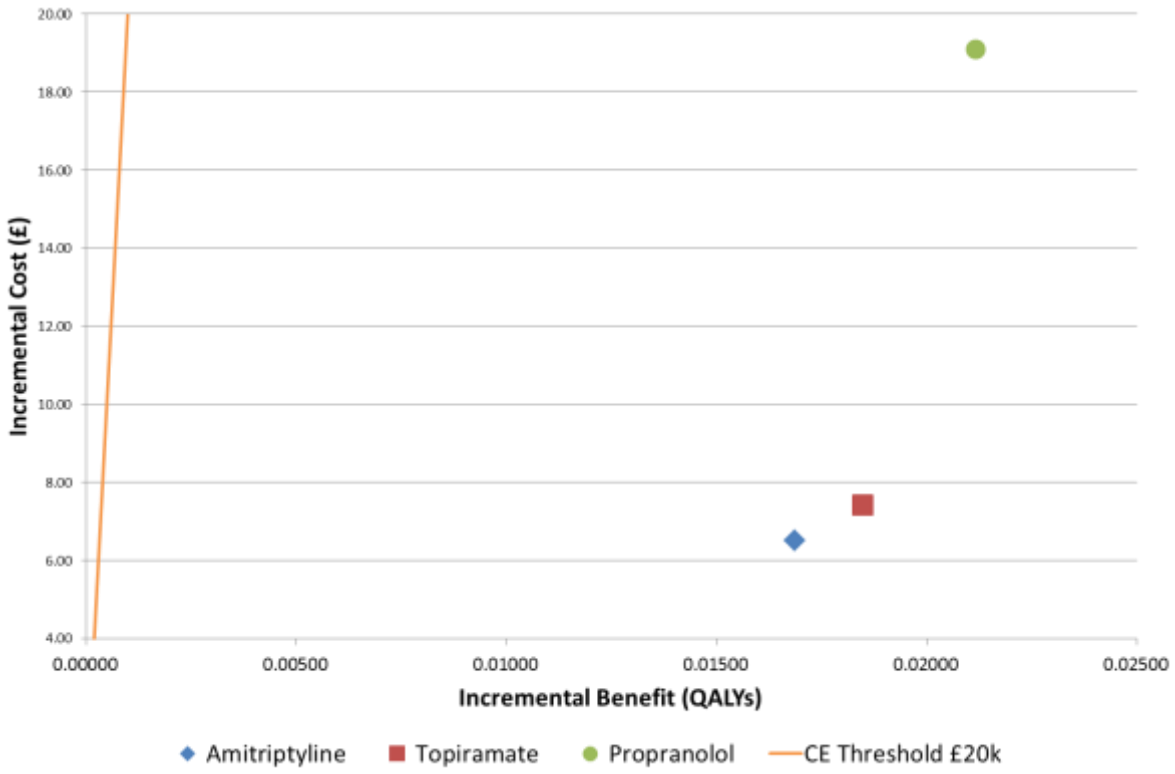


Figure 57: Rank probability plot for base case analysis of prophylactic medicines compared with no prophylaxis based on incremental net monetary benefit and a cost-effectivenes threshold of £20,000 per quality adjusted life year

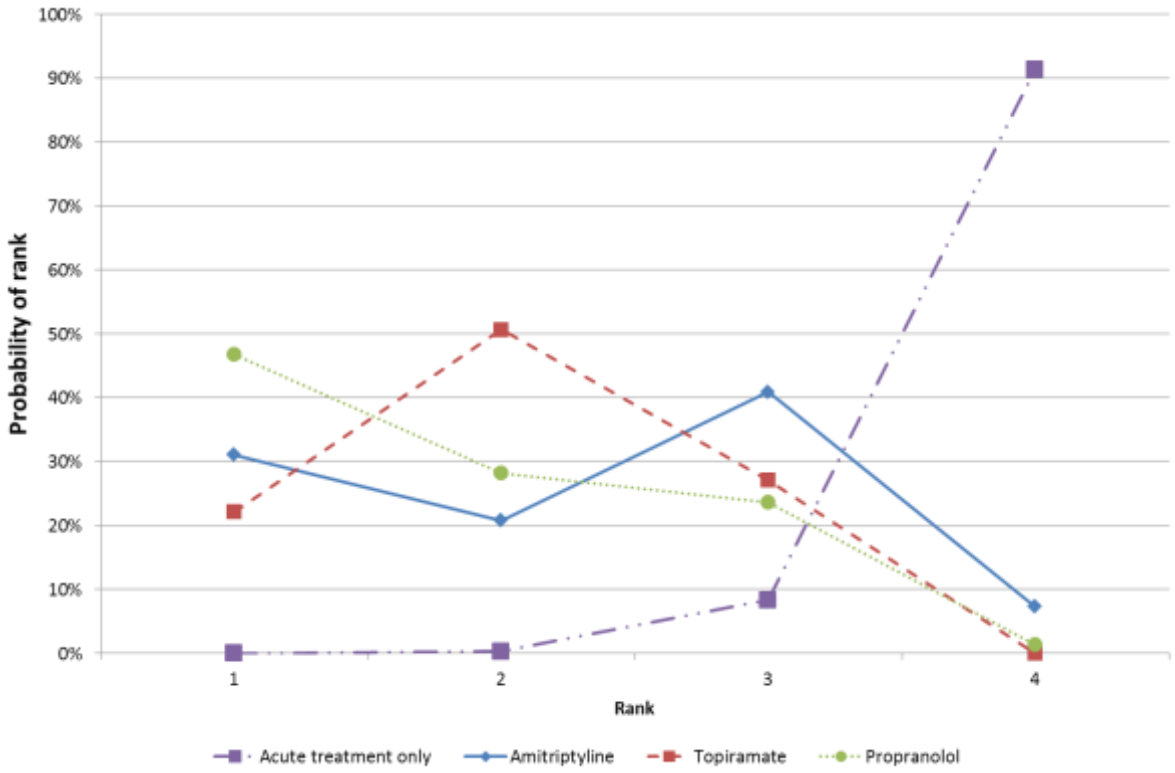
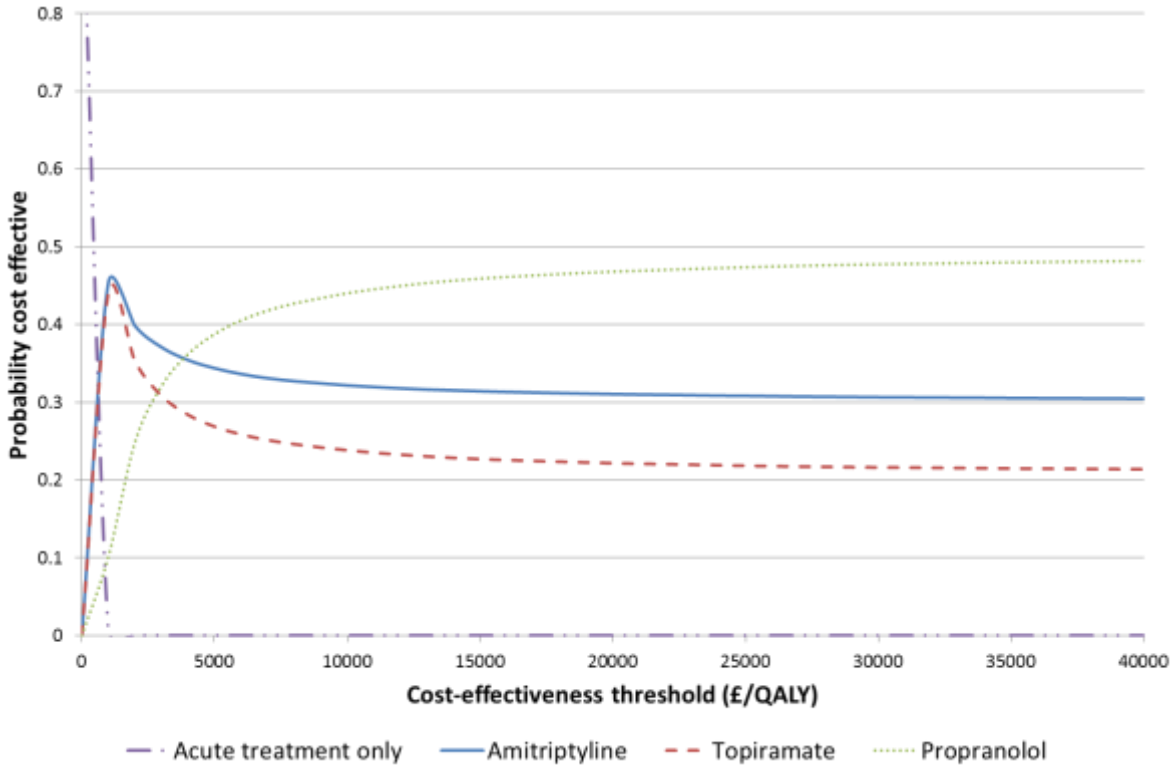


Figure 58: Cost-effectiveness acceptability curve for base case analysis of prophylactic medicines compared with no prophylaxis



SA1 Oral Solution

There is no oral solution form of topiramate. ICERs for amitriptyline and propranolol increased, reflecting the higher cost of oral solutions. The ICERs are still well below the £20,000 threshold. Both INMBs have decreased but are still positive indicating that the oral solution forms of amitriptyline and propranolol are cost effective. Propranolol is the most cost effective option with the highest INMB, £388, lowest ICER, $1,690 and highest probability of being cost effective, 62%.

Table 81: Probabilistic results of sensitivity analysis 1 - cost effectiveness of oral solution forms of prophylactic medicines compared with no prophylaxis

Treatment	Incremental Cost (£)	Incremental Benefit (QALYs)	Incremental cost-effectiveness ratio (£/QALY)	Incremental Net Monetary Benefit (£)	Probability Best
No prophylaxis	-	-	-	-	1%
Amitriptyline	48.27	0.01688	2860	289	37%
Topiramate	-	-	-	-	-
Propranolol	35.83	0.02121	1690	388	62%

SA2 Lower disutility for migraine

A lower disutility for migraines reduced the cost-effectiveness of prophylactic medicines because the health reduction they prevented is less. The ICERs were higher than the base case but still well under the £20,000 cost-effectiveness threshold.

Table 82: Probabilistic results of sensitivity analysis 2 – cost effectiveness of prophylactic medicines compared with no prophylaxis using a reduced disutility for migraine

Treatment	Incremental Cost (£)	Incremental Benefit (QALYs)	Incremental cost-effectiveness ratio (£/QALY)	Incremental Net Monetary Benefit (£)	Probability Best
No prophylaxis	-	-	-	-	0%
Amitriptyline	6.52	0.01339	487	261	31%
Topiramate	7.40	0.01473	502	287	23%
Propranolol	19.07	0.01689	1129	319	47%

SA3 Adverse events

The inclusion of adverse events had minimal impact on the results. Despite the reduction in health benefits achieved, there was also a reduction in cost because of the assumption that people discontinue prophylactic treatment.

Table 83: Probabilistic results of sensitivity analysis 3 – cost effectiveness of prophylactic medicines compared with no prophylaxis when adverse events due to prophylactic medicines are included

Treatment	Incremental Cost (£)	Incremental Benefit (QALYs)	Incremental cost-effectiveness ratio (£/QALY)	Incremental Net Monetary Benefit (£)	Probability Best
No prophylaxis	-	-	-	-	0%
Amitriptyline	0.93	0.01619	33	323	30%
Topiramate	2.18	0.01802	120	358	21%
Propranolol	6.31	0.02073	304	408	49%

O.6 Discussion

This cost effectiveness analysis found that propranolol was the preferred prophylactic medicine. It also had the highest probability of being most cost effective. This adaption of the 2012 NCGC model is different from its predecessor in a number of ways. Firstly, the treatments compared are different. The 2012 NCGC model compared propranolol, topiramate, telmisartan and acupuncture. Acupuncture was outside the scope of this update. Telmisartan was excluded from the 2015 NICE model because the clinical network meta-analysis found that it was not associated with a reduction in migraine days. Amitriptyline was included in the 2015 NICE model but excluded from the 2012 NCGC model because the single study comparing amitriptyline against topiramate was not included in the 2012 NCGC network meta-analysis. Secondly, the cost of GP consultations was excluded from the 2015 NICE model for reasons already discussed. Thirdly, the 2012 NCGC model did not include adverse events due to insufficient evidence. Insufficient evidence was identified to include adverse events in the base case again in the 2015 NICE model. However, a sensitivity analysis was conducted to explore what impact this may have on the results by calculating the number of people that dropped out due to adverse events. The inclusion of adverse events did not change the conclusions of the analysis. Fourthly, the 2015 NICE model used more recent disutilities to represent the experience of migraines and uncertainty was accounted for in this parameter. The disutility used in the 2015 NICE model (mean -0.493) was larger than that used in the 2012 NCGC model (-0.3) making prophylactic medicines more cost effective, all other things being equal. A sensitivity analysis was undertaken using an alternative, lower disutility (mean -0.186) from the same recent study and results were again robust to this change in the parameter.

This analysis has a number of limitations. The relatively simplistic approach taken to calculating cost consequences means that potential implications on other resource use were not taken into account. However, if prophylactic medicines result in a reduction in the use of other healthcare resources as found by Wu et al. (2012), Wertz et al. (2009) and Silberstein et al. (2007), it would only enhance the cost effectiveness of prophylactic treatment. The 6 month timeframe is also a limitation of the analysis. However, it is consistent with the 2012 NCGC model and topic experts advised it would be difficult to reliably populate a model beyond this timeframe. Another limitation of this analysis is that the relative effectiveness of treatments is driven by the change in migraine days found by the clinical network-analysis and does not include other outcomes such as change in migraine intensity or frequency. However, the topic experts advised that change in migraine days is the most important outcome for people with migraine and this approach is consistent with both the clinical and economic analyses conducted in 2012 for CG150.

The findings of this analysis are broadly consistent with the conclusions of published economic studies. The 2012 NCGC model found that topiramate was likely to be the most cost effective treatment but did not include amitriptyline. Propranolol had a positive INMB and there was a high degree of uncertainty surrounding results. Brown et al. (2006) found that topiramate was cost effective compared to no prophylaxis. An analysis of Yu et al (2011) based on direct costs found that topiramate and timolol were the most cost effective interventions although the authors found amitriptyline to be the most cost effective in their base case analysis including productivity consequences. The relevance of these studies to the present decision-making context, and comparability to the 2015 NICE model, is limited due to the higher costs for both prophylaxis and acute treatment when these analyses were conducted.

Acknowledgements

The model was initially developed by health economists at the National Clinical Guidelines Centre. Sofia Dias and Edna Keeney from the University of Bristol provided assistance with coding in WinBUGS and general technical advice.

Appendix P: WinBUGS code for cost-effectiveness analysis (base case)

INTRODUCTION. Cost-effectiveness analysis: medicines for the prophylaxis of migraine. This WinBUGS file is the cost-effectiveness model constructed as part of the update to the NICE headaches guideline 2012 (CG150) investigating prophylactic treatment options for migraine. It is an adaption of the model initially developed by the National Clinical Guidelines Centre for CG150. It should be reviewed in conjunction with the full technical report which can be found as an appendix to the addendum for the 2015 udpate.

USING THIS MODEL. Using this model requires relevant technical expertise. The computations for the economic model are conducted entirely within WinBUGS. The coda does not need to be exported to Excel other than for the presentation of results in chart format.

CONFIDENTIALITY. The economic model and its contents are confidential and are protected by intellectual property rights, which are owned by NICE and the NCGC. It cannot be used for any other purpose than to inform the recipient's understanding of the draft guideline update. The economic model cannot be published by stakeholders, in whole or in part, or used to inform the development of other economic models. The model must not be run for purposes other than to test its reliability.

```
# Normal likelihood, identity link, Arm and Trial-level data (treatment differences)
# Random effects model for multi-arm trials
model{              # *** PROGRAM STARTS
for(i in 1:ns.a){    # LOOP THROUGH STUDIES WITH ARM DATA
 w.a[i,1] <- 0       # adjustment for multi-arm trials is zero for control arm
 delta[i,1] <- 0     # treatment effect is zero for control arm
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na.a[i]) { # LOOP THROUGH ARMS
   var.a[i,k] <- pow(se.a[i,k],2) # calculate variances
   prec.a[i,k] <- 1/var.a[i,k] # set precisions
   y.a[i,k] ~ dnorm(theta[i,k],prec.a[i,k]) # normal likelihood
   theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
   dev[i,k] <- (y.a[i,k]-theta[i,k])*(y.a[i,k]-theta[i,k])*prec.a[i,k]
  }
```

```
# summed residual deviance contribution for this trial
 resdev[i] <- sum(dev[i,1:na.a[i]])
 for (k in 2:na.a[i]) { # LOOP THROUGH ARMS
   delta[i,k] ~ dnorm(md[i,k],taud.a[i,k]) # trial-specific LOR distributions
# mean of LOR distributions, with multi-arm trial correction
   md[i,k] <- d[t.a[i,k]] - d[t.a[i,1]] + sw.a[i,k]
# precision of LOR distributions (with multi-arm trial correction)
   taud.a[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
   w.a[i,k] <- (delta[i,k] - d[t.a[i,k]] + d[t.a[i,1]])
# cumulative adjustment for multi-arm trials
   sw.a[i,k] <- sum(w.a[i,1:k-1])/(k-1)
  }
}
for(i in 1:ns.t){    # LOOP THROUGH STUDIES WITH TRIAL DATA
 w[i,1] <- 0 # adjustment for multi-arm triatsuls is zero for control arm
 delta[i+ns.a,1] <- 0 # treatment effect is zero for control arm
 for (k in 2:na[i]) { # LOOP THROUGH ARMS
   var[i,k] <- pow(se[i,k],2) # calculate variances
   prec[i,k] <- 1/var[i,k] # set precisions
   y[i,k] ~ dnorm(delta[i+ns.a,k],prec[i,k]) # normal likelihood
#Deviance contribution
   dev[i+ns.a,k] <- (y[i,k]-delta[i+ns.a,k])*(y[i,k]-delta[i+ns.a,k])* prec[i,k]
  }
# summed residual deviance contribution for this trial
 resdev[i+ns.a] <- sum(dev[i+ns.a,2:na[i]])
 for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
   delta[i+ns.a,k] ~ dnorm(md[i+ns.a,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
   md[i+ns.a,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
   taud[i,k] <- tau *2*(k-1)/k
```

```
# adjustment, multi-arm RCTs
   w[i,k] <- (delta[i+ns.a,k] - d[t[i,k]] + d[t[i,1]])
   sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
 }
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0              # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
sd ~ dunif(0,5)       # vague prior for between-trial SD
tau <- pow(sd,-2)     # between-trial precision = (1/between-trial variance)
```

###Only the treatments that result in a reduction in migraine days are now carried forward to the economic model. eff[i]=Number of headache days avoided per month with treatment i. This code changes the sign of the effect (d) which is mean change in headache days with treatment, which is negative if effective.###

```
eff[1] <- 0     #Placebo
eff[2] <- -d[3] #Amitriptyline
eff[3] <- -d[6] #Topiramate
eff[4] <- -d[7] #Propranolol
```

###Cost effectiveness calculations###

##The calculations below are to work out the probability of responding to triptan + NSAID during a migraine attack. This is done by adjusting the QALYs for a migraine attack using the triptan + NSAID efficacy, as is done in the acute model in CG150. ###

```
#
#Baseline effect for triptan
BR ~ dnorm(meanBR,precBR)
#
#Relative effect for triptan + NSAID
RE ~ dnorm(meanRE,precRE)
#
#Overall probability of response for triptan + NSAID
logit(r) <- BR + RE
```

```
#Beta distribution for disutility due to migraine. Mean and confidence interval taken from Xu et al. 2011 and converted to alpha and beta for beta distribution using method of moments.#

utilMig ~ dbeta(alphaMig,betaMig)


##The following lines of code work out the incremental QALYs (incQALYs), incremental cost (incCost) and incremental net benefit for each treatment. incNBmain is used to calculate the base case NB and the probability of a treatment being best based on a threshold of £20k. incNB is used to calculate probCE at different thresholds. ##

for (i in 1:4){

  incQALYs[i] <- (6*eff[i]*(utilNoMig-(((22/24)*(r*utilNoMig+(1-r)*-utilMig))+((2/24)*-utilMig))))/365

  incCost[i] <- cost[i]-(eff[i]*cost_trip*6)

          incNBmain[i] <- (incQALYs[i]*20000)-incCost[i]

  for (j in 1:51){

# for WTP = (j-1) i.e. from zero to 50,000

    incNB[i,j]<-(incQALYs[i]*(j-1)*1000)-incCost[i] # INB for treat i at WTP j-1

# prob(cost eff) treat i at WTP j-1

    probCE[i,j] <- equals(rank(incNB[,j],i),4)

  }

}


#Calculate probability best for incNBmain

for(k in 1:4){ #calcuate rank and probability of each rank for each treatment

 rk2[k] <- 5-rank(incNBmain[],k)

 best2[k] <- equals(rk2[k],1)

 for (h in 1:4){

          prob2[k,h]<-equals(rk2[k],h)    # probability treat k is ranked h

          }

}


}                              # *** PROGRAM ENDS



 Data
```

ns.a= number of studies with arm level information; ns.t= number of studies with trial level information; nt=number of treatments

#cost = cost of a course of prophylactic medicine over 6 months in the following order: no prophylaxis, amitriptyline, topiramate, propranolol

#cost_trip = cost of triptan + NSAID in acute model

#utilNoMig = utility for well

#alphaMig and betaMig = parameters of the beta distribution for utility of a migraine

#meanBR, precBR, meanRE and precRE are parameters taken from the acute treatment model

#In the data specified below,the following numbers correspond to the following treatments:

#1=placebo, 2=telmisartan. 3=amitriptyline, 4=divalproex sodium, 5=gabapentin, 6=topiramate, 7=propranolol, 8=propranolol/nadolol

list(ns.a=9,ns.t=2, nt=8, alphaMig=77.9171, betaMig=80.1297, utilNoMig=1, meanBR=-1.423, precBR=39.6, meanRE=0.5536, precRE=63.8977, cost=c(0,8.33,9.39,21.36), cost_trip=0.32)

Arm-level data

t.a[,1]	t.a[,2]	t.a[,3]	t.a[,4]	y.a[,1]	y.a[,2]	y.a[,3]	y.a[,4]	se.a[,1]		se.a[,2]		
	se.a[,3]		se.a[,4]		na.a[]	#study						
1	2	NA	NA	-1.14	-1.65	NA	NA	0.57	0.547	NA	NA	2
	#	Diener	2009									
1	4	4	4	-2.8	-3.1	-2.2	-2.8	0.358	0.422	0.37	0.323	4
	#	Apostol		2008								
1	6	6	6	-1.3	-2.9	-2.6	-1.7	0.32	0.32	0.31	0.3	4
	#	Brandes		2004								
1	6	6	NA	-2.6	-4.9	-3.6	NA	0.553	0.527	0.497	NA	3
	#	Lewis	2009									
1	6	NA	NA	-5.3	-6.6	NA	NA	0.275	0.278	NA	NA	2
	#	Lipton	2011									
1	6	6	6	-1.3	-2.7	-2.7	-2.7	0.3	0.308	0.271	0.281	4
	#	Silberstein		2004								
1	6	NA	NA	-2.4	-3.1	NA	NA	0.4	0.289	NA	NA	2
	#	Winner	2005									
1	6	6	7	-1.1	-1.3	-1.8	-1.9	0.24	0.25	0.25	0.25	4
	#	Diener	2004									
1	8	NA	NA	-3.3	-3.9	NA	NA	0.153	0.179	NA	NA	2
	#	Holroyd		2010								

END

Trial-level data

```
t[,1]   t[,2]   y[,2]   se[,2]  na[]    #       study
1       5       0       0.663   2       #       Silberstein 2013 1800mg/d dose only
        2013 1800mg/d dose only
3       6       -0.1    0.41    2       #       Dodick 2009
END
```

Initial values

```
# Initial Values
# Initial values for delta can be generated by WinBUGS.
#chain 1
list(d=c( NA, 0,0,0,0,0,0,0), sd=1, mu=c(0, 0, 0,0,0,0,0,0,0))
#chain 2
list(d=c( NA, -1,-3,-1,1,2,-2,-1), sd=4,  mu=c(-3, -3, -3,-3,-3,-3,-3,-3,-3))
#chain 3
list(d=c( NA, 2,2,2,2,2,2,2), sd=2 mu=c(-3, 5, -1,4,3,-2,-3,-1,-4))
```

Appendix Q: WinBUGS code for meta-analysis of dropouts due to adverse events

```
model{                    # *** PROGRAM STARTS
for (i in 1:ns){          # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])          # Likelihood
   logit(p[i]) <- mu[i]                    # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)     # Random effects model
# expected value of the numerators
      rhat[i] <- p[i] * n[i]
#Deviance contribution
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))
          +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
 }
totresdev <- sum(dev[])       # Total Residual Deviance
mu.new ~ dnorm(m,tau.m)          # predictive dist. (log-odds)
m ~ dnorm(0,.0001)           # vague prior for mean
var.m <- 1/tau.m             # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)            # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m                # posterior probability of response
logit(R.new) <- mu.new       # predictive probability of response
}
```

```
list(ns=7)
r[]    n[]
32       120
37       139
34       172
```

3 35

21 177

24 125

7 108

END

list(mu=c(0,0,0,0,0,0,0), sd.m=1, m=0)

list(mu = c(-1,-1,-1,-1,-1,-1,-1), sd.m=3, m= -1)

node	mean	sd	2.5%	median	97.5%	sample
R	0.1648	0.0457	0.08567	0.1615	0.2651	160000
R.new	0.1891	0.1276	0.02861	0.162	0.5354	160000
dev[1]	1.092	1.517	0.001075	0.5042	5.437	160000
dev[2]	1.083	1.508	0.001069	0.4995	5.37	160000
dev[3]	0.9514	1.343	9.251E-4	0.4352	4.758	160000
dev[4]	0.9152	1.211	9.72E-4	0.4565	4.269	160000
dev[5]	0.9446	1.337	9.748E-4	0.4276	4.775	160000
dev[6]	0.9244	1.311	8.814E-4	0.4213	4.639	160000
dev[7]	1.361	1.792	0.001463	0.6711	6.443	160000
m	-1.659	0.3362	-2.366	-1.647	-1.02	160000
mu.new	-1.659	0.9037	-3.525	-1.643	0.1453	160000
totresdev	7.271	3.905	1.753	6.583	16.72	160000

****

Binomial likelihood, logit link

Baseline fixed effects model

model{ # *** PROGRAM STARTS

for (i in 1:ns){ # LOOP THROUGH STUDIES

r[i] ~ dbin(p[i],n[i]) # Likelihood

```
   logit(p[i]) <- m                          # Log-odds of response
# expected value of the numerators
      rhat[i] <- p[i] * n[i]
#Deviance contribution
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))
          +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
 }
totresdev <- sum(dev[])        # Total Residual Deviance
m ~ dnorm(0,.0001)             # vague prior for mean
logit(R) <- m                  # posterior probability of response
}

list(ns=6)
r[]   n[]
14    114
15    143
1     33
18    175
11    115
2     49
END


list(m=0)


list(m= -1)
```

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

	Dbar	Dhat	pD	DIC
r	28.546	27.549	0.997	29.543
total	28.546	27.549	0.997	29.543

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
R	0.09695	0.01177	3.108E-5	0.07516	0.09653	0.1212	20001	160000
dev[1]	1.034	0.8548	0.002211	0.01357	0.8385	3.17	20001	160000
dev[2]	0.3448	0.4609	0.001164	3.647E-4	0.1673	1.643	20001	160000
dev[3]	2.251	0.5931	0.001569	1.214	2.21	3.527	20001	160000
dev[4]	0.362	0.4993	0.001256	3.685E-4	0.1696	1.781	20001	160000
dev[5]	0.1828	0.2585	6.609E-4	1.818E-4	0.08382	0.9162	20001	160000
dev[6]	2.246	0.7428	0.001967	0.9852	2.182	3.874	20001	160000
m	-2.239	0.1351	3.554E-4	-2.51	-2.236	-1.981	20001	160000
totresdev	6.421	1.414	0.003585	5.421	5.877	10.44	20001	160000