NCGC National Clinical Guideline Centre

Headaches

Diagnosis and management of headaches in young people and adults

Clinical Guideline 150

Methods, evidence and recommendations

September 2012

Commissioned by the National Institute for Health and Clinical Excellence

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Update information

December 2021: We changed the strength of recommendation 1.3.15 from 'offer' to 'consider' to better reflect the balance between the benefits and harms associated with the use of metoclopramide and prochlorperazine. See the surveillance report for details.
February 2020: A footnote was added to recommendation 1.3.17 on the potential risk of propranolol overdose in people with migraine who also have depression.
November 2015: New and updated recommendations on the prophylactic treatment of migraine were added.

These changes can be seen in the short version of the guideline at https://www.nice.org.uk/guidance/CG150

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1 Introduction

Headaches are one of the most common neurological problems presented both to general practitioners and to neurologists[101,138,166,192,264]. Evidence indicates that in primary care, 4.4/100 patients per year consult with headache[138] and headache accounts for up to 30% of neurology out-patient appointments[134,272].

Headache disorders are classified as primary or secondary. The aetiology of primary headaches is poorly understood and they are classified according to their clinical pattern. The most common primary headache disorders are tension-type headache, migraine and cluster headache. Secondary headaches are attributed to underlying disorders and include, for example, headaches associated with medication overuse, giant cell arteritis, raised intracranial pressure and infection. Medication overuse headache most commonly occurs in those taking medication for a primary headache disorder. The major health and social burden of headaches is caused by the primary headache disorders and by medication overuse headache.

Headache disorders are a cause of pain and disability. They also have a substantial societal burden. Migraine, for example, occurs in 15% of the UK adult population, and more than 100,000 people are absent from work or school as a result of migraine every working day. Cluster headaches are less common affecting, perhaps, 1% of the population at some time in their life. Bouts of cluster headaches can be extremely disabling.

Although primary headaches can affect people of any age their main impact is in young adults many of whom have both work and family commitments that are affected by their headaches. The impact is not just during a headache but the uncertain anticipation of a headache can cause a significant burden between attacks. Globally migraine and tension type headache contribute similar proportions to the headache burden[244]. As well as impact on the person with headaches primary headaches can a have a substantial effect on the life of other family members[244]. Across Europe the cost of migraine alone may be as high as €27 billion per annum.

Current practice

Many non-specialist healthcare professionals can find the diagnosis of headache difficult, and both people with headache and their healthcare professionals can be concerned about possible serious underlying causes. This leads to variability in care and may mean that people with headaches are not always offered the most appropriate treatments. People with headache alone are unlikely to have a serious underlying disease. Comparisons between people with headache referred to secondary care and those treated in primary care show that they do not differ in terms of headache impact or disability[212].

Many people with headache do not have an accurate diagnosis of headache type. GPs lack confidence in their ability to diagnose common headache disorders. They can feel under pressure to refer people for specialist opinion and investigation. Most common headache types can be diagnosed on clinical history and can be managed in primary care. If specialist advice is needed on headache diagnosis and management this can be provided by a neurologist with an interest in headache or a GP with a special interest (GPwSI) in headaches, or for young people under 18 years of age; a general hospital or community based paediatrician or paediatric neurologist. Within this guideline the term specialist is used to mean either a neurologist, GPwSI, paediatric neurologist or paediatrician with a special interest in headache.

This guideline does not cover secondary headaches that require more specialist management, for example headaches that are due to an underlying infection (e.g. meningitis) and cervicogenic headache. Facial pain and occipital neuralgia are also beyond the remit of this guideline.

Improved recognition of primary headaches would help the generalist clinician to manage headaches more effectively, allow better targeting of treatment and potentially improve quality of life and reduce unnecessary investigations. Improved diagnosis of primary headaches and better use of available treatments has the potential to substantially reduce the population burden of headache without needing substantial additional resources.

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help people to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- guideline topic is referred to NICE from the Department of Health
- stakeholders register an interest in the guideline and are consulted throughout the development process
- the scope is prepared by the National Clinical Guideline Centre (NCGC)
- the NCGC establishes a guideline development group
- a draft guideline is produced after the group assesses the available evidence and makes recommendations
- there is a consultation on the draft guideline
- the final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- information for the public (‘understanding NICE guidance’ or UNG) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

To develop a clinical guideline for the diagnosis and management of headaches in adolescents and adults.

Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Martin Underwood in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every 5-6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.3 What this guideline covers

This guideline covers the following populations:

Young people (12 years and older) and adults in all settings in which NHS healthcare is provided.

The following clinical issues are covered:

- Diagnosis of the following primary headaches: migraine with or without aura, menstrual related migraine, chronic migraine, tension-type headache and cluster headache. Consideration will also be given to people whose headaches have characteristics of more than one primary headache disorder.
- Diagnosis of medication overuse headache.
- Characteristics of headaches that may be related to serious underlying disease and need specific investigations and management.

- Acute pharmacological management of the specified primary headaches with: antiemetics, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, oxygen, paracetamol and triptans.
- Prophylactic pharmacological treatment for specified primary headaches with: ACE inhibitors and angiotensin II receptor antagonists, antidepressants (serotonin–norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors and tricyclics), beta blockers, calcium channel antagonists, corticosteroids, lithium, melatonin, neuromodulators or antiepileptics and serotonergic modulators (for example, pizotifen).
- Non-pharmacological treatment for the specified primary headaches with: acupuncture, dietary supplements, education and self-management programmes, imaging, lifestyle factors (dietary manipulation and exercise), manual therapies and psychological therapies.
- Information and support for patients and carers.
- Prevention and treatment of medication overuse headache.
- Management during pregnancy.
- Choice of contraception in women with migraine.

For further details please refer to the scope in Appendix A (and review questions in section 2.6).

2.4 What this guideline does not cover

This guideline does not cover:

- Children aged under 12.
- Management of primary headaches other than those specified in 2.3.
- Investigation and management of secondary headache other than medication overuse headache.
- Diagnosis and management of cranial neuralgias and facial pain.
- Management of comorbidities.

2.5 Relationships between the guideline and other NICE guidance

Related NICE Health Technology Appraisals:

Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. NICE technology appraisal 260 (2012).

Related NICE Interventional Procedures:

Deep brain stimulation for intractable trigeminal autonomic cephalalgias. NICE interventional procedure 381 (2011).

Percutaneous closure of patent foramen ovale for recurrent migraine. NICE interventional procedure guidance 370 (2010).

Related NICE Clinical Guidelines:

Patient experience in adult NHS service. NICE clinical guideline 138 (2012).

The epilepsies. NICE clinical guideline 137 (2012).

Hypertension. NICE clinical guideline 127 (2011).

Anxiety. NICE clinical guideline 113 (2011).

Depression in adults. NICE clinical guideline 90 (2009).

Glaucoma. NICE clinical guideline 85 (2009).

Medicines adherence. NICE clinical guideline 76 (2009).

Stroke. NICE clinical guideline 68 (2008).

Head injury. NICE clinical guideline 56 (2007).

Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005).

NICE is developing the following guidance (details available from www.nice.org.uk):

Head injury. NICE clinical guideline 56 (2007). Currently being updated. Publication tbc.

Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005). Currently being updated. Publication expected March 2014.

Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009[181].

Particular consideration will be given to the needs of girls and women of reproductive age.

2.6 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy, and population, presence or absence of risk factors and list of ideal minimum confounding factors for reviews of prognostic factors. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A). Further information on the outcome measures examined follows this section.

For questions on prognostic factors, protocols stated the risk factor that would be searched for instead of the intervention and comparison.

The review question to determine the diagnostic criteria for primary headaches was the one exception to the usual systematic review process. The GDG agreed that these criteria were well established by the International Headache Society in the International Classification of Headache Disorders criteria [106]. The GDG used these criteria as a basis to form the recommendations in a format intended to be useful to a clinician. Full details are in chapter 7.

Table 1: Review questions

Chapter	Review questions	Outcomes
Assessment and diagnosis: **Indications for consideration of additional investigation**	For young people and adults with HIV presenting with new onset headache, how common are serious intracranial abnormalities?	• Occurrence of serious intracranial abnormalities (as reported)
	For young people and adults with a history of malignancy presenting with new onset headache, how common are serious intracranial abnormalities?	• Occurrence of serious intracranial abnormalities (as reported)
	For young people and adults presenting with early morning headache or new onset frequent headache that lasts for more than one month, how common are serious intracranial abnormalities?	• Occurrence of serious intracranial abnormalities (as reported)
Assessment and diagnosis: **Identifying people with primary headache**	What is the accuracy of case finding questionnaires for diagnosing primary headache disorders and medication overuse headache?	• Positive predictive value • Negative predictive value • Sensitivity • Specificity.
Assessment and diagnosis: **Headache diaries for the**	What is the clinical effectiveness of using diaries for the diagnosis of people with suspected primary headaches and medication overuse headache?	• Number of people correctly diagnosed • Positive predictive value • Negative predictive value

Chapter	Review questions	Outcomes
diagnosis and management of primary headaches and medication overuse headache		• Sensitivity • Specificity.
	What is the clinical effectiveness, and patients' and practitioners' experience, of using diaries for the management of people with primary headaches and medication overuse headache?	• Clinical headache outcomes (for RCTs) • Patients' and practitioners' experience of using diaries.
Assessment and diagnosis: **Diagnosis of primary headaches and medication overuse headache**	For young people and adults with headache, what are the key diagnostic features of the following headaches: • Migraine with or without aura • Menstrual related migraine • Chronic migraine • Tension-type headache • Cluster headache • Medication overuse headache.	N/A
Assessment and diagnosis: **The role of imaging in diagnosis and management of primary headaches**	Should young people and adults with suspected primary headaches be imaged to rule out serious pathology?	Percent with the following serious abnormalities: • Tumour/neoplasm (subdivide into types) • Abscess • Subdural haematoma • Hydrocephalus • Arterio-venous malformations.
	For people with the following primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache), what is the clinical evidence and cost-effectiveness of imaging as a management strategy?	• Resource use including GP consultation, A&E attendance, investigations and referral to secondary care • Change in headache frequency and intensity (with e.g. headache impact test or migraine disability assessment test) • Percentage responders with 25%, 50% and 75% reduction in baseline headache frequency • Change in frequency of acute medication use • Change in anxiety and depression (e.g. HAD) • Change in health related quality of life (e.g. SF-36 or EuroQoL) • Incidental radiological findings.
Management: **Information and support**	What information and support do patients with primary headaches say they want?	• Patients' preferences
Management:	In people with tension type headache, what is the clinical evidence and cost-	• Time to freedom from pain • Headache response at up to 2

Chapter	Review questions	Outcomes
Acute pharmacological treatment of tension type headache	effectiveness for acute pharmacological treatment with: aspirin, NSAIDs, opioids and paracetamol?	hours • Pain free at 2 hours • Pain intensity difference • Sustained headache response at 24 hours • Sustained freedom from pain at 24 hours • Functional health status and health related quality of life (e.g. SF-36 or EuroQoL) • Incidence of serious adverse events.
Management: **Acute pharmacological treatment of migraine**	In people with migraine with or without aura, what is the clinical evidence and cost-effectiveness for acute pharmacological treatment with: antiemetics, aspirin, NSAIDs, opioids, paracetamol, triptans, ergots and corticosteroids?	• Time to freedom from pain • Headache response at up to 2 hours • Freedom from pain at up to 2 hours • Sustained headache response at 24 hours • Sustained freedom from pain at 24 hours • Headache specific quality of life • Functional health status and health related quality of life • Incidence of serious adverse events.
Management: **Acute pharmacological treatment of cluster headache**	In people with cluster headache, what is the clinical evidence and cost-effectiveness for acute pharmacological treatment with: aspirin, paracetamol, oxygen, triptans, ergots, NSAIDs and opioids?	• Time to freedom from pain • Headache response up to 2 hours • Reduction in pain at 30 minutes • Functional health status and health related quality of life • Incidence of serious adverse events.
Management: **Prophylactic pharmacological treatment of tension type headache**	In people with tension type headache, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: ACE inhibitors and angiotensin II receptor antagonists (ARBs), antidepressants (SNRIs, SSRIs, tricyclics), beta blockers and antiepileptics?	• Change in patient-reported headache days, frequency and intensity • Functional health status and health-related quality of life • Responder rate • Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events.
Management: **Prophylactic**	In migraine with or without aura and chronic migraine, what is the clinical evidence and cost-effectiveness for	• Change in patient-reported headache days, frequency and intensity

Chapter	Review questions	Outcomes
pharmacological treatment of migraine	prophylactic pharmacological treatment with: ACE inhibitors and angiotensin II receptor antagonists (ARBs), antidepressants (SNRIs, SSRIs, tricyclics), beta blockers, calcium channel blockers, antiepileptics and other serotonergic modulators?	• Responder rate • Functional health status and health-related quality of life Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events.
Management: **Prophylactic pharmacological treatment of menstrual migraine**	In people with pure menstrual and menstrual related migraine, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: ACE inhibitors and angiotensin II receptor antagonists, antidepressants (SNRIs, SSRIs, tricyclics), beta blockers, calcium channel blockers, antiepileptics, triptans, other serotonergic modulators, NSAIDs and hormonal therapy (contraceptives)?	• Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events.
Management: **Prophylactic pharmacological treatment of cluster headache**	In people with cluster headache, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: calcium channel blockers, corticosteroids, lithium, melatonin, antiepileptics, triptans and other serotonergic modulators?	• Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events.
Management: **Prophylactic non-pharmacological management of primary headaches with acupuncture**	For people with primary headaches, what is the clinical evidence and cost-effectiveness of management with acupuncture?	• Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events.
Management:	For people with primary headaches, what is	• Change in patient-reported

Chapter	Review questions	Outcomes
Prophylactic non-pharmacological management of primary headaches with manual therapies	the clinical evidence and cost-effectiveness of non-pharmacological management with manual therapies?	headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events.
Management: **Prophylactic non-pharmacological management of primary headaches with psychological therapies**	For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with psychological therapies?	• Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events.
Management: **Prophylactic non-pharmacological management of primary headaches with herbal remedies and dietary supplements**	For people with primary headaches, what is the clinical evidence and cost-effectiveness of management with herbal remedies?	• Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events.
	For people with primary headaches, what is the clinical evidence and cost-effectiveness of management with dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin (vitamin B2)).	• Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse

Chapter	Review questions	Outcomes
		events.
Management: **Prophylactic non-pharmacological management of primary headaches with exercise**	For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with exercise programmes?	• Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events.
Management: **Prophylactic non-pharmacological management of primary headaches with education and self-management**	For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with education and self-management programmes?	• Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Patient's perception of the usefulness of programmes.
Management: **Medication overuse headache**	What is the clinical evidence and cost-effectiveness of withdrawal strategies (of abortive treatments), psychological therapies, corticosteroids and NSAIDs for the treatment of probable medication overuse headache (MOH)?	• Change in acute medication use (up to 3 months) • Relapse back to MOH • Responder rate (proportion who no longer have probable MOH) • Change in patient reported headache days, frequency and intensity • Headache specific quality of life • Resource use • Functional health status and health related quality of life.
Management during pregnancy and contraceptive use: **Management of primary headaches during pregnancy**	What is the evidence for adverse fetal events in females with primary headaches during pregnancy using triptans?	• Fetal adverse events.
	What is the evidence for adverse fetal events in females using oxygen or verapamil during pregnancy?	• Fetal adverse events.
Management during pregnancy and contraceptive use:	What risks are associated with use of hormonal contraception in females aged 12 or over with migraine?	• Incidence of serious adverse events • Worsening effect on headache disorder.

Chapter	Review questions	Outcomes
Combined hormonal contraception use in girls and women with migraine		

2.7 Searching for evidence

2.7.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual [2009][181]. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on MEDLINE and Embase. The Cochrane Library was searched for all intervention questions. Additional subject specific databases were used for some questions: Cinahl for diaries, treatment questions and patient information; PsycINFO for education and self-management programmes, psychological therapies, medication over use headaches and patient information; AMED for non-pharmacological treatment of headaches. All searches were updated on 13 March 2012. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. A full list of websites is included in Appendix D. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/).

2.7.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the guideline population in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE, with a specific economic filter, from 2008, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix D. All searches were updated on 18 January 2012. No papers published after this date were considered.

2.8 Evidence of clinical effectiveness

2.8.1 Literature review

The process for review of evidence of effectiveness is as follows:

The Research Fellows:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C, excluded studies lists are in Appendix O. The excluded studies list only details studies excluded after the full papers were ordered. Many would have previously been excluded when the titles and abstracts were reviewed.
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual[181].
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix E.
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups) and produced evidence statements indicating the number of included studies, sample size (number randomised), direction of effect, uncertainty and GRADE quality rating:
    - Randomised studies: meta analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
    - Observational studies: data presented as a range of values in adapted GRADE profiles
    - Diagnostic studies: data presented as a range of values in adapted GRADE profiles
    - Prognostic studies: data presented as a range of values in adapted GRADE profiles
    - Qualitative studies: the quality of reporting for each study was summarised for three criteria in the guideline text: population, methods and analysis.

2.8.2 Inclusion/exclusion

See the review protocols in Appendix C for full details.

Note these key points:

The age range for this guideline was 12 years and over. Studies that included people younger than 12 were included only if the mean age of the population was over 12 years.

Crossover trials were only included in the review questions for acute treatment, however they were only included if it was clear from the paper that all participants included in the analysis had treated one headache attack only with each treatment, or if the data for the first crossover period only was available, in which case the study could be analysed as a parallel trial.

Placebo controlled trials were not included for the review question on the acute treatment of migraine as the GDG agreed that people seeking medical help for a migraine attack would have already tried over the counter medications. Therefore drug trials only were included if there was a head-to-head comparison.

The GDG agreed that for the majority of intervention review questions a sample size cut-off of 50 participants (25 per arm) was appropriate due to there being sufficient evidence with sample sizes greater than 50 which would provide a better estimate of the effect size. For most prognostic and diagnostic review questions, lager sample size cut-offs were applied (Chapters 5, 24 and 25). There were some exceptions in which lower sample size cut-offs were applied, or not cut-off values, when the GDG were aware that sufficient evidence at larger sample sizes would be lacking. These were:

- Indications for consideration of additional investigation (Chapter 4) – Minimum n=any
- Headache diaries for the diagnosis and management of primary headaches and medication overuse headache (Chapter 6) – Minimum n=any
- Imaging for diagnosis in people with suspected primary headache (Chapter 8.2) – Minimum n=any
- Imaging as a management strategy for people with suspected primary headaches (Chapter 8.3) – Minimum n=20 per arm
- Patient information and support (Chapter 9) – Minimum n=any
- Acute pharmacological treatment of cluster headache (Chapter 12) – Minimum n=any
- Prophylactic pharmacological treatment of cluster headache (Chapter 16) – Minimum n=any
- Prophylactic non-pharmacological management of primary headaches with psychological therapies (Chapter 19) – Minimum n=25 total
- Prophylactic non-pharmacological management of primary headaches with education and self management (Chapter 22) – Minimum n=25 total.

2.8.3 Methods of combining clinical studies

Data synthesis for intervention reviews

Available case analysis

Estimates of effect from individual studies were based on available case analysis (ACA) where it was possible to extract these data. ACA was defined as analysis using all participants with data available for the outcome being considered. For example, for dichotomous outcomes, the denominator is the number of participants with available data and the numerator is the number who experienced the event. Participants for whom data for that outcome were not available are assumed to be missing at random. Where ACA was not possible data were reported as in the study and this is explained in the introduction of the relevant clinical review.

Meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5.1) software (http://ims.cochrane.org/revman).

Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: responder rate; resource use including GP consultation, accident and emergency attendance, investigations and referral to secondary care; percentage responders with 25%, 50% and 75% reduction in baseline headache frequency; incidental radiological findings; headache response up to 2 hours; freedom from pain at up to 2 hours; sustained freedom from pain at 24 hours; sustained headache response at 24 hours; acute medication use; incidence of serious adverse events.

The continuous outcomes (change in patient-reported headache days, frequency and intensity; change in anxiety and depression (e.g. HAD); change in health related quality of life (e.g. SF-36 or EuroQoL); change in headache specific quality of life) were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Final values were reported where available for continuous outcomes in preference of change scores. However, if change scores only were available, these were reported and meta-analysed with final values.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at p<0.1 or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant heterogeneity was present, we carried out predefined subgroup analyses if possible. Subgroups were: age (12<18, or 18 and over), dose or route of administration.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. When the only evidence was based on studies which only presented means, this information was summarised in the GRADE tables without calculating the relative and absolute effect.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Network meta-analyses

Network meta-analysis was conducted for the review questions on the acute and prophylactic treatment of migraine. This allowed indirect comparisons of all the drugs included in the review when no direct comparison was available. A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials. The model used was based on a random effects logistic regression, with parameters estimated by Markov chain Monte Carlo simulation.

Four network meta-analyses were run for the acute treatment of migraine, each for binary outcomes: headache response at up to 2 hours; freedom from pain at up to 2 hours; sustained headache response at 24 hours and sustained freedom from pain at 24 hours. The log odds ratios were calculated and converted into relative risks for comparison to the direct comparisons. The ranking of interventions was also calculated based on their relative risks compared to the control group. For the acute treatment of migraine, one network was run for change in patient reported migraine days. The change in migraine days for each treatment was calculated, as well as the overall ranking of each treatment based on the effect size compared to placebo.

Data synthesis for prognostic factor reviews

Odds ratio, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers, and standard errors were calculated from the 95% confidence intervals. The log of the effect size with its standard error was entered into the generic inverse variance technique in the Cochrane Review Manager (RevMan5) software (http://ims.cochrane.org/revman). Studies were not combined in a meta-analysis for observational studies.

The quality of studies was assessed and presented in an adapted GRADE profile according to criteria stated in the methodology checklist for prognostic studies in the guidelines manual. Results were reported as ranges.

Data synthesis for diagnostic test accuracy review

Evidence for diagnostic data were evaluated by study, using version two of the Quality Assessment of Diagnostic Accuracy Studies checklists (QUADAS-2) (http://www.bris.ac.uk/quadas/quadas-2).

For diagnostic test accuracy studies, the following outcomes were reported: sensitivity, specificity, positive predictive value and negative predictive value. In cases where the outcomes were not reported, 2 by 2 tables were constructed from raw data to allow calculation of these accuracy measures. Summary receiver operative characteristic (ROC) curves, would have been generated if appropriate, however there were no data in the diagnostic reviews included in this guideline that could be combined to produce an ROC curve or diagnostic meta-analysis.

Data synthesis for qualitative review

Themes were identified from these studies by two reviewers independently, and then verified jointly. These themes were supplemented with data from surveys where available. Common themes relevant to the question are reported in a narrative in the guideline text.

Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as two separate tables in this guideline. The 'Clinical/Economic Study Characteristics' table includes details of the quality assessment while the 'Clinical /Economic Summary of Findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of people with an adverse event, the event rates (n/N: number of people with events divided by sum of number of people) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent. Each outcome was examined separately for the quality elements listed and defined in Table 2 and each graded using the quality levels listed in Table 3. The main criteria considered in the rating of these elements are discussed below (see section 2.8.4 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few participants and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

2.8.4 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias were rated down -1 or -2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections 2.8.5 to 2.8.8.

2.8.5 Study limitations

The main limitations for randomised controlled trials are listed in Table 4.

The GDG agreed that wherever possible, except for acute pharmacological treatment of migraine (see chapter 11 for more information), comparators for intervention studies should be a placebo (or an active control for the case of non-pharmacological treatments) or another active intervention in a double blind situation. The GDG accepted that there were some non-pharmacological intervention studies were participant blinding was impossible or very hard to achieve in most situations (exercise, chapter 21, manual therapy, chapter 18, and education and self-management, chapter 22). Nevertheless, open-label studies for these intervention studies were downgraded to maintain a consistent approach in quality rating across the guideline; however, with interventions where a placebo or active control was possible, open label studies would be excluded.

Table 4 lists the limitations considered for randomised controlled trials.

Table 4: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling participants are aware of the group to which the next enrolled person will be allocated (major problem in 'pseudo' or 'quasi' randomised trials with allocation by day of week, birth date, chart number, etc).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which participants are allocated.
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other limitations	For example: • Stopping early due to poor recruitment in randomised trials • High level of unexplained drop-outs

2.8.6 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity existed (Chi square p<0.1 or I-squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

2.8.7 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

In this guideline the age range was people aged 12 and older. In cases where the population in the studies included children younger than 12, the studies were included if the average age was over 12, but the evidence would be down-graded for indirectness.

If the headache population included people with mixed headache types in the intervention reviews, the evidence would also be down-graded.

2.8.8 Imprecision

Imprecision refers to the certainty in the effect for the outcome. When results are imprecise or very imprecise we are uncertain if there is an important difference between interventions or not.

Minimally important difference (MID)

The thresholds of important benefits or harms, or the MID for an outcome are important considerations for determining whether there is a "clinically important" difference between intervention and control groups and in assessing imprecision.

For continuous outcomes, the MID is defined as "the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the person or clinician to consider a change in the management"[93,107,222,223]. For dichotomous outcomes, the MID is considered in terms of changes of both absolute and relative risk.

The GDG were asked at the outset of the guideline if they were aware of any established values for MIDs for the outcomes included in the review. Two published values were highlighted for the following outcomes; migraine specific quality of life questionnaire (MSQ) and; the headache impact test. The values reported in these publications were used to determine imprecision of the point estimates for these two outcomes:

- Migraine-Specific Quality of Life Questionnaire (MSQ)[41]
  - Role restrictive domain: 3.2
  - Role preventive domain: 4.6
  - Emotional functioning domain: 7.5.
- Headache Impact Test (HIT-6)[38]: 2.3.

For the majority of the outcomes, there were no published MIDs. The GDG agreed that the default values stated in the GRADEpro were appropriate for these outcomes, and would account for the >20% improvement rate in placebo arms of headache trials. The default thresholds suggested by GRADE are a relative risk reduction of 25% (relative risk of 0.75 for negative outcomes) or a relative risk increase of 25% (risk ratio 1.25 for positive outcomes) for dichotomous outcomes. For continuous outcomes two approaches were used. When only one trial was included as the evidence base for an outcome, the mean difference was converted to the standardized mean difference (SMD) and checked to see if the confidence interval crossed 0.5. However, the mean difference (95% confidence interval) was still presented in the Grade tables. If two or more included trials reported a quantitative outcome then the default approach of multiplying 0.5 by standard deviation (taken as the median of the standard deviations across the meta-analyzed studies) was employed.

There was one exception, the GDG chose to apply a specific MID for change in migraine / headache days as this was deemed the most important outcome for prophylactic reviews. After discussion, the GDG agreed by informal consensus that an MID of 0.5 days was appropriate for this outcome.

Assessing imprecision

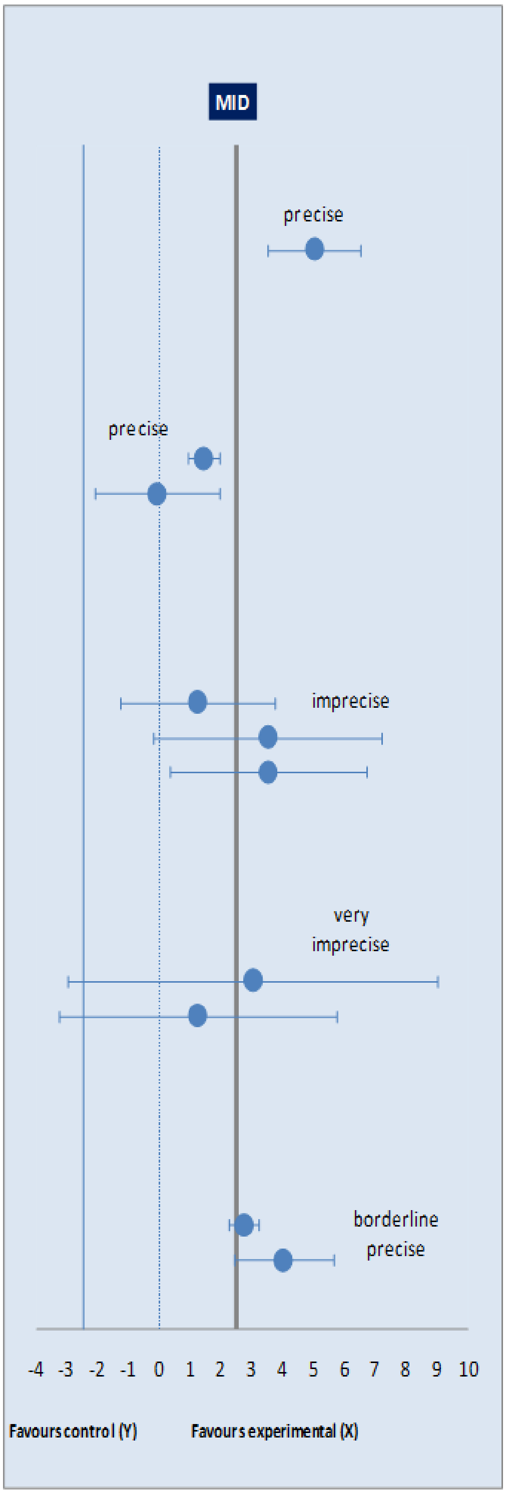
The confidence interval for the pooled or best estimate of effect was considered in relation to the MIDs to assess imprecision. If the confidence interval crossed the MID threshold, there was uncertainty in the effect estimate supporting our recommendation (because the CI was consistent with two decisions) and the effect estimate was rated as having serious imprecision. If both MIDs were crossed, the effect estimate was rated as having very serious imprecision.

Assessing clinical importance

For the purposes of this guideline, clinical importance was assessed by comparing the effect estimate against the MID and reviewing the absolute effect reported in the GRADE summary table. For example, if the effect size was small (less than the MID), this finding suggests that there may not be enough difference to recommend one intervention over the other based on that outcome, unless in exceptional circumstances, the GDG agreed that the absolute effect was great enough to reach clinical importance. An effect estimate larger than the MID is considered to be clinically important.

Figure 1 illustrates how the clinical importance of effect estimates were considered along with imprecision. This is documented in the evidence statements throughout this guideline.

Figure 1: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot in relation to the MID



Source: NCGC methods manual

Evidence statements

Evidence statements were formed for each outcome indicating the quantity and quality of evidence available, and the outcome and population to which they relate. Below are some examples to illustrate how the wording indicates the imprecision (uncertainty) and clinical importance:

- Precise, both the point estimate and confidence intervals are outside the MID :

  Xx studies with xx people **showed** that intervention *a* is **more clinically effective** than intervention *b*. [GRADE quality].
- Precise, both the point estimate and confidence intervals are between the MID and no difference:

  Xx studies with xx people **showed** that intervention *a* is more effective than intervention *b*, **but the effect size was too small to be clinically important**. [GRADE quality].
- Serious imprecision, point estimate outside the MID, and the confidence interval crosses the MID:

  Xx studies with xx people **suggested** that intervention *a* **may be** more clinically effective than intervention *b*, **but there is some uncertainty.** [GRADE quality].
- Serious imprecision, point estimate between the MID and no difference, and the confidence interval crosses the MID:

  Xx studies with xx people **suggested** that intervention *a* **may be** more effective than intervention *b*, **but the effect size is too small to be clinically important**, and there is **some uncertainty**. [GRADE quality].
- Very serious imprecision, point estimate outside the MID, and the confidence interval crosses the MID in both directions:

  Xx studies with xx people **suggested** that intervention *a* **may be** more clinically effective than intervention *b*, **but there is considerable uncertainty**. [GRADE quality].
- Very serious imprecision, point estimate between the MID and no difference, and the confidence interval crosses the MID in both directions:

  Xx studies with xx people **suggested** that intervention *a* **may be** more effective than intervention *b*, **but the effect size is too small to be clinically important**, and there is **considerable uncertainty**. [GRADE quality].
- Precise, point estimate close to line of no difference, confidence intervals just cross line of no difference:

  Xx studies with xx people showed that there is no difference between intervention *a* and intervention *b*. [GRADE quality].

When imprecision could not be assessed, the following statement will be used: "the difference is uncertain as no comparative analysis could be carried out".

For diagnostic reviews, the imprecision was based on the outcome deemed to be most important, for example in cases where it was most important not to have a high number of false negative test results, the imprecision assessment would be based on specificity. No MID was defined for any of the diagnostic outcomes. The GDG were asked to review the evidence and agree the level of imprecision based on the confidence intervals around the effect size and absolute effect estimate.

2.9 Evidence of cost-effectiveness

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

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analysis in priority areas.

2.9.1 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 / exclusion criteria to identify relevant studies (see below for details)
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual[181]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix E).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

2.9.1.1 Inclusion/exclusion

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 addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per person), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

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 other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist in The Guidelines Manual[181] and the health economics research protocol in Appendix C.

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

2.9.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment.

These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual[181]. It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. See Table 5 for more details.

Table 5: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study 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 conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

**Limitations and applicability were assessed using the economic evaluation checklist from The Guidelines Manual*[181]

Where economic studies compare multiple strategies, results are presented in the economic evidence profiles for the pair-wise comparison specified in the review question, irrespective of whether or not that comparison was 'appropriate' within the analysis being reviewed. A comparison is 'appropriate' where an intervention is compared with the next most expensive non-dominated option – a clinical strategy is said to 'dominate' the alternatives when it is both more effective and less costly. Footnotes indicate if a comparison was 'inappropriate' in the analysis.

For particular studies or original models comparing multiple strategies, results are not reported in the standard economic profile but are instead presented at the end of the relevant chapter in a paragraph summarising the study/model as a whole.

2.9.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendices J and L for details of the health economic analyses undertaken for the guideline.

2.9.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDG members should consider when judging whether an intervention offers good value for money[180].

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. 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
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG 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 'from 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 the 'Social value judgements: principles for the development of NICE guidance' [180].

2.10 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices E and F.
- Summary of clinical and economic evidence and quality (as presented in chapters 4-25).
- Forest plots (Appendix G).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendices J and L).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion by informal consensus. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were formed through discussions in the GDG meetings, and voting when there was not clear agreement.

The main considerations specific to each recommendation are outlined in the linking evidence to recommendation section preceding the recommendation section.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is evidence to support that use[10]. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations. Drug dosages are specified in recommendations where the dosage for that indication is not included in the 'British national formulary'.

2.10.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

2.10.2 Validation process

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

2.10.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual[181], NICE will ask a National Collaborating Centre or the National Clinical Guideline Centre to advise NICE's Guidance executive whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

2.10.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the person, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.10.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

3 Guideline summary

3.1 Algorithms

Algorithm to be developed as part of NICE pathways.

3.2 Key priorities for implementation

From the full set of recommendations, the GDG selected ten key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual[181]. The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter. The recommendations are listed in the order they appear in the NICE guideline, and accordingly.

Diagnosis

Tension-type headache, migraine and cluster headache

- Diagnose tension-type headache, migraine or cluster headache according to the headache features in the table. [1.2.1]

Medication overuse headache

- Be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for 3 months or more:
  - triptans, opioids, ergots or combination analgesic medications on 10 days per month or more **or**
  - paracetamol, aspirin or an NSAID, either alone or any combination, on 15 days per month or more. [1.2.7]

Management

All headache disorders

- Do not refer people diagnosed with tension-type headache, migraine, cluster headache or medication overuse headache for neuroimaging solely for reassurance. [1.3.3]

Information and support for people with headache disorders

- Include the following in discussions with the person with a headache disorder:
  - a positive diagnosis, including an explanation of the diagnosis and reassurance that other pathology has been excluded **and**
  - the options for management **and**
  - recognition that headache is a valid medical disorder that can have a significant impact on the person and their family or carers. [1.3.4]

Migraine with or without aura

Acute treatment

- Offer combination therapy with an oral triptan[a] and an NSAID, or an oral triptana and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For young people aged 12–17 years consider a nasal triptan in preference to an oral triptana. [1.3.10]
- For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:
  - o offer a non-oral preparation of metoclopramide, or prochlorperazine[b] **and**
  - o consider adding a non-oral NSAID or triptana if these have not been tried. [1.3.15]

Prophylactic treatment

- Offer topiramate[c] or propranolol 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. [1.3.17]

Cluster headache

Acute treatment

- Offer oxygen and/or a subcutaneous[d] or nasal triptan[e] for the acute treatment of cluster headache. [1.3.27]

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[a] At the time of publication (September 2012), triptans (with the exception of nasal sumatriptan) did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[b] At the time of publication (September 2012), prochlorperazine (except for a buccal preparation) did not have a UK marketing authorisation for this indication but is licensed for the relief of nausea and vomiting.The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[c] At the time of publication (September 2012), topiramate did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[d] At the time of publication (September 2012), subcutaneous triptans did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[e] At the time of publication (September 2012), nasal triptans did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the

- When using oxygen for the acute treatment of cluster headache:
  - o use 100% oxygen at a flow rate of at least 12 litres per minute with a non-rebreathing mask and a reservoir bag **and**
  - o arrange provision of home and ambulatory oxygen. [1.3.28]
- When using a subcutaneous[f] or nasal triptan[g], ensure the person is offered an adequate supply of triptans calculated according to their history of cluster bouts, based on the manufacturer's maximum daily dose. [1.3.29]

Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[f] At the time of publication (September 2012), subcutaneous triptans did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[g] At the time of publication (September 2012), nasal triptans did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

3.3 Full list of recommendations

All recommendations apply to adults and young people aged 12 years and over unless specifically stated otherwise in the recommendation.

Assessment

1.1.1 Evaluate people who present with headache and any of the following features, and consider the need for further investigations and/or referral[h] :

- worsening headache with fever
- sudden-onset headache reaching maximum intensity within 5 minutes
- new-onset neurological deficit
- new-onset cognitive dysfunction
- change in personality
- impaired level of consciousness
- recent (typically within the past 3 months) head trauma
- headache triggered by cough, valsalva (trying to breathe out with nose and mouth blocked) or sneeze
- headache triggered by exercise
- orthostatic headache (headache that changes with posture)
- symptoms suggestive of giant cell arteritis
- symptoms and signs of acute narrow-angle glaucoma
- a substantial change in the characteristics of their headache.

1.1.2 Consider further investigations and/or referral for people who present with new-onset headache and any of the following:

- compromised immunity, caused, for example, by HIV or immunosuppressive drugs
- age under 20 years and a history of malignancy
- a history of malignancy known to metastasise to the brain
- vomiting without other obvious cause.

1.1.3 Consider using a headache diary to aid the diagnosis of primary headaches.

1.1.4 If a headache diary is used, ask the person to record the following for a minimum of 8 weeks:

- frequency, duration and severity of headaches
- any associated symptoms
- all prescribed and over the counter medications taken to relieve headaches
- possible precipitants
- relationship of headaches to menstruation.

[h] For information on referral for suspected tumours of the brain or central nervous system see Referral guidelines for suspected cancer (NICE clinical guideline 27); update under development (publication date to be confirmed).

Diagnosis

Tension-type headache, migraine and cluster headache

1.2.1 Diagnose tension-type headache, migraine or cluster headache according to the headache features in the table.

Table Diagnosis of tension-type headache, migraine and cluster headache

Headache feature	Tension-type headache		Migraine (with or without aura)		Cluster headache	
Pain location[a]	Bilateral		Unilateral or bilateral		Unilateral (around the eye, above the eye and along the side of the head/face)	
Pain quality	Pressing/tightening (non-pulsating)		Pulsating (throbbing or banging in young people aged 12-17 years)		Variable (can be sharp, boring, burning, throbbing or tightening)	
Pain intensity	Mild or moderate		Moderate or severe		Severe or very severe	
Effect on activities	Not aggravated by routine activities of daily living		Aggravated by, or causes avoidance of, routine activities of daily living		Restlessness or agitation	
Other symptoms	None		Unusual sensitivity to light and/or sound or nausea and/or vomiting **Aura**[b] Aura symptoms can occur with or without headache: • are fully reversible • develop over at least 5 minutes • last 5–60 minutes. Typical aura symptoms include visual symptoms such as flickering lights, spots or lines and/or partial loss of vision; sensory symptoms such as numbness and/or pins and needles; and/or speech disturbance.		On the same side as the headache: • red and/or watery eye • nasal congestion and/or runny nose • swollen eyelid • forehead and facial sweating • constricted pupil and/or drooping eyelid	
Duration of headache	30 minutes–continuous		4–72 hours in adults 1–72 hours in young people aged 12-17 years		15–180 minutes	
Frequency of headache	< 15 days per month	≥ 15 days per month for more than 3 months	< 15 days per month	≥ 15 days per month for more than 3 months	1 every other day to 8 per day[c], with remission[d] > 1 month	1 every other day to 8 per day[c], with a continuous remission[d] < 1 month in a 12-month period
Diagnosis	**Episodic tension-type headache**	**Chronic tension type headache**[e]	**Episodic migraine (with or without aura)**	**Chronic migraine**[f] **(with or without aura)**	**Episodic cluster headache**	**Chronic cluster headache**

a Headache pain can be felt in the head, face or neck.
b See recommendations 1.2.2, 1.2.3 and 1.2.4 for further information on diagnosis of migraine with aura.
c The frequency of recurrent headaches during a cluster headache bout.

d The pain-free period between cluster headache bouts.
e Chronic migraine and chronic tension-type headache commonly overlap. If there are any features of migraine, diagnose chronic migraine.
f NICE has developed technology appraisal guidance on Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).

Migraine with aura

1.2.2 Suspect aura in people who present with or without headache and with neurological symptoms that:

- are fully reversible **and**
- develop gradually, either alone or in succession, over at least 5 minutes **and**
- last for 5–60 minutes.

1.2.3 Diagnose migraine with aura in people who present with or without headache and with one or more of the following typical aura symptoms that meet the criteria in recommendation 1.2.2:

- visual symptoms that may be positive (for example, flickering lights, spots or lines) and/or negative (for example, partial loss of vision)
- sensory symptoms that may be positive (for example, pins and needles) and/or negative (for example, numbness)
- speech disturbance.

1.2.4 Consider further investigations and/or referral for people who present with or without migraine headache and with any of the following atypical aura symptoms that meet the criteria in recommendation 1.2.2:

- motor weakness **or**
- double vision **or**
- visual symptoms affecting only one eye **or**
- poor balance **or**
- decreased level of consciousness.

Menstrual-related migraine

1.2.5 Suspect menstrual-related migraine in women and girls whose migraine occurs predominantly between 2 days before and 3 days after the start of menstruation in at least 2 out of 3 consecutive menstrual cycles.

1.2.6 Diagnose menstrual-related migraine using a headache diary (see recommendation 1.1.4) for at least 2 menstrual cycles.

Medication overuse headache

1.2.7 Be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for 3 months or more:

- triptans, opioids, ergots or combination analgesic medications on 10 days per month or more **or**
- paracetamol, aspirin or an NSAID, either alone or in any combination, on 15 days per month or more.

Management

All headache disorders

1.3.1 Consider using a headache diary:

- to record the frequency, duration and severity of headaches
- to monitor the effectiveness of headache interventions
- as a basis for discussion with the person about their headache disorder and its impact.

1.3.2 Consider further investigations and/or referral if a person diagnosed with a headache disorder develops any of the features listed in recommendation 1.1.1.

1.3.3 Do not refer people diagnosed with tension-type headache, migraine, cluster headache or medication overuse headache for neuroimaging solely for reassurance.

Information and support for people with headache disorders

1.3.4 Include the following in discussions with the person with a headache disorder:

- a positive diagnosis, including an explanation of the diagnosis and reassurance that other pathology has been excluded **and**
- the options for management **and**
- recognition that headache is a valid medical disorder that can have a significant impact on the person and their family or carers.

1.3.5 Give the person written and oral information about headache disorders, including information about support organisations.

1.3.6 Explain the risk of medication overuse headache to people who are using acute treatments for their headache disorder.

Tension-type headache

Acute treatment

1.3.7 Consider aspirin[i], paracetamol or an NSAID for the acute treatment of tension-type headache, taking into account the person's preference, comorbidities and risks of adverse events.

1.3.8 Do not offer opioids for the acute treatment of tension-type headache.

Prophylactic treatment

1.3.9 Consider a course of up to 10 sessions of acupuncture over 5–8 weeks for the prophylactic treatment of chronic tension-type headache.

Migraine with or without aura

Acute treatment

1.3.10 Offer combination therapy with an oral triptan[j] and an NSAID, or an oral triptanj and paracetamol, for the acute treatment of migraine, taking into account the person's

[i] Because of an association with Reye's syndrome, preparations containing aspirin should not be offered to people aged under 16 years.

preference, comorbidities and risk of adverse events. For young people aged 12–17 years consider a nasal triptan in preference to an oral triptan[j].

1.3.11 For people who prefer to take only one drug, consider monotherapy with an oral triptan[j], NSAID, aspirin[k] (900 mg) or paracetamol for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events.

1.3.12 When prescribing a triptan[j], start with the one that has the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans.

1.3.13 Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting.

1.3.14 Do not offer ergots or opioids for the acute treatment of migraine.

1.3.15 For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:

- offer a non-oral preparation of metoclopramide or prochlorperazine[l] and
- consider adding a non-oral NSAID or triptan[j] if these have not been tried.

Prophylactic treatment

1.3.16 Discuss the benefits and risks of prophylactic treatment for migraine with the person, taking into account the person’s preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life.

1.3.17 Offer topiramate[m] or propranolol 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.

[j] At the time of publication (September 2012), triptans (with the exception of nasal sumatriptan) did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council’s Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[k] Because of an association with Reye’s syndrome, preparations containing aspirin should not be offered to people aged under 16 years.

[l] At the time of publication (September 2012), prochlorperazine (except for a buccal preparation) did not have a UK marketing authorisation for this indication but is licensed for the relief of nausea and vomiting.The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council’s Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[m] At the time of publication (September 2012), topiramate did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council’s Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

1.3.18 If both topiramate[n] and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5–8 weeks or gabapentin[o] (up to 1200 mg per day) according to the person's preference, comorbidities and risk of adverse events.

1.3.19 For people who are already having treatment with another form of prophylaxis such as amitriptyline[p], and whose migraine is well controlled, continue the current treatment as required.

1.3.20 Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment.

1.3.21 Advise people with migraine that riboflavin (400 mg[q] once a day) may be effective in reducing migraine frequency and intensity for some people.

Combined hormonal contraceptive use by women and girls with migraine

1.3.22 Do not routinely offer combined hormonal contraceptives for contraception to women and girls who have migraine with aura.

Menstrual-related migraine

1.3.23 For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan[r] (2.5 mg twice a day) or zolmitriptan[s] (2.5 mg twice or three times a day) on the days migraine is expected.

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[n] At the time of publication (September 2012), topiramate did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[o] At the time of publication (September 2012), gabapentin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[p] At the time of publication (September 2012), amitriptyline did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[q] At the time of publication (September 2012), riboflavin did not have a UK marketing authorisation for this indication but is available as a food supplement. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[r] At the time of publication (September 2012), frovatriptan did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[s] At the time of publication (September 2012), zolmitriptan did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the

Treatment of migraine during pregnancy

1.3.24 Offer pregnant women paracetamol for the acute treatment of migraine. Consider the use of a triptan[t] or an NSAID after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy.

1.3.25 Seek specialist advice if prophylactic treatment for migraine is needed during pregnancy.

Cluster headache

Acute treatment

1.3.26 Discuss the need for neuroimaging for people with a first bout of cluster headache with a GP with a special interest in headache or a neurologist.

1.3.27 Offer oxygen and/or a subcutaneous[u] or nasal triptan[v] for the acute treatment of cluster headache.

1.3.28 When using oxygen for the acute treatment of cluster headache:

- use 100% oxygen at a flow rate of at least 12 litres per minute with a non-rebreathing mask and a reservoir bag **and**
- arrange provision of home and ambulatory oxygen.

1.3.29 When using a subcutaneousu or nasal triptanv, ensure the person is offered an adequate supply of triptans calculated according to their history of cluster bouts, based on the manufacturer's maximum daily dose.

1.3.30 Do not offer paracetamol, NSAIDS, opioids, ergots or oral triptans for the acute treatment of cluster headache.

Prophylactic treatment

1.3.31 Consider verapamil[w] for prophylactic treatment during a bout of cluster headache. If unfamiliar with its use for cluster headache, seek specialist advice before starting verapamil, including advice on electrocardiogram monitoring.

Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[t] At the time of publication (September 2012), triptans (with the exception of nasal sumatriptan) did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[u] At the time of publication (September 2012), subcutaneous triptans did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[v] At the time of publication (September 2012), nasal triptans did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

1.3.32 Seek specialist advice for cluster headache that does not respond to verapamil[w].

1.3.33 Seek specialist advice if treatment for cluster headache is needed during pregnancy.

Medication overuse headache

1.3.34 Explain to people with medication overuse headache that it is treated by withdrawing overused medication.

1.3.35 Advise people to stop taking all overused acute headache medications for at least 1 month and to stop abruptly rather than gradually.

1.3.36 Advise people that headache symptoms are likely to get worse in the short term before they improve and that there may be associated withdrawal symptoms, and provide them with close follow-up and support according to their needs.

1.3.37 Consider prophylactic treatment for the underlying primary headache disorder in addition to withdrawal of overused medication for people with medication overuse headache.

1.3.38 Do not routinely offer inpatient withdrawal for medication overuse headache.

1.3.39 Consider specialist referral and/or inpatient withdrawal of overused medication for people who are using strong opioids, or have relevant comorbidities, or in whom previous repeated attempts at withdrawal of overused medication have been unsuccessful.

1.3.40 Review the diagnosis of medication overuse headache and further management 4–8 weeks after the start of withdrawal of overused medication.

3.4 Key research recommendations

1. Is amitriptyline a clinically and cost effective prophylactic treatment for recurrent migraine?
2. Is pizotifen a clinically and cost effective prophylactic treatment for recurrent migraine?
3. Is topiramate a clinically and cost effective prophylactic treatment for recurrent cluster headache?
4. Does a psychological intervention such as cognitive behavioural therapy (CBT) improve headache outcomes and quality of life for people with chronic headache disorders?
5. Does a course of steroid treatment or pharmacological treatments used for headache prophylaxis help people with medication overuse headaches withdraw from medication?

[w] At the time of publication (September 2012), verapamil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

Assessment and diagnosis

4 Indications for consideration of additional investigation

4.1 Introduction

This guideline is primarily concerned with the diagnosis and management of primary headache disorders. Headache may also be part of a presentation of other disorders. Scoping for the guideline indicated that healthcare professionals wished for guidance about when people require further investigations. It is not possible to provide comprehensive guidance on appropriate pathway for all people who present with headache but the GDG wished to ensure that healthcare professionals were clear about when they should *not* proceed to diagnose primary headache disorders, or medication overuse headache, and consider further evaluation of the individual and the need for further investigation.

4.1.1 Review introduction

The GDG used a two stage process to develop recommendations in this area. A list of known characteristics possibly indicating a serious disorder requiring further investigation that had been previously published was compiled by the technical team and added to by the GDG[22,123,224]. Three categories were agreed and a group discussion was held to determine which symptoms should go in each category. The categories were as follows:

1. Symptoms and signs that are associated with the known pathophysiology of individual disorders and should clearly direct healthcare professionals away from a pathway of considering a primary headache disorder e.g. new neurological deficit, impaired conscious level
2. Presentations where there was less likelihood of a major underlying disease but caution should be exercised by a healthcare professional
3. Presentations where the GDG considered there was significant uncertainty and that a review of the evidence would inform the GDG and the healthcare community about the importance of these factors.

The categorisation of symptoms and signs was agreed by the GDG using informal consensus and is shown in Table 6.

Table 6: Symptoms and signs for possible further investigation

Action required	Symptom / sign
Further investigation	Worsening headache with fever Sudden onset headache (onset to maximum severity <5 minutes) New onset neurological deficit New onset cognitive dysfunction Change in personality Impaired level of consciousness History of head trauma within 6 weeks Headache triggered by cough, valsava, sneeze or exertion Headache that changes with posture Suspected meningitis Suspected glaucoma Suspected temporal arteritis
Think about further investigation	Change in migraine New onset headache with vomiting (without other obvious cause) Compromised immunity, for example due to immunosuppressive drug use
Uncertain [(a)]	HIV Malignancy Early morning headache New onset daily headache (without other symptoms) lasting at least one month

(a) These symptoms and signs were to be included in the systematic review.

A literature search was conducted for cohort studies and case control studies comparing the incidence of serious intracranial abnormalities occurring in:

- HIV positive people who had headaches in isolation of other symptoms compared to those who did not have headaches.
- People with a history of malignancy who had headaches in isolation of other symptoms compared to those who did not have headaches.
- People with new onset headaches that lasted more than one month and was in isolation of other symptoms compared to those without headache.

See protocols in appendix C.1.1.

4.2 HIV positive with new onset headache

4.2.1 Clinical question

For young people and adults with HIV presenting with new onset headache, how common are serious intracranial abnormalities?

4.2.1.1 Clinical evidence

See evidence table E.1.1, Appendix E, forest plots in Figures 1 - 2, Appendix G.1.1.

Two studies were identified in this review[89,235,236]. One study did not have a control group but was included as it evaluated headache in HIV positive people in isolation of other symptoms[89,89]. The second study, reported in two papers, compared the two groups as stated in the review protocol;

however, the headaches were not evaluated in isolation of other symptoms [235,236]. Both studies were conducted in the period before Highly Active Retroviral Treatment (HAART) was available which may limit the relevance of the findings.

Table 7: HIV+ with headache vs HIV+ without headache - Quality assessment

Outcome	Representative population sample	Attrition bias	Prognostic factors measured appropriately	Outcomes adequately measured	Key confounders accounted for and appropriate analysis used
CNS infection at baseline[235,236]	Unclear [(a)]	None	Yes	Yes	No [(b)]
New HIV-1 associated neurologic disease at 1 year[235,236]	Unclear [(a)]	None	Yes	Yes	No [(b)]
Presence of intracranial mass lesions[89]	No [(c)]	None	Yes	Yes	No [(d)]

(a) Headache was not in isolation of other symptoms; the proportion of participants with evidence of prior associated neurological disease differed in the two groups, therefore may not be comparable at baseline.
(b) Confounding factors not listed and not accounted for in the analysis.
(c) Study conducted in a selected group of people who presented with headache and had a CT scan; the study did not have a control group.
(d) Confounders were not identified a priori or accounted for in the analysis.

Table 8: HIV+ with headache vs HIV+ without headache – Clinical summary of findings

Outcome	HIV+ with headache	HIV+ without headache	Odds ratios (95% CI)	Quality
CNS infection at baseline[235,236]	2/98 (2%)	4/131 (3.1%)	0.66 (0.12 to 3.69)	LOW
New HIV-1 associated neurologic disease at 1 year[235,236]	7/34 (20.6%)	8/109 (7.3%)	3.27 (1.09 to 9.83)	LOW
Presence of intracranial mass lesions [89]	0/35 (0%, 95% CI 0% to 10%)	NR (no control group)	NR (no control group)	VERY LOW

CNS=central nervous system.

4.2.1.2 Economic evidence

No relevant economic evaluations were identified which compared the two groups of individuals (people with HIV and headache and people with HIV without headache).

4.2.1.3 Evidence statements

Although imprecision was not assessed for prognostic reviews the statement of uncertainty reflects the GDG's confidence of the evidence.

Clinical:

One study with 229 people suggested that people who are HIV positive without headache may be at higher risk of opportunistic infections of the central nervous system than people who are HIV positive with headache but there is considerable uncertainty. [Low quality].

One study with 229 people suggested that people who are HIV positive and have headache may be at higher risk of new HIV-1 associated neurologic disease at one year than people who are HIV positive without headache but there is some uncertainty. [Low quality].

One study with 35 people who were HIV positive who presented with headache in isolation of any other symptoms found no occurrences of intracranial mass lesions. [Very low quality].

Economic:

No economic evidence was found on this question.

4.2.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 4.5.

4.3 History of malignancy with new onset headache

4.3.1 Clinical question

For young people and adults with a history of malignancy presenting with new onset headache, how common are serious intracranial abnormalities?

4.3.1.1 Clinical evidence

See evidence table in Appendix section E.1.1.

One study was identified which evaluated the incidence of serious intracranial abnormalities in young people aged under 20 with a history of malignancy presenting with isolated headache[8,8]. The study did not have a control group.

Table 9: History of malignancy with headache - Quality assessment

Outcome	Representative population sample	Attrition bias	Prognostic factors measured appropriately	Outcomes adequately measured	Key confounders accounted for and appropriate analysis used
Intracranial metastatic lesions[8]	No [(a)]	None	Yes	Yes	No [(b)]

(a) The study did not have a control group.
(b) Confounders were not identified a priori or accounted for in the analysis.

Table 5: History of cancer with headache - Clinical summary of findings

Outcome	Cancer with headache	Cancer without headache	Odds ratios (95% CI)	Quality
Intracranial metastatic lesions	3/21 (14.3%)	N/A *	-	VERY LOW

** No control group*

4.3.1.2 Economic evidence

No relevant economic evaluations were identified which compared the two groups of individuals (people with a history of malignancy and new onset headache and people with a history of malignancy without headache).

4.3.1.3 Evidence statements

Although imprecision was not assessed for prognostic reviews the statement of uncertainty reflects the GDG's confidence of the evidence.

Clinical:

One study with 21 people with history of malignancy who were diagnosed with intracranial metastatic lesions showed that three people had presented with headache as an isolated presenting symptom. [Very low quality].

Economic:

No economic evidence was found on this question.

4.3.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 4.5.

4.4 Early morning headache or new onset frequent headache lasting for more than one month

4.4.1 Clinical question

For young people and adults presenting with early morning headache or new onset frequent headache that lasts for more than one month, how common are serious intracranial abnormalities?

4.4.1.1 Clinical evidence

Two studies were identified which evaluated the incidence of serious intracranial abnormalities in people presenting with undifferentiated headache[120,121]. However, the GDG agreed that the populations in these studies did not meet the criteria of the target population in the review protocol therefore the studies were excluded from the review.

4.4.1.2 Economic evidence

No relevant economic evaluations were identified which compared the two groups of individuals (people with new onset frequent headache that lasts for more than one month and people with no headache).

4.4.1.3 Evidence statements

No clinical or economic evidence was found on this question.

4.5 Recommendations and link to evidence

Recommendations	**Evaluate people who present with headache and any of the following features, and consider the need for further investigations and/or referral[x]:** • **worsening headache with fever** • **sudden-onset headache reaching maximum intensity within 5 minutes** • **new-onset neurological deficit** • **new-onset cognitive dysfunction** • **change in personality** • **impaired level of consciousness** • **recent (typically within the past 3 months) head trauma** • **headache triggered by cough, valsalva (trying to breathe out with nose and mouth blocked) or sneeze** • **headache triggered by exercise** • **orthostatic headache (headache that changes with posture)** • **symptoms suggestive of giant cell arteritis** • **symptoms and signs of acute narrow-angle glaucoma** • **a substantial change in the characteristics of their headache.** **Consider further investigations and/or referral if a person diagnosed with a headache disorder develops any of the features listed in recommendation 1.1.1.**
Relative values of different outcomes	This recommendation was based on GDG informal consensus using well established symptoms and presentations that are associated with the pathophysiology of individual disorders.
Trade off between clinical benefits and harms	Early assessment is likely to be beneficial for all of the above scenarios.
Economic considerations	There are some costs associated with further investigations and/or referral and with additional examination of the false positives; however the GDG considered the features listed in the recommendation to be serious and alarming enough to warrant further consideration for investigations and/or referral. The GDG believe these features will help minimise the number of false positives (patients unnecessarily referred for further assessment).
Quality of evidence	This recommendation was based on GDG informal consensus.
Other considerations	GDG consensus opinion (informal consensus methods used) was that these symptoms and presentations should direct healthcare professionals away from a pathway of considering a primary headache disorder. The GDG did not feel it appropriate or possible for them to indicate the pathway of care for people with these symptoms but wished to alert healthcare professionals to the need

[x] For information on referral for suspected tumours of the brain or central nervous system see Referral guidelines for suspected cancer (NICE clinical guideline 27); update under development (publication date to be confirmed).

	to evaluate these people appropriately. The GDG were aware that the NICE guideline on referral for suspected cancer is currently being updated and is examining indications for referral for suspected brain tumour in adults and children. The GDG also discussed recommendations from 'Headsmart' (www.headsmart.org.uk) who have a particular interest in diagnosis of brain tumours in children and young people. They draw attention to the consideration of brain tumour when a young person has delayed or precious puberty or growth problems[99]. The GDG considered that good clinical practice would also consider environmental precipitants of headache, in particular carbon monoxide poisoning, which causes about 15 deaths per year in the UK and which may cause headache[100]. If a primary headache disorder has already been diagnosed, these symptoms should still be considered as an indication of the need for further evaluation and for further investigations and/or referrals appropriate.

Recommendations	**Consider further investigations and/or referral for people who present with new-onset headache and any of the following:** • **compromised immunity, caused, for example, by HIV or immunosuppressive drugs** • **age under 20 years and a history of malignancy** • **a history of malignancy known to metastasise to the brain** • **vomiting without other obvious cause.**
Relative values of different outcomes	For compromised immunity / HIV, brain infection was considered to be the most important outcome by the GDG. For malignancy known to metastasise to the brain, intracranial metastasis was considered to be the most important outcome. The recommendation for vomiting without other obvious cause was based on GDG informal consensus.
Trade off between clinical benefits and harms	The GDG decided that it was important to facilitate a diagnosis of brain infection as it is treatable. The benefit of the treatment of an isolated metastasis was compared to the harm caused by radiation exposure due to some imaging techniques. Anxiety experienced by the individual and their relatives and by health care professionals was also considered as important.
Economic considerations	There are some costs associated with conducting further investigations; however there is a serious risk of fatal illness in a population with compromised immunity if symptoms such as new onset headache are not investigated and appropriate treatment given. The GDG believed that in this population the high risk justifies the cost. In a population with a history of malignancy, a new onset headache could be a symptom of brain metastasis. The GDG believed that in this population prompt identification and treatment of brain metastasis justify the cost.
Quality of evidence	**HIV:** Evidence was found from one study on opportunistic infections of the central nervous system in people with HIV. This was of very low quality as the study did not evaluate headache in isolation of other symptoms and was therefore indirect to the target population. No economic evidence was identified on this question.

	History of malignancy: Evidence was found from one study in people aged under 20 for the incidence of intracranial metastasis. Although the study evaluated headache as an isolated presenting symptom, the evidence was of very low quality as the study did not have a control group. The decision was therefore based on the evidence available and GDG informal consensus. **Vomiting:** This recommendation was made by GDG informal consensus. The GDG considered that if there is no other obvious explanation for the vomiting and headache, there is the possibility that the person may have serious pathology. No economic evidence was identified on this question.
Other considerations	The studies included in the review were from the pre-HAART period and this may limit the relevance of their findings. Compromised immunity is indicated by a CD4 count <200 cells /micro litre Cancers that metastasise to the brain include, for example breast, lung, thyroid or kidney cancer, malignant melanoma and Hodgkin's lymphoma. The GDG used informal consensus to agree that new onset headache and vomiting may warrant further investigation if this was in isolation of other symptoms. The GDG were aware that headache and vomiting can co-exist in a variety of situations where serious cause can be excluded with history of examination such as viral infections and alcohol intoxication.

5 Identifying people with primary headache

5.1 Introduction

The diagnosis of primary headache is important in directing people with headache towards appropriate treatment. Studies indicate that primary headache disorders are under diagnosed[122]. The GDG wished to consider whether questionnaires could help to identify people likely to have primary headache disorder prior to a taking a comprehensive history in order to facilitate the subsequent consultation, i.e. are there a small number of features that have a sufficient sensitivity and specificity to diagnose a primary headache when compared with the formal International classification of headache disorders (ICHD-II) definition[106]. See chapter 7 for further information about the ICHD-II. This approach is recognised in other conditions such as anxiety and depression where the answer to a few questions can be used to target more comprehensive assessment e.g. the two item Generalised Anxiety Disorder scale, Whooley questions[130,267]. The GDG were aware that some questionnaires had been designed to identify people with migraine and wished to consider whether these could be used for potential case finding of primacy headaches in people presenting with headache in clinical settings.

5.1.1 Clinical question

What is the accuracy of case finding questionnaires for diagnosing primary headache disorders and medication overuse headache?

A literature search was conducted for diagnostic studies and validation studies comparing the accuracy of different case finding questionnaires to identify people with primary headaches and medication overuse headache with the gold standard diagnosis by a clinician based on ICHD-II criteria. See protocol C.1.2.

The GDG were interested in questionnaires for migraine, tension type headache, cluster headache and medication overuse headache. However no studies were found evaluating questionnaires for tension type headache or medication overuse headache.

No MID was defined for any of the diagnostic outcomes. The GDG were asked to review the evidence and agree the level of imprecision based on the confidence intervals around the effect size and absolute effect estimate.

5.1.2 Migraine

5.1.2.1 Clinical evidence

See evidence table E.1.2, Appendix E, forest plots in Figures 3 - 4, Appendix G.1.2.1.

Nine studies were identified[21,74,90,117,124,125,155,178,217], seven of these were looking at the diagnostic accuracy of the ID migraine questionnaire[21,74,90,117,124,125,178]. One[155] was the development study of the ID migraine and has been included for information in the evidence tables, but not in the data analysis. The final study assessed the structured migraine interview[217]. The studies were carried out in a range of settings and the studies have been separated for analysis according to setting as baseline risks will differ. The populations were: (1) those presenting with headache as a primary complaint (four studies); (2) three studies used a prior study to only include those who were headache sufferers, and; (3) the remaining study was a diagnostic study on the accuracy of the structured migraine interview in a population of people with primary headache which was unable to be managed by other healthcare providers.

Table 10: ID Migraine quality assessment and clinical summary of findings

Setting	No. of studies	Design	n	Limitations	Inconsistency	Indirectness	Imprecision	Pre-test probability	TP (%)	FP (%)	FN (%)	TN (%)	Sensitivity %	Specificity %	PPV %	NPV %	Quality
GP clinics[124]	1	Diagnostic	584	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	15%*	189 (32)	34 (6)	173 (30)	188 (32)	50	84	85	52	MODERATE
								Effect/ 1000	75	136	75	714	-	-	-	-	
Headache clinics[21,90]	2	Diagnostic	353	Serious [(b)]	No serious inconsistency	No serious indirectness	Serious[(c)]	84%	221 (63)	39 (11)	12 (3)	81 (23)	94-95	60-72	80-88	85-87	LOW
								Effect / 1000	-	-	-	-	-	-	-	-	
Headache clinic post A&E[178]	1	Diagnostic	2199	Serious [(b)]	No serious inconsistency	Serious[(d)]	Serious[(c)]	84% †	172 (86)	3 (2)	11 (6)	13 (7)	94	81	98	54	VERY LOW
								Effect/ 1000	790	30	50	130	-	-	-	-	
Neurology[1 17]	1	Diagnostic	1816	No serious limitations	No serious inconsistency	Serious[(e)]	No serious imprecision	*15%**	842 (46)	329 (18)	75 (4)	570 (31)	92	63	72	88	MODERATE
								Effect/ 1000	138	315	12	536	-	-	-	-	
TMJ Orofacial pain clinics[125]	1	Diagnostic	176	Serious [(f)]	No serious inconsistency	Serious[(e)]	Serious[(c)]	*15%**	19 (11)	3 (2)	14 (8)	140 (80)	58	98	86	91	VERY LOW
								Effect/ 1000	87	17	63	833	-	-	-	-	
Mixed secondary care[74]	1	Diagnostic	1021	Serious [(f)]	No serious inconsistency	Serious[(e)]	No serious imprecision	*15%**	539 (53)	100 (10)	90 (88)	292 (29)	80-88	74-76	80-86	67-83	LOW
								Effect/ 1000	-	-	-	-	-	-	-	-	

(a) Assumed questionnaires were interpreted independently, but only states that they were collected independently. Unclear if clinician or study investigator assigned gold standard diagnosis.
(b) One study excluded people without definite ICHD-II diagnosis / probable migraine.
(c) Confidence intervals for specificity values were wide.
(d) People diagnosed at A&E visit then discharged to headache clinic.
(e) People not reporting with headache as their primary complaint but were pre-screened for headache for inclusion.
(f) Unclear if results of ID migraine and reference standard interpreted blind to the other results.
** Prevalence based on UK population survey, Tepper et al. 2004[248]. †Prevalence based on a GP population of people reporting with headaches, Steiner et al. 2003[241].*

Table 11: The structured migraine interview – Quality assessment

Setting	No. of studies	Design	N	Limitations	Inconsistency	Indirectness	Imprecision
Headache clinic[217]	1	Diagnostic Cross-sectional	170	Serious (a)	No serious inconsistency	Serious (b)	Very serious (c)

(a) Not specifically stated that ICHD-II criteria used for reference standard, assumed due to the clinic study was based in. Not all participants included in the analysis (30 could not be diagnosed by the clinician and excluded).
(b) Population was those with significant headaches that could not be managed by other healthcare providers, very specific group.
(c) Very wide confidence intervals for specificity, agreed by GDG to indicate imprecision.

Table 12: The structured migraine interview – Clinical summary of findings

Pre-test probability	TP (%)	FP (%)	FN (%)	TN (%)	Sensitivity %	Specificity %	PPV %	NPV %	Quality
84% †	138 (81)	5 (3)	20 (12)	7 (4)	87 (81-92)	58 (28-85)	97	26	VERY LOW
Effect per 1000	731	67	109	93					

† Prevalence based on a GP population of people reporting with headaches, Steiner et al. 2003[241].

5.1.2.2 Economic evidence

No economic evidence on screening questionnaires for the diagnosis of primary headache was identified.

5.1.2.3 Evidence statements

Clinical:

One study with 584 people showed that the ID migraine has a sensitivity of 50% and specificity of 84% for diagnosing migraine in people presenting to GP clinics with primary headache. [Moderate quality].

Two studies with 353 people suggested that the ID migraine has a sensitivity of between 94-95% and specificity of between 60-72% for diagnosing migraine in people attending headache clinics with primary headache, but there is some uncertainty. [Low quality].

One study with 2199 people suggested that the ID migraine has a sensitivity of 94% and a specificity of 81% for diagnosing migraine in people attending a headache clinic after being diagnosed with a primary headache at A&E, but there is some uncertainty. [Very low quality].

One study with 1816 people showed that the ID migraine has a sensitivity of 92% and a specificity of 63% for diagnosing migraine in people attending a neurology clinic for any condition and identified as headache sufferers. [Moderate quality].

One study with 176 people suggested that the ID migraine has a sensitivity of 58% and a specificity of 98% for diagnosing migraine in people attending a temporomandibular disorder and orofacial pain clinic identified as being headache sufferers, but there is some uncertainty. [Very low quality].

One study with 1021 people showed that the ID migraine has a sensitivity of between 80-88% and a specificity of between 74-76% for diagnosing migraine in people attending either neurology, ear nose and throat or ophthalmology clinics. [Low quality].

One study with 170 people suggested that the structured migraine interview has a sensitivity of 87% and a specificity of 51% for diagnosing migraine in people attending a specialist headache clinic with primary headaches that could not be managed by other healthcare providers, but there is considerable uncertainty. [Very low quality].

Economic:

No economic evidence on case finding questionnaires for the diagnosis of primary headache was identified.

5.1.3 Cluster headache

5.1.3.1 Clinical evidence

See evidence tables in appendix E.1.2, forest plots, Figures 5, Appendix G.1.2.1.

Two studies were identified[62,253]; one was a development study of a case finding questionnaire for cluster headache and has been included for information in the evidence tables, but not in the data analysis[62]. The remaining study was included, the population included people aged 15 or over who had previously been diagnosed with migraine or cluster headache.

Table 13: Cluster headache screening questionnaire – Quality assessment

Setting	No. of studies	Design	N	Limitations	Inconsistency	Indirectness	Imprecision
Headache clinic[62]	1	Diagnostic Cross-sectional	96	No serious limitations	No serious inconsistency	No serious imprecision	Serious[(a)]

(a) Confidence intervals for specificity values were wide, agreed by GDG to indicate imprecision.

Table 14: Cluster headache screening questionnaire – Clinical summary of findings

Setting	TP (%)	FP (%)	FN (%)	TN (%)	Sensitivity %	Specificity %	PPV %	NPV %	Quality
Headache clinic	29 (30)	0	8 (8)	59 (61)	78.4 (62-90)	100 (94-100)	100	88.1	MODERATE

5.1.3.2 Economic evidence

No economic evidence on screening questionnaires for the diagnosis of cluster headache was identified.

5.1.3.3 Evidence statements

Clinical:

One study of 96 people suggested that the cluster headache screening questionnaire has a sensitivity of 78% and a specificity of 100% for diagnosing people with cluster headache in people attending a headache clinic with primary headache, but there is some uncertainty. [Moderate quality].

Economic:

No economic evidence on screening questionnaires for the diagnosis of cluster headache was identified.

5.2 Recommendations and link to evidence

The GDG decided not to make any recommendations for case finding questionnaires for the diagnosis of primary headache.

Recommendations	
Relative values of different outcomes	The ideal questionnaire would have high specificity and high sensitivity. The GDG agreed that for use in general settings a questionnaire or questions with high sensitivity was most important to rule people out and not require the healthcare professional to do a more comprehensive assessment.
Trade off between clinical benefits and harms	It was agreed as important to ensure that an accurate diagnosis was made as the consequences of a false negative can mean people suffering unnecessarily and not being offered appropriate treatment. A false positive however would also have serious consequences as this may lead to inappropriate treatment and delayed diagnosis of the real cause of the headache.
Economic considerations	Using screening questionnaires would have negligible costs. Their cost-effectiveness would be determined by their accuracy. In the absence of definite evidence on their diagnostic accuracy, it is not possible to decide if they are cost-effective.
Quality of evidence	The reviewed evidence varied from very low to moderate for ID migraine, the structured migraine interview and the cluster headache screening questionnaire. The study in primary care using ID migraine was of moderate quality but found ID migraine to have a sensitivity of 50%, specificity of 84% and a negative predictive value of only 52%. The GDG were aware that sensitivity of 'Whooley' questions to identify people with suspected depression is 0.95 (0.91-0.97) and considered that this level of sensitivity was required before they could recommend a tool. Sensitivities were higher in headache and neurology clinics but the value of a case identification questionnaire in these settings where full assessment is likely is unclear. No economic evidence was available on screening questionnaires.
Other considerations	The GDG were primarily interested in advising professionals working in general clinical settings and considered the evidence did not support using these questionnaires to target a fuller clinical history.

6 Headache diaries for the diagnosis and management of primary headaches and medication overuse headache

6.1 Introduction

Headache diaries are often recommended for people who have disorders that are intermittent. It is thought that diaries will be more accurate than recall and allow patterns of events to be more clearly seen. This can potentially be helpful to both the person with the headache and doctor. Headache diaries may be useful in self-management as they allow the person to identify any patterns and precipitating factors in their symptoms. Diaries may help people to better understand their condition as well be alerted to any changes in the regularity or severity of attacks and the effectiveness of new drugs that may be introduced.

The GDG considered it important to assess the evidence for headache diaries for people with headache rather than recommend them uncritically. They were interested in two aspects of headache diary use – an assessment of the use of headache diaries in diagnosis of headache and their potential to facilitate other aspects of care e.g. self-management or doctor-patient communication. These areas were assessed in two separate reviews.

6.2 Headache diaries as an aid to diagnosis

6.2.1 Clinical question

What is the clinical effectiveness of using diaries for the diagnosis in people with suspected primary headaches and medication overuse headache?

A literature search was conducted for diagnostic studies comparing the use of headache diaries to clinician diagnosis according to ICHD-II criteria[106], see protocol C.1.3.

No MID was defined for any of the diagnostic outcomes. The GDG were asked to review the evidence and agree the level of imprecision based on the confidence intervals around the effect size and absolute effect estimate.

6.2.1.1 Clinical evidence

See evidence table in appendix section E.1.3.

Three studies were identified[189,216,247]. Diaries used in the studies were diagnostic headache diaries. They were required to be filled in at the end of each headache day in two of the studies[200,216] and on a daily basis in one study[247]. The diaries used were similar to one another in the recording of headache intensity, frequency, duration, location and associated symptoms.

Two studies[200,216] included in the review were in populations who were already diagnosed with specific headache types, only one study was in an undiagnosed population[247]. It was not possible to pool any results due to the differences in diagnoses and populations.

Table 15: Headache diaries for diagnosis - quality assessment

Condition diagnosed	Limitations	Inconsistency	Indirectness	Imprecision
Russell et al. 1992[216]				
Migraine with aura	Very serious (a)	No serious inconsistency	Serious (b)	Very serious (c)
Migraine without aura	Very serious (a)	No serious inconsistency	Serious (b)	Very serious (c)
Episodic tension-type headache	Very serious (a)	No serious inconsistency	Serious (b)	Very serious (c)
Chronic tension-type headache	Very serious (a)	No serious inconsistency	Serious (b)	Very serious (c)
Phillip 2007 et al. [200]				
Migraine	Very serious (d)	No serious inconsistency	Serious (e)	Very serious (c)
Tension-type headache	Very serious (d)	No serious inconsistency	Serious (e)	Very serious (c)
Chronic tension-type headache	Very serious (d)	No serious inconsistency	Serious (e)	Very serious (c)
Tassorelli et al. 2008[247]				
Migraine	Serious (f)	No serious inconsistency	Serious (g)	Very serious (c)
Tension-type headache	Serious (f)	No serious inconsistency	Serious (g)	Very serious (c)
Medication overuse headache	Serious (f)	No serious inconsistency	Serious (g)	Very serious (c)

a) No randomisation of participants; Only people with a diagnosis of migraine included; small sample size.
b) Participants recruited from a specialist headache clinic; Only people with migraine included.
c) Wide confidence intervals observed for sensitivity and specificity, agreed by GDG to indicate imprecision.
d) Unclear randomisation; Participants did not all receive the same reference standard; participants not all included in the analysis (high loss to follow up).
e) Study included only 'difficult to diagnose' people which may have excluded other diagnosis of primary headaches; unclear whether already diagnosed.
f) Unclear randomisation; small sample size.
g) Study conducted in specialist headache clinic.

Table 16: Headache diaries for diagnosis– Clinical summary of findings

Condition diagnosed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Quality
Russell et al. 1992[216]					
Migraine with aura	72.73%	72.00%	36.36%	92.31%	VERY LOW
Migraine without aura	94.34%	50.00%	92.59%	57.14%	VERY LOW
Episodic tension-type headache	84.21%	45.24%	41.03%	86.36%	VERY LOW
Chronic tension-type headache	21.05%	100.00%	100.00%	73.68%	VERY LOW
Phillip et al. 2007[200]					
Migraine	84.85%	75.00%	90.32%	64.00%	VERY LOW

Condition diagnosed	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Quality
Tension-type headache	88.10%	66.67%	97.37%	29.00%	VERY LOW
Chronic tension-type headache	77.78%		100.00%		VERY LOW
Tassorelli et al. 2008 [247]					
Migraine	92.19%	58.33%	92.19%	58.33%	LOW
Tension-type headache	75.00%	58.33%	51.22%	80.00%	LOW
Medication overuse headache	75.00%	86.67%	60.00%	92.86%	LOW

6.2.1.2 Economic evidence

No relevant economic evaluations on the use of headache diaries for diagnosis of primary headaches were identified.

We estimated the cost of evaluating headache diaries in terms of time spent by the health care professional in doing this.

From the literature we found no data on the average cost or time spent by the GP or other health care professionals to evaluate the diary. The GDG experts estimated this additional time to be from 1 to 2 minutes and that diaries can be evaluated by any health care professional.

We combined the GDG estimates with the cost data reported in the PSSRU publication[45] to obtain the cost of the intervention (Table 17).

Table 17: Cost of evaluating headache diaries

Health care professional involved	Cost per minute of visit	Additional cost time = 1minute	Additional cost time = 2 minutes
GP	£2.80 [(a)]	£2.80	£5.60
Consultant	£2.82 [(b)]	£2.82	£5.64

(a) Based on the cost of GP clinic per minute, including qualification[45].
(b) Based on the cost per person-related hour of consultant medical including qualification[45].

The cost of using headache diaries is estimated between £2.80 and £5.64 per person.

6.2.1.3 Evidence statements

Clinical:

One study with 61 people recruited in specialist headache centres suggested that headache diaries have a sensitivity of 94% and specificity of 50% in the diagnosis of migraine without aura, but there is considerable uncertainty. [Very low quality].

One study with 61 people recruited in specialist headache centres suggested that headache diaries have a sensitivity of 72% and specificity of 72% in the diagnosis of migraine with aura, but there is considerable uncertainty. [Very low quality].

One study with 61 people recruited in specialist headache centres suggested that headache diaries have a sensitivity of 84% and specificity of 45% in the diagnosis of episodic tension type headache, but there is considerable uncertainty. [Very low quality].

One study with 61 people recruited in specialist headache centres suggested that headache diaries have a sensitivity of 21.5% and specificity of 100% in the diagnosis of chronic tension type headache, but there is considerable uncertainty. [Very low quality].

One study with 49 people with ‘difficult to diagnose’ headaches recruited in a university hospital suggested that headache diaries have a sensitivity of 84.5% and specificity of 75% in the diagnosis of migraine, but there is considerable uncertainty. [Very low quality].

One study with 49 people with ‘difficult to diagnose’ headaches recruited in a university hospital suggested that headache diaries have a sensitivity of 88% and specificity of 67% in the diagnosis of tension type headache, but there is considerable uncertainty. [Very low quality].

One study with 49 people with ‘difficult to diagnose’ headaches recruited in a university hospital suggested that headache diaries have a sensitivity of 78% and a positive predictive value of 100% in the diagnosis of chronic tension type headache, but there is considerable uncertainty. [Very low quality].

One study with 76 people with undiagnosed headache recruited in specialist headache centres suggested that headache diaries have a sensitivity of 92% and specificity of 58% in the diagnosis of migraine, but there is considerable uncertainty. [Low quality].

One study with 76 people with undiagnosed headache recruited in specialist headache centres suggested that headache diaries have a sensitivity of 75% and specificity of 58% in the diagnosis of tension type headache, but there is considerable uncertainty. [Low quality].

One study with 76 people with undiagnosed headache recruited in specialist headache centres suggested that headache diaries have a sensitivity of 75% and specificity of 86% in the diagnosis of medication overuse headache, but there is considerable uncertainty. [Low quality].

Economic:

Using headache diaries for the diagnosis of the headache type has a maximum cost of £5.64 per person, based on the incremental time spent by the health care professional to evaluate the diary.

6.2.2 Recommendations and link to evidence

Recommendations	**Consider using a headache diary to aid the diagnosis of primary headaches.**
Relative values of different outcomes	Sensitivity, specificity, positive predictive value, negative predictive value, and number of people diagnosed were extracted. The GDG considered that number of people diagnosed was of least value. The other outcomes were considered important in evaluating use of diaries, but the large confidence intervals meant that it was difficult to draw conclusions.
Trade off between clinical benefits and harms	The GDG agreed clinical history should remain the basis for diagnosis of primary headaches and the diary used as an adjunct only. Some people may consider the diaries burdensome to complete and therefore there may be some issues with compliance. This should be considered when deciding if a diary is an appropriate tool to use. Recall in a consultation may not be accurate so a diary can assist in diagnosis.
Economic considerations	Using headache diaries for the diagnosis of the headache type has a cost of £2.80 to £5.64 per person, which includes the cost of the additional time the GP or consultant spent during a consultation in order to evaluate the diary. The additional cost could be offset by the more accurate diagnosis of the correct type of headache, which is important to provide the most cost-effective treatment according to the recommendations in this guideline.
Quality of evidence	The quality of the evidence varied between low and very low. Outcomes were downgraded due to study limitations including small sample sizes, non-random methods of selection and all were conducted in tertiary care centre, therefore the evidence only relates to these specific populations. The economic evidence was based on a simple cost analysis.
Other considerations	The recommendation was based on GDG informal consensus due to the low quality of evidence available. Equality issues should be considered when developing and using headache diaries including; reading and writing skills, language and cultural differences. The diaries used in the studies were diagnostic headache diaries recording daily details of headache intensity, frequency, duration, location, associated symptoms and use of symptomatic medication. The GDG were aware of multiple diaries available both on line and from clinics which record the above information and may prove useful.

Recommendations	**If a headache diary is used, ask the person to record the following for a minimum of 8 weeks:** • **frequency, duration and severity of headaches** • **any associated symptoms** • **all prescribed and over the counter medications taken to relieve headaches** • **possible precipitants** • **relationship of headaches to menstruation.**
Relative values of different outcomes	Sensitivity, specificity, positive predictive value, negative predictive value, and number of people diagnosed were extracted. The GDG considered that number of people diagnosed was of least value. The other outcomes were considered important in evaluating use of diaries, but the large confidence intervals meant that it was difficult to draw conclusions.

Recommendations	**If a headache diary is used, ask the person to record the following for a minimum of 8 weeks:** • **frequency, duration and severity of headaches** • **any associated symptoms** • **all prescribed and over the counter medications taken to relieve headaches** • **possible precipitants** • **relationship of headaches to menstruation.**
Trade off between clinical benefits and harms	The GDG agreed clinical history should remain the basis for diagnosis of primary headaches and the diary used as an adjunct only. Some people may consider the diaries burdensome to complete and therefore there may be some issues with compliance. This should be considered when deciding if a diary is an appropriate tool to use. Recall in a consultation may not be accurate so a diary can assist in diagnosis.
Economic considerations	Using headache diaries for the diagnosis of the headache type has a cost of £2.80 to £5.64 per person, which includes the cost of the additional time the GP or consultant spent during a consultation in order to evaluate the diary. The additional cost could be offset by the more accurate diagnosis of the correct type of headache, which is important to provide the most cost-effective treatment according to the recommendations in this guideline.
Quality of evidence	The quality of the evidence varied between low and very low. Outcomes were downgraded due to study limitations including small sample sizes, non-random methods of selection and all were conducted in tertiary care centre, therefore the evidence only relates to these specific populations. The economic evidence was based on a simple cost analysis.
Other considerations	The recommendation was based on GDG informal consensus due to the low quality of evidence available. Equality issues should be considered when developing and using headache diaries including; reading and writing skills, language and cultural differences. The diaries used in the studies were diagnostic headache diaries recording daily details of headache intensity, frequency, duration, location, associated symptoms and use of symptomatic medication. A temporal association between headache and menstruation is required for the diagnosis of menstrual migraine and using a diary can help to establish this. This is further discussed in chapter 7. The GDG were aware of multiple diaries available both on line and from clinics which record the above information and may prove useful.

6.3 Headache diaries as an aid to management

6.3.1 Clinical question

What is the clinical effectiveness, and patients' and practitioners' experience of using diaries for the management of people with suspected primary headaches and medication overuse headache?

A literature search was conducted for RCTs assessing the effectiveness of headache diaries for the management of primary headache. The GDG agreed that this search should be widened to observational and qualitative studies if no RCT evidence was found (See protocol C.1.4).

6.3.1.1 Clinical evidence

See evidence table in appendix section E.1.3.

No RCT evidence was identified for the use of headache diaries as a management tool in primary headache. Therefore the review focuses on evidence from observational and qualitative studies of patient's and practitioners' experience of using diaries for management as pre-specified in the protocol (see appendix C.1.4).

Four studies were identified [13,37,39,108,203] which reported patients' and physicians' experience of using headache diaries for the management of primary headaches. Three studies [13,108,203] used surveys and the fourth study (reported in two papers)[37,39] used focus group discussions as methods of data collection. A customised quality assessment for qualitative studies (see Table 18) was carried out on the three studies and a narrative summary of the findings is presented.

Table 18: Headache diaries for the management of primary headaches - quality assessment

Study	Population	Methods	Analysis	Relevance to guideline population
Porter 1981[203]	Well reported	Poorly reported	Poorly reported	US tertiary care setting with people seeking specialised headache care
Baos 2005[13]	Well reported	Adequately reported	Poorly reported	People with headache enrolled from primary care physicians' group practices in 12 cities in Spain
Coeytaux 2007[37,39]	Well reported	Adequately reported	Poorly reported	People with headache from a university based, tertiary care headache clinic who had recently participated in a RCT (USA)
Jensen 2011[108]	Well reported	Adequately reported	Adequately reported	People with headache awaiting first consultation at specialised headache centres in 12 countries across Europe and Latin America.

6.3.1.2 Clinical summary of evidence

Porter et al. 1981[203]

Thirty eight percent of participants felt the diary was helpful and 8% thought it was a hindrance; 69% thought that it would be useful to their physicians. The average level of headache pain over the second two week period decreased in 54.2%, increased in 40.5% and remained unchanged in 5.1% of participants. The number of days with any level of headache increased in 41%, decreased in 22.6%, and remained unchanged in 36.3% of participants over the second two week period. Average level of negative feelings over second two week period increased in 41%, decreased in 50.4%, and remained unchanged in 8.5% of participants over the second two week period.

Baos et al. 2005[13]

Seventy percent of people reported being more satisfied with the level of medical care compared to before using the diary and 88% felt that the diary helped them communicate better with their physicians.

Ninety one percent of physicians felt that the diary helped them to communicate better with their patients and 100% felt that it enabled them to assess differences in pain intensity and disability across attacks within the same person. 46% of physicians felt a difference in evaluation and differentiation between headaches pre and post study and 68% felt that the diary influenced decisions regarding prescription medication for migraine.

Coeytaux et al. 2007[37,39]

This study provided a narrative summary of the opinions of people regarding the use of a diary for the management of headaches.

Participants felt that the diary was useful and not overly burdensome, provided a meaningful expression of their level of pain and was useful in measuring pain severity and frequency. They also felt that it allowed them to see improvement of which they might have been otherwise unaware.

Jensen et al. 2011[108]

The headache diary along with the clinical interview was found to provide adequate information for diagnosis in 97.7% of cases. Information from the clinical interview alone was found to be adequate for diagnosis in 86.8% of cases.

The study reported that 97.5% of people did not have any difficulty in understanding the diary and providing information. Participants evaluated the diary as being useful for making them aware of medication usage but less useful for understanding headache triggers or deciding when to treat their headache. Also, 97% of physicians did not report any difficulty in understanding the diary and interpreting the information. Physicians evaluated the diary as being helpful in diagnosing medication overuse headache and informing people about medication intake and regarded it as less useful in informing them about headache triggers.

6.3.1.3 Economic evidence

No relevant economic studies comparing the use of headache diaries with no diaries were identified.

Please see 6.2.1.2 for cost analysis of evaluating headache diaries.

Economic:

Using headache diaries for the management of primary headaches has a maximum cost of £5.60 per person, based on the incremental time spent by the GP to evaluate the diary.

6.3.2 Recommendations and link to evidence

Recommendations	**Consider using a headache diary:** • **to record the frequency, duration and severity of headaches** • **to monitor the effectiveness of headache interventions** • **as a basis for discussion with the person about their headache disorder and its impact.**
Relative values of different outcomes	Any detail of patients' or practitioners' experience of using diaries in the management of primary headaches expressed in the studies reviewed was considered as of equal value by the GDG.
Trade off between clinical benefits and harms	Some people may consider the diaries burdensome to complete and therefore there may be some issues with compliance. This should be considered when deciding if a diary is an appropriate tool to use.
Economic considerations	Using headache diaries for the management of the headache type has a cost of £2.80 to £5.60 per visit, which is based on the cost of the additional time the GP spent during a consultation in order to evaluate the diary. The GDG considered the role of diaries in deciding on headache management strategy and the increased effectiveness derived from the most optimal choice.
Quality of evidence	The evidence was of low quality, based on questionnaires and surveys reported in three studies. The limitations of the studies included poor reporting of the methods and analysis. Two of the studies were conducted in tertiary care settings with one including people from a clinical trial and hence, were indirect to the target population in the clinical question. The economic evidence was based on a simple cost analysis where cost data were taken from a national source while resource estimates were elicited from GDG opinion.
Other considerations	The GDG used the evidence and their experience when considering the use of diaries. The GDG agreed that the importance of communication and understanding the impact of headache should not be undervalued and diaries played an important role in acknowledging this. Diaries can help in the legitimisation of headache. Equality issues should be considered when developing and using headache diaries including; reading/writing skills, language and cultural differences.

7 Diagnosis of primary headaches and medication overuse headache

7.1 Introduction

The pathophysiology of primary headaches and medication overuse headache is poorly understood. Their classification is based on symptoms and defined by expert opinion drawing upon a number of elements that include clinical pattern, longitudinal and epidemiological studies and treatment outcomes. A substantial proportion of people with primary headache or medication overuse headache do not obtain an accurate diagnosis[122]. Possible barriers to the accurate diagnosis of primary headache include under recognition of specific disorders by people themselves, under consultation by headache sufferers and failure to provide a diagnosis for those that consult[154].

The International Headache Society Classification of Headache Disorders provides a starting point for a formal diagnosis of primary headache[106]. The International Headache Society (IHS) is an international organisation whose aim is to promote research into headache and to provide education for healthcare professionals and patients. The IHS developed a classification of headaches in 1988 and this was revised in 2005. The intention of the classification was to allow standardisation of diagnosis for use in clinical research and in practice. The classification was developed using a variety of sources including clinical description, longitudinal studies of cohorts of people, epidemiological studies, treatment results, genetics, neuroimaging and pathophysiology. The classification is a hierarchical classification with all headache disorders classified into major groups and each group then subdivided one, two or three times into headache types, subtypes and subforms. Primary headaches are classified according to the description of the headache and secondary headaches classified according to aetiology. It is intended that a generalist healthcare professional can use first levels of classification but that a headache specialist could diagnose at second and third levels and may need to do so for people who are more difficult to treat. The criteria are available at this website:http://ihs-classification.org/en/02_klassifikation/02_teil1/.

The GDG were primarily interested in reviewing the ICHD-II classification to develop recommendations that would help the non–headache specialist diagnosis headache disorders in NHS settings.

In adolescents particularly there can be a significant overlap between migraine and tension type headache with significant variability in attacks[275].

Medication overuse headache is a common accompaniment of migraine and tension type headache. People with a migrainous predisposition seem particularly at risk whereas it is rare in cluster headache. All acute relief medications have been implicated. Medication overuse headache can occur in headache-prone people when acute headache medications are taken for indications other than headache. The mechanism is unknown but changes in pain modulatory pathways are probably implicated. The presentation of the medication overuse headache combined with a primary headache can provide a challenge to the clinician unless a medication history is taken. If the person has an underlying primary headache disorder, this will usually return to its previous pattern within one month of discontinuing the over-used medication.

7.1.1 Clinical question

For young people and adults with headache, what are the key diagnostic features of the following headaches: migraine with or without aura; menstrual related migraine; chronic migraine; tension-type headache; cluster headache and medication overuse headache?

The GDG agreed that the recommendations for the diagnosis of primary headache should be based on the existing classification criteria: the International Headache Society ICHD-II[106]. These criteria are well established and accepted across the clinical headache community. The classification criteria were developed for use in both clinical practice and research settings. The second edition does not change the principles of the classification but is an update in the light of new evidence. GDG consensus opinion was used to word these as recommendations that would be useful for clinicians in practice (by informal consensus methods).

No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.

7.1.2 Recommendations and link to evidence

Recommendations	**Diagnose tension-type headache, migraine or cluster headache according to the headache features in the table.**
Relative values of different outcomes	An accurate diagnosis of primary headache disorder will help direct appropriate treatment.
Trade off between clinical benefits and harms	No harms were considered likely from accurate diagnosis.
Economic considerations	Considering specific characteristics for the diagnosis of headache does not have any economic implications. However diagnosing the correct type of headache is important to provide cost-effective treatments as identified and recommended in this guideline (see Chapters 10-22).
Quality of evidence	The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.
Other considerations	The GDG chose to make a recommendation about attack separately from headache disorder to create a clearer pathway for the non-specialist. They considered that the distinction between episodic and chronic tension type headache disorder was useful for the non-specialist but that further subdivision into frequent and infrequent episodic type tension headache would not be required and would not influence choice of treatment. In relation to the duration of headache, when the person falls asleep during migraine and wakes up without it, its duration is reckoned until the time of awakening. Aggravation by routine physical activity (e.g. walking about), bright lights (photophobia) or loud noise (phonophobia) can be implied by avoidance behaviour. The GDG agreed that chronic migraine and chronic tension type headache commonly overlap and should be diagnosed as chronic migraine alone when migrainous features are frequently present. During the development of the Headaches clinical guideline, 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). The TA relates to the ICHD II definition of chronic migraine (headache for at least 15 days a month, with at least 8 of those days being migraine). For cluster headache, the GDG considered it important that non-specialists understand the frequency of attacks per day that may occur during a bout of cluster headache is different from migraine. Some separate considerations apply for children and young people: Migraine headache is commonly bilateral in children; an adult pattern of unilateral pain usually emerges in late adolescence or early adult life: Migraine headache is usually frontotemporal; occipital headache in children, whether unilateral or bilateral, is rare and calls for diagnostic caution; many cases are attributable to structural lesions.

Table Diagnosis of tension-type headache, migraine and cluster headache

Headache feature	Tension-type headache		Migraine (with or without aura)		Cluster headache	
Pain location[a]	Bilateral		Unilateral or bilateral		Unilateral (around the eye, above the eye and along the side of the head/face)	
Pain quality	Pressing/tightening (non-pulsating)		Pulsating (throbbing or banging in young people aged 12-17 years)		Variable (can be sharp, boring, burning, throbbing or tightening)	
Pain intensity	Mild or moderate		Moderate or severe		Severe or very severe	
Effect on activities	Not aggravated by routine activities of daily living		Aggravated by, or causes avoidance of, routine activities of daily living		Restlessness or agitation	
Other symptoms	None		Unusual sensitivity to light and/or sound or nausea and/or vomiting **Aura[b]** Aura symptoms can occur with or without headache: • are fully reversible • develop over at least 5 minutes • last 5–60 minutes. Typical aura symptoms include visual symptoms such as flickering lights, spots or lines and/or partial loss of vision; sensory symptoms such as numbness and/or pins and needles; and/or speech disturbance.		On the same side as the headache: • red and/or watery eye • nasal congestion and/or runny nose • swollen eyelid • forehead and facial sweating • constricted pupil and/or drooping eyelid	
Duration of headache	30 minutes–continuous		4–72 hours in adults 1–72 hours in young people aged 12-17 years		15–180 minutes	
Frequency of headache	< 15 days per month	≥ 15 days per month for more than 3 months	< 15 days per month	≥ 15 days per month for more than 3 months	1 every other day to 8 per day[c], with remission[d] > 1 month	1 every other day to 8 per day[c], with a continuous remission[d] < 1 month in a 12-month period
Diagnosis	**Episodic tension-type headache**	**Chronic tension type headache[e]**	**Episodic migraine (with or without aura)**	**Chronic migraine[f] (with or without aura)**	**Episodic cluster headache**	**Chronic cluster headache**

a Headache pain can be felt in the head, face or neck.
b See recommendations 1.2.2, 1.2.3 and 1.2.4 for further information on diagnosis of migraine with aura.
c The frequency of recurrent headaches during a cluster headache bout.
d The pain-free period between cluster headache bouts.
e Chronic migraine and chronic tension-type headache commonly overlap. If there are any features of migraine, diagnose chronic migraine.
f NICE has developed technology appraisal guidance on Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).

Recommendations	**Suspect aura in people who present with or without headache and with neurological symptoms that:** • **are fully reversible and** • **develop gradually, either alone or in succession, over at least 5 minutes and** • **last for 5–60 minutes.**
Relative values of different outcomes	An accurate diagnosis of primary headache disorder will help direct appropriate treatment.
Trade off between clinical benefits and harms	No harms were considered likely from accurate diagnosis.
Economic considerations	Considering specific characteristics for the diagnosis of headache does not have any economic implications. However diagnosing the correct type of headache is important to provide cost-effective treatments as identified and recommended in this guideline (see Chapters 10-22).
Quality of evidence	The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.
Other considerations	The GDG considered it important that healthcare professionals understand that diagnosis of aura requires consideration of symptoms, their reversibility, the timing of onset and resolution.

Recommendations	**Diagnose migraine with aura in people who present with or without headache and with one or more of the following typical aura symptoms that meet the criteria in recommendation 1.2.2:** • **visual symptoms that may be positive (for example, flickering lights, spots or lines) and/or negative (for example, partial loss of vision)** • **sensory symptoms that may be positive (for example, pins and needles) and/or negative (for example, numbness)** • **speech disturbance.**
Relative values of different outcomes	An accurate diagnosis of primary headache disorder will help direct appropriate treatment.
Trade off between clinical benefits and harms	No harms were considered likely from accurate diagnosis.
Economic considerations	Considering specific characteristics for the diagnosis of headache does not have any economic implications. However diagnosing the correct type of headache is important to provide cost-effective treatments as identified and recommended in this guideline (see Chapters 10-22).
Quality of evidence	The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.

Other considerations	The GDG considered it important to emphasise that migraine with aura is diagnosed even in people who do not get headache associated with their aura.

Recommendations	**Consider further investigations and/or referral for people who present with or without migraine headache and with any of the following atypical aura symptoms that meet the criteria in recommendation 1.2.2:** • **motor weakness or** • **double vision or** • **visual symptoms affecting only one eye or** • **poor balance or** • **decreased level of consciousness.**
Relative values of different outcomes	An accurate diagnosis of primary headache disorder will help direct appropriate treatment.
Trade off between clinical benefits and harms	No harms were considered likely from accurate diagnosis.
Economic considerations	The GDG considered the opportunity cost of referring people for further investigation and concluded that given the seriousness of the potential alternative diagnoses in people with rare aura symptoms, making the correct diagnosis justifies the extra cost.
Quality of evidence	The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on further investigation for people with possible rare aura symptoms.
Other considerations	The GDG considered that the non-specialist needed to be aware of atypical aura but that people with these symptoms needed specialist assessment to make the diagnosis. Clinical terms have been reworded in lay language in the recommendation, however symptoms may also be referred to as: dysarthria (slurred speech), diplopia (double vision), monocular visual symptoms (visual symptoms in one eye only), ataxia (poor balance). Possible subtypes of atypical migraine specified in the ICHD-II include: basilar type migraine, familial hemiplegic migraine and sporadic hemiplegic migraine.

Recommendations	**Suspect menstrual-related migraine in women and girls whose migraine occurs predominantly between 2 days before and 3 days after the start of menstruation in at least 2 out of 3 consecutive menstrual cycles.**
Relative values of different outcomes	An accurate diagnosis of primary headache disorder will help direct appropriate treatment.
Trade off between clinical benefits and harms	No harms were considered likely from accurate diagnosis.
Economic considerations	Considering specific characteristics for the diagnosis of headache does not have any economic implications. However diagnosing the correct type of headache is important to provide cost-effective treatments as identified and recommended in this guideline (see Chapter 15).

Quality of evidence	The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II, as well as additional evidence from an expert advisor for menstrual migraine. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.
Other considerations	The GDG considered that there was no need to differentiate between menstrual related migraine and pure menstrual migraine as treatment options would be the same and would be tailored according to the individual. If migraine occurs at the time of menstruation in two consecutive menstrual cycles, the GDG agreed that a diagnosis of menstrual related migraine can be made.

Recommendations	**Diagnose menstrual-related migraine using a headache diary (see recommendation 1.1.4) for at least 2 menstrual cycles.**
Relative values of different outcomes	An accurate diagnosis of primary headache disorder will help direct appropriate treatment.
Trade off between clinical benefits and harms	The GDG considered that relying on recall for diagnosis of menstrual migraine may not be reliable. Specific management for menstrual related migraine is only appropriate if the diagnosis has been confirmed. Providing treatment without first confirming diagnosis may lead to unnecessary treatment and associated risks.
Economic considerations	Considering specific characteristics for the diagnosis of headache does not have any economic implications. However diagnosing the correct type of headache is important to provide cost-effective treatments as identified and recommended in this guideline (see Chapter 15). Using headache diaries for the diagnosis of menstrual related migraine is associated with costs (cost of the additional time the GP or consultant spent during a consultation in order to evaluate the diary). The additional cost could be offset by the more accurate diagnosis of the correct type of headache, which is important to provide the most cost-effective treatment according to the recommendations in this guideline.
Quality of evidence	This recommendation was based on evidence from an expert advisor for menstrual migraine (Anne MacGregor, Associate Specialist Barts Sexual Health Centre, St Bartholomew's Hospital). The GDG used informal consensus to agree the wording. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.
Other considerations	The GDG considered that there was no need to differentiate between menstrual related migraine and pure menstrual migraine as treatment options would be the same, but would be tailored according to the individual. If migraine occurs at the time of menstruation in two consecutive menstrual cycles, the GDG agreed that a diagnosis of menstrual related migraine can be made. It was considered that a diary would increase the accuracy of the history taken and would be superior to relying on recall for diagnosis.

Recommendations	**Be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for 3 months or more:** • **triptans, opioids, ergots or combination analgesic medications on 10 days per month or more or** • **paracetamol, aspirin or an NSAID, either alone or in any combination, on 15 days per month or more.**
Relative values of different outcomes	An accurate diagnosis of primary headache disorder will help direct appropriate treatment.
Trade off between clinical benefits and harms	No harms were considered likely from accurate diagnosis but significant benefit is likely for the person with medication overuse headache if an accurate diagnosis is made.
Economic considerations	Considering specific characteristics for the diagnosis of headache does not have any economic implications. However diagnosing the correct type of headache is important to provide cost-effective treatment according to the recommendations in this guideline (see chapter 23).
Quality of evidence	The recommendations for diagnosis are based on existing criteria from the International Headache Society Classification: ICHD-II. The GDG used informal consensus to agree the wording of the recommendations, adapting the ICHD-II criteria for use by non-headache specialists. No economic evidence was found on the use of key diagnostic features to diagnose different types of headaches.
Other considerations	The diagnosis of medication overuse headache according to ICHD-II requires improvement in headache when drugs used for acute treatment are stopped. Confirmation of the diagnosis can therefore not be made until the person has withdrawn the pain relieving medication.

8 The role of imaging in diagnosis and management of primary headaches

8.1 Introduction

The diagnosis of primary headache is based on the clinical history and the absence of any indicators of serious underlying pathology that would mandate further investigation. Despite this there is often anxiety from the patient and concern from the doctor that other serious pathology such as a brain tumour is not missed. As a consequence there can be pressure on the practitioner to arrange for imaging to investigate a headache for reassurance of both patient and doctor[212].

The decision to investigate a primary headache is based upon a number of complex factors that include therapeutic and economic value, clinical confidence, time constraints within the consultation, availability of imaging, practitioner's and patient's approach to risk and uncertainty, reassurance and medico-legal concerns. The context in which the decision is made also plays an important part. General practitioners experience difficulty in diagnosing primary headaches while in secondary care, people will often anticipate the exclusion of secondary pathology and consultants will be under pressure to make a diagnosis at the first appointment. These contextual factors and the poor evidence base have resulted in a wide range of investigation patterns in both primary and secondary care.

Imaging to investigate suspected headache disorders is not risk free. The identification of incidental pathology, its clinical relevance and the unnecessary anxiety it incurs is well recognised and can be substantial. Studies of the general population yield abnormalities ranging from 0.6% to 2.8% (26)[119,177,274] but in selected populations the rates are higher. For example, a study of people with headache referred by general practitioners (GPs) for CT scans gave a 10% rate of incidental findings[251]. There are also concerns about the long term effects of exposing young people to high radiation doses associated with some imaging techniques.

The GDG were interested in reviewing (1) the usefulness of imaging as a diagnostic tool in people with suspected primary headache, and (2) use of imaging as a management strategy to reassure people with primary headache.

8.2 Imaging for diagnosis in people with suspected primary headaches

8.2.1 Clinical question

Should young people and adults with suspected primary headaches undergo brain imaging to rule out serious pathology?

A literature search was conducted for cohort studies and case controlled studies that assessed the use of imaging with computerised tomography (CT), magnetic resonance imaging (MRI) or MRI variants to determine the utility of imaging to detect serious underlying pathology in people with suspected primary headache (see protocol C.1.6.1).

8.2.1.1 Clinical evidence

See evidence table in appendix section E.1.4.

Seven studies were included in the evidence review. Two were prospective cohorts[44,95] and the remaining studies were retrospective analyses[48,113,225,255,263].

The studies differed with regards to population. One had a population of people with migraine with or without aura[44.]. Two included people with a range of primary headache disorders[225,263]. Four studies did not state what sort of primary headache diagnosis had been made[48,95,113,255]. In two studies it was unclear whether the population had primary headache[44,95,113]. One study included people over the age of 15 years [225].

Four studies used only MRI as an imaging technique[95,113,255,263], and three studies used CT or MRI as an imaging technique[44,48,225].

No outcomes could be meta-analysed. Therefore the data are presented in Table 19 and Table 20.

Table 19: Results summary

Study	Setting; Imaging technique	Imaging technique	Tumour/ neoplasm	Abscess	Subdural haematoma	Hydrocephalus	Arteriovenous malformation	Stroke	Total serious abnormalities
Cull 1995[44]	Neurology outpatient clinics, UK and Holland	CT/MRI	0/67	0/67	NR	NR	0/67	0/67	0/67
Demaerel 1996[48]	Department of radiology, University hospital, Belgium.	CT/MRI	9/363 2.48%)	0/363	0/363	0/363	0/363	0/363	9/363 (2.48%)
Grimaldi 2009[95]	8 Emergency Departments, Italy	MRI	0/103	0/103	0/103	0/103	0/103	0/103	0/103
Jordan 2000[113]	Long beach memorial medical centre, USA	MRI	1/328 (0.30%)	0/328	0/328	0/328	1/328 (0.30%)	0/328	2/328 (0.61%)
Sempere 2005[225]	Neurology clinics, Spain.	CT/MRI	7/1857 (0.38%)	0/1857	0/1857	2/1857 (0.11%)	1/1857 0.054%)	1/1857 (0.054%)	10/1857 (0.54%)
Tsushima 2005[255]	Department of radiology, Japan.	MRI	1/306 (0.33%)	0/306	1/306 (0.33%)	0/306	0/306	0/306	2/306 (0.65%)
Wang 2001A[263]	Department of radiology, USA.	MRI	4/402 (1.0%)	0/402	1/402 (0.25%)	3/402 (0.75%)	1/402 (0.25%)	0/402	9/402 (2.24%)

Table 20: Summary of results by headache type

Study	Setting	Tumour/ Neoplasm	Abscess	Subdural haematoma	Hydrocephalus	Arteriovenous malformation	Stroke	Total serious abnormalities
Sempere 2005[225]	Neurology clinics, Spain.	**Cluster:** 1/21 (0.04%) (History) **Migraine**: 1/919 (0.1%) (new onset) **Indeterminate**: 1/203 (0.45%)	-	-	**Cluster:** 0/21 **Migraine:** 1/919 (0.1%) (History of episodic) **Indeterminate:** 1/203 (chronic)	**Cluster:** 0/21 **Migraine**: 1/919 (0.1%) (history of episodic) **Indeterminate:** 0/ 203	**Cluster**: 0/21 **Migraine:** 1/203 (new onset) **Indeterminate**: 0/ 203	**Cluster:** 1/21 (0.04%) **Migraine:** 3/919 (0.3%) **Indeterminate:** 2/203 (0.9%)
Wang 2001A[263]	People referred to department of radiology, New York, USA.	**Atypical headache:** 4/64 (6.3%) **Migraine:** 0/161 **TTH:** 0/71	-	**Atypical headache:** 1/64 (1.6%) **Migraine:** 0/161 **TTH:** 0/71	**Atypical headache:** 2/64 (3.1%) **Migraine:** 0/161 **TTH:** 1/71	**Atypical headache:** 1/64 (1.6%) **Migraine:** 0/161 **TTH:** 0/71	-	**Atypical:** 8/64 (12.5%) **Migraine:** 0/161 **TTH:** 1/171 (0.5%)

Table 21: Imaging for diagnosis– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Serious abnormalities*[4] [4,48,95,113,225,255,263]	7	Retrospective	Very serious [(a)]	N/A[(b)]	Serious [(c)]	N/A[(b)]

(a) In one study, of those people identified as having an abnormal CT, the nature of abnormality is not detailed and in several studies it is unclear whether people had previously had a CT. There was a mixture of imaging techniques used in the studies; some used CT only, some used CT or MRI and some carried out CT initially then carried out MRI on a subset of people. In one study there is a discrepancy in number of people included in study. 120 included, 17 dropped out, but n=80 included in analysis. In one study, it is unclear why MRI was carried out in certain people; only carried out in 8/11 people with significant abnormality.
(b) Could not be assessed as data could not be pooled for meta-analysis.
(c) Unclear in some studies whether population included people with secondary headaches.
** All abnormalities in Table 20.*
N/A=not applicable.

Table 22: Imaging for diagnosis – Clinical summary of findings

Outcome	Total number of serious abnormalities detected with imaging (CT or MRI)	Quality
Serious abnormalities	32/ 3426 (0.93%)	VERY LOW

8.2.1.2 Economic evidence

No relevant economic evaluations were included on this question. Three studies[7,12,114] that were excluded from the clinical review contained also some economic information; however the same exclusion criteria were applied to the economic evidence and these studies were not included in this economic review. The other two studies[113,135] were excluded due to their limited applicability to the UK NHS setting as they were conducted in the USA.

Performing an imaging test in people presenting with headache is associated with additional costs relative to the test performed. In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Table 23 to aid consideration of cost effectiveness.

Table 23: Unit cost of imaging tests

Item	Average Unit Cost	Notes
CT scan	£101	Diagnostic Imaging: Outpatient – currency code RA08Z - Computerised Tomography Scan, one area, no contrast
MRI scan	£174	Diagnostic Imaging: Outpatient – currency code RA01Z - Magnetic Resonance Imaging Scan, one area, no contrast.
Doppler US scan	£55	Diagnostic Imaging: Outpatient – currency code RA23Z - Ultrasound Scan less than 20 minutes

Source: National Schedule of Reference Costs Year: '2009-10' - NHS Trusts and PCTs combined

Imaging tests might also add some health benefits; for example, as a consequence of the test another condition could be detected early, and this could have some QALY gains associated with an early intervention to treat the condition.

The clinical review does not show a benefit from performing imaging tests in terms of number of important diagnoses made after imaging.

Considering the costs and the increase in radiation exposure due to some imaging tests, the few abnormal cases detected by the tests do not appear to be cost-effective.

New analysis was not prioritised for this question. However, given the availability of clinical data and details on the resources used, we conducted a simple cost-effectiveness analysis based on the results of our clinical review.

Using the unit cost of imaging tests (Table 23) and the number of abnormalities found in the studies included in our clinical review (Table 24), we could estimate the incremental cost per abnormality detected.

Table 24: Summary of resources used and effectiveness from studies included in our clinical review

Study	Number of MRI scans	Number of CT scans	Number of Doppler US scans	Number of serious abnormalities detected
Cull 1995[44]	2	67	38	0
Demaerel 1996[48]	29	363[a]	0	9
Grimaldi 2009[95]	153	0	0	0
Jordan 2000[113]	328	0[b]	0	2
Sempere 2005[225]	580	1432	0	10
Tsushima 2005[255]	306	0	0	2
Wang 2001A[263]	402	0	0	9
TOTAL	***1800***	***1862***	***38***	***32***

(a) CT was carried out both with and without contrast material
(b) It was unclear if participants had CT previous to MRI. We assume they did not have any.

We combined these overall resources estimates with the unit costs of imaging tests to calculate the incremental cost per abnormality detected (Table 25).

Table 25: Cost-effectiveness analysis – incremental cost per abnormality detected

	Unit cost[a] (A)	Number of units used[b] (B)	Total cost (A*B)	Number of serious abnormalities detected[b]	Incremental cost per abnormality detected
MRI scan	£174	1800	£313,200		
CT scan	£101	1862	£188,062		
Doppler US scan	£55	38	£2,090		
Total	-	-	***£503,352***	***32***	***£15,730***

(a) See Table 23
(b) See Table 24

According to this analysis, more than £15,000 would be spent in order to detect one abnormality in people presenting with headache.

8.2.1.3 Evidence statements

Clinical:

In seven studies with 3426 people who were diagnosed with primary headache and underwent imaging in either neurology clinics, radiology departments or emergency departments there were 22 people identified with tumour or neoplasm. [Very low quality].

In seven studies with 3426 people who were diagnosed with primary headache and underwent imaging in either neurology clinics, radiology departments or emergency departments there were no people identified with an abscess. [Very low quality].

In six studies with 3359 people who were diagnosed with primary headache and underwent imaging in either neurology clinics, radiology departments or emergency departments there were 2 people identified with a subdural haematoma. [Very low quality].

In six studies with 3359 people who were diagnosed with primary headache and underwent imaging in either neurology clinics, radiology departments or emergency departments there were 5 people identified with hydrocephalus. [Very low quality].

In seven studies with 3426 people who were diagnosed with primary headache and underwent imaging in either neurology clinics, radiology departments or emergency departments there were 3 people identified with an arteriovenous malformation. [Very low quality].

In seven studies with 3426 people who were diagnosed with primary headache and underwent imaging in either neurology clinics, radiology departments or emergency departments there was 1 person identified with signs of stroke. [Very low quality].

In seven studies with 3426 people who were diagnosed with primary headache and underwent imaging in either neurology clinics, radiology departments or emergency departments there were 32 people in total who were identified with serious abnormality. [Very low quality].

Economic:

No economic evidence on the diagnostic value of imaging in people with headache was found.

A simple cost analysis showed that performing MRI or CT would cost £174 and £101 respectively for each person receiving the test.

A cost-effectiveness analysis showed that imaging strategies have an incremental cost per abnormality detected above £15,000.

8.2.2 Recommendations and link to evidence

See recommendations and link to evidence in section 8.3.2.

8.3 Imaging as a management strategy for people with suspected primary headaches

8.3.1 Clinical question

For people with the following primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache), what is the clinical evidence and cost-effectiveness of imaging as a management strategy?

A literature search was conducted for RCTs that compared people with primary headache who had received a scan (computerised tomography (CT), magnetic resonance imaging (MRI) or MRI variants) to those who hadn't, to determine the effectiveness of imaging as a management strategy for primary headache disorders (see protocol C.1.6.2).

8.3.1.1 Clinical evidence

See evidence table in appendix section E.1.5 and forest plots in Figures 6-19, Appendix G.1.3.

One study was included in this review[105] which had a population of people with chronic daily headache, attending a specialist headache clinic.

Table 26: Imaging – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
GP use after 1 year[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Neurologist use after 1 year[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Psychiatrist/therapist use after 1 year[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Outpatient use after 1 year[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]
Other imaging use after 1 year[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Test use after 1 year[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Inpatient care use after 1 year[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]
Other service use after 1 year[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]
Sick note use after 1 year[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]
VAS worry[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
HAQ health, worry and preoccupation[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]
HAQ fear of illness[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]
HAQ reassurance seeking behaviour[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
HAQ life interference[105]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]

a) *Method of randomisation unclear, allocation concealment unclear, single blind (participants not blinded to treatment).*
b) *The confidence interval crosses one minimal important difference making the effect size uncertain.*
c) *The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.*

Table 27: Imaging vs no imaging - Clinical summary of findings

Outcome	Scan	No scan	Relative risk (95% CI)	Absolute effect	Quality
GP use after 1 year	67/68 (98.5%)	66/69 (95.7%)	RR 1.03 (0.97 to 1.09)	29 more per 1000 (from 29 fewer to 86 more)	MODERATE
Neurologist use after 1 year	1/68 (1.5%)	17/69 (24.6%)	RR 0.06 (0.01 to 0.44)	232 fewer per 1000 (from 138 fewer to 244 fewer)	MODERATE
Psychiatrist/therapist after 1 year	1/68 (1.5%)	8/69 (11.6%)	RR 0.13 (0.02 to 0.99)	101 fewer per 1000 (from 1 fewer to 114 fewer)	LOW
Outpatient use after 1 year	30/68 (44.1%)	32/69 (46.4%)	RR 0.95 (0.66 to 1.38)	23 fewer per 1000 (from 158 fewer to 176 more)	VERY LOW
Other imaging use after 1 year	13/68 (19.1%)	21/69 (30.4%)	RR 0.63 (0.34 to 1.15)	113 fewer per 1000 (from 201 fewer to 46 more)	LOW
Test use after 1 year	21/68 (30.9%)	29/69 (42%)	RR 0.73 (0.47 to 1.15)	113 fewer per 1000 (from 223 fewer to 63 more)	LOW
Inpatient care use after 1 year	5/68 (7.4%)	10/69 (14.5%)	RR 0.51 (0.18 to 1.41)	71 fewer per 1000 (from 119 fewer to 59 more)	VERY LOW
Other service use after 1 year	6/68 (8.8%)	6/69 (8.7%)	RR 1.01 (0.34 to 2.99)	1 more per 1000 (from 57 fewer to 173 more)	VERY LOW
Sick note use after 1 year	6/68 (8.8%)	7/69 (10.1%)	RR 0.87 (0.31 to 2.46)	13 fewer per 1000 (from 70 fewer to 148 more)	VERY LOW

Outcome	Scan	No scan	Relative risk (95% CI)	Absolute effect	Quality
VAS worry	54	42	-	MD -4.47 (-15.27 to 6,33)	VERY LOW
HAQ health, worry and preoccupation	48	34	-	MD 0.22 (-1.26 to -1.7)	VERY LOW
HAQ fear of illness	50	33	-	MD 0.31 (-0.84 to 1.45)	VERY LOW
HAQ reassurance seeking behaviour	50	35	-	MD -0.39 (-0.93 to 0.16)	LOW
HAQ life interference	51	33	-	MD 0.2 (-1.12 to 0.72)	VERY LOW

8.3.1.2 Economic evidence

One economic study[105] comparing the use of imaging as a management strategy vs no imaging was included. This is summarised in the economic evidence profile below (Table 28 and Table 29). See also the full study evidence table in Appendix F.

This study was also included in our review of clinical evidence (8.3.1.1).

Table 28: Imaging vs no imaging - Economic study characteristics

Study	Limitations	Applicability	Other comments
Howard (2005)[105] - UK	Potentially serious limitations (a)	Partially applicable (b)	RCT included in the clinical review (8.3.1.1). Outcomes assessed at 1 year from randomisation. Two subgroups were assessed separately: • subgroup A (people unlikely to have a psychiatric disorder) • subgroup B (people very likely to have a psychiatric disorder as detected by the Hospital Anxiety and Depression Scale [HADS])

(a) No analysis of uncertainty was conducted. Randomisation was unclear. Participants swapped groups. Allocation concealment unclear. Incomplete reporting of data.
(b) Value of health effects not expressed in terms of QALYs.

Table 29: Imaging vs no imaging – Economic summary of findings

Study	Incremental cost (a)	Incremental effects	ICER	Uncertainty
Howard (2005)[105] - UK	Subgroup A: £112 Subgroup B: -£465	(b)	Not calculated	Not explored

(a) 2005 GBP; cost of CT scan [£119] was used instead of MRI because this is what would be used in routine practice; other costs components were cost of GP visits, neurologist visits, psychiatrist/therapist visits, outpatient and inpatient care, other tests.
(b) There was no statistically significant difference between interventions in the change in anxiety and depression measures with the following instruments: VAS worry; HAQ health, worry and preoccupation; HAQ fear of illness; HAQ reassurance seeking behaviour; HAQ life interference.

The study showed that providing imaging is associated with an immediate increase in costs (the intervention cost) but with some future savings. There were statistically significant lower costs associated with neurologist, psychiatrist/therapist visits and other imaging.

However, when considering health outcomes such as quality of life measured on the Hospital Anxiety and Depression (HAD) scale or on the anxiety Visual Analogue Scale (VAS) there was not clear evidence of benefits from the imaging strategy.

8.3.1.3 Evidence statements

Clinical :

One study with 150 people showed no difference between imaging compared to not imaging in reducing GP visits in people with primary headache at one year follow up. [Moderate quality].

One study with 150 people showed that imaging is more clinically effective than no imaging in reducing neurologist visits in people with primary headache at one year follow up. [Moderate quality].

One study with 150 people suggested that imaging may be more clinically effective than not imaging in reducing psychologist/therapist visits in people with primary headache at one year follow up, but there is some uncertainty. [Low quality].

In one study with 150 people there is too much uncertainty to determine whether there is a difference between imaging and not imaging in reducing outpatient visits in people with primary headache at one year follow up. [Very low quality].

One study with 150 people suggested that imaging may be more effective than not imaging in reducing subsequent imaging in people with primary headache at one year follow up, but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

One study with 150 people suggested that there may be no difference between imaging and not imaging in reducing further tests in people with primary headache at one year follow up, but there is some uncertainty. [Low quality].

One study with 150 people suggested that imaging may be more effective than not imaging in reducing subsequent inpatient care in people with primary headache at one year follow up, but the effect size is too small to be clinically important and there is considerable uncertainty. [Very low quality].

In one study with 150 people there is too much uncertainty to determine whether there is a difference between imaging and not imaging in reducing visits to other healthcare services in people with primary headache at one year follow up. [Very low quality].

In one study with 150 people there is too much uncertainty to determine whether there is a difference between imaging and not imaging in reducing number of sick notes issued in people with primary headache at one year follow up. [Very low quality].

One study with 150 people suggested that imaging may be more clinically effective than not imaging in reducing worry assessed by VAS at one year, but there is considerable uncertainty. [Very low quality].

One study with 150 people suggested that there may be no difference between imaging and not imaging in reducing health, worry and preoccupation assessed by the health assessment questionnaire at one year follow up, but there is some uncertainty . [Very low quality].

One study with 150 people suggested that there may be no difference between imaging and not imaging in reducing fear of illness assessed by the health assessment questionnaire at one year follow up, but there is some uncertainty. [Very low quality].

One study with 150 people suggested that imaging may be more clinically effective in reducing reassurance seeking behaviour assessed by the health assessment questionnaire at one year follow up, but there is some uncertainty. [Low quality].

One study with 150 people suggested that there is no difference between imaging and not imaging in reducing life interference assessed by the health assessment questionnaire at one year follow up, but there is some uncertainty. [Very low quality].

Economic:

Providing imaging as a management strategy has considerable costs involved. A cost consequence analysis conducted alongside a RCT showed that in people unlikely to have psychiatric disorders, providing imaging increases costs with no clear evidence of benefits. This evidence has potentially serious limitations and partial applicability.

8.3.2 Recommendations and link to evidence

Recommendations	**Do not refer people diagnosed with tension-type headache, migraine, cluster headache or medication overuse headache for neuroimaging solely for reassurance.**
Relative values of different outcomes	The GDG were interested in clinical outcomes indicating effect of imaging on headache frequency and intensity, anxiety and depression and medication use. Resource use including GP consultation, A&E attendance, investigations and referral to secondary care were also of interest. Service use and change in anxiety and depression were the only outcomes in the protocol reported in the study included in the review. The GDG agreed that a clinical outcome such as headache impact would have been appropriate to indicate whether or not the person had improved.
Trade off between clinical benefits and harms	The GDG considered that the benefits reported in the only study identified were minimal, no reduction in anxiety and depression levels was observed with imaging. No evidence of clinical benefits was provided. The only reduction in resource use was in psychiatrist and neurologist referrals, but both of these had wide confidence intervals. The benefits should also be balanced against the risks to the patient from exposure to radiation that occurs with CT imaging and anxiety that the patient may experience, either due to the imaging process or incidental findings from imaging.
Economic considerations	Providing imaging as a management strategy has considerable costs involved. An economic study conducted alongside an RCT showed that providing imaging is associated with an immediate increase in costs (the intervention cost) but with some future savings. In fact, there were statistically significant lower costs associated with neurologist, psychiatrist/therapist visits and other imaging. However, when considering health outcomes such as quality of life measured on the Hospital Anxiety and Depression (HAD) scale or on the anxiety Visual Analogue Scale (VAS) there was no clear evidence of benefits from the imaging strategy. The GDG considered the uncertain benefits not enough to justify the high cost of this strategy.
Quality of evidence	Only one study was identified. Of the outcomes reported, reduction in neurologist use was the only outcome where evidence was graded as of moderate quality. All other outcomes were of low or very low quality. The economic evidence was based on a cost consequence analysis conducted alongside an RCT. This evidence has potentially serious limitations and partial applicability.
Other considerations	The only study available was carried out nearly 10 years ago with people recruited between October 1999 and April 2001. Many general practitioners now have direct access to imaging. The GDG considered that many healthcare professionals consider that imaging may be useful for reassurance and it was important to be clear that the evidence did not support this.

The GDG agreed that a separate recommendation was not required relating to imaging for diagnosis of tension type headache or migraine.

Recommendations	
Relative values of different outcomes	The GDG considered that tumour and/or neoplasm was the most important abnormality for migraine and tension type headache.
Trade off between clinical benefits and harms	The identification of serious abnormalities should also be balanced against the risks to the patient from exposure to radiation that occurs with CT imaging. The identification of serious abnormalities should be balanced against the anxiety that the patient may experience, either due to the imaging process or incidental findings from imaging.
Economic considerations	An original cost-effectiveness analysis based on our clinical review found that imaging strategies have an incremental cost per abnormality detected above £15,000. It is likely that this is an underestimate as the cost of the imaging strategy was calculated based on a mix of MRI, CT and ultrasound, as used in the included clinical studies, while in reality most people would have the most costly MRI. The GDG believed that many of the abnormalities identified would not require specific treatment and change in management, The GDG considered the opportunity cost of finding an abnormality and concluded that extensive imaging for all people presenting with headache would not be cost-effective, while selecting specific populations where the likelihood of finding an abnormality is higher might be more cost-effective.
Quality of evidence	There was very low quality evidence for the outcome of serious abnormalities in people with primary headache. There is a possibility that the evidence may be indirect because the majority of studies were not undertaken in a primary care setting and it was not clear whether the population of some studies had primary headache. Where possible, the incidence of serious abnormalities in different primary headache disorders has been reported; however, the majority of evidence for this review comes mainly from undifferentiated headache. There was no evidence identified for the use of imaging people with primary headache in a population aged 12- 15 years. The economic evidence was based on an original cost-effectiveness analysis based on the data from the clinical review and from national sources of cost data.
Other considerations	The GDG considered that for those people who satisfy the IHS criteria for primary headache, imaging is not recommended. Imaging should be carried out on those people in whom there is a suspicion of an underlying disorder based on additional symptoms and signs that do not fit the clinical diagnosis of primary headache. The GDG considered that a separate recommendation was not required and that the recommendations in section 4.5 indicated those areas where imaging should be considered. The GDG were aware of other evidence which supported the findings of the review. When a general practitioner makes a diagnosis of a primary headache in an adult the risk of developing a brain tumour in the subsequent year is 0.045% compared with 0.017% for patients presenting to their GP for other non-headache problems[121]. When a diagnosis is made under the age of eighteen, there is no increase in rate over the background rate[120].

Recommendations	**Discuss the need for neuroimaging for people with a first bout of cluster headache with a GP with a special interest in headache or a neurologist.**
Relative values of different outcomes	The GDG considered that excluding vascular abnormalities including carotid dissection is the most important outcome in a person with first bout of cluster headache.
Trade off between clinical benefits and harms	The potential clinical benefit is the diagnosis of an underlying disorder that needs alternative treatment. Harm can arise from unnecessary exposure to radiation and the detection of incidental findings. Imaging has been shown to detect a high level of incidental findings with uncertain clinical relevance. This can cause considerable anxiety amongst practitioners and patients.
Economic considerations	The GDG considered the opportunity cost of finding an abnormality and concluded that extensive imaging for all people presenting with headache would not be cost-effective, while selecting specific populations where the likelihood of finding an abnormality is higher might be more cost-effective. The GDG thought the likelihood of abnormalities in a population with a first bout of cluster headache might be higher than the average headache population and the patient and clinical presentation should therefore be discussed with a healthcare professional who is a specialist in this area.
Quality of evidence	**First bout:** This recommendation is based on consensus opinion of the GDG. **Repeated bouts:** There was very low quality evidence for the outcome of serious abnormalities in people with primary headaches. This evidence is indirect for a cluster headache population as it was not clear whether the population of some studies had primary headache. Where possible, the incidence of serious abnormalities in different primary headache disorders has been reported; however, the majority of evidence for this review comes mainly from undifferentiated headache. There was no evidence identified for the use of imaging people with primary headache in a population aged 12-15 years. No economic evidence was found on neuroimaging for people with cluster headache.
Other considerations	The GDG did not consider that most people with cluster headache would require imaging. If the healthcare professional is confident of the diagnosis imaging may not be necessary. Most healthcare professionals will however not have experience of seeing many people with cluster headache and may not be confident in making the diagnosis. The GDG therefore considered that rather than recommend all these people receive imaging, it was more important that expert advice is sought. If imaging is to be considered, the GDG considered that magnetic resonance angiography and pituitary imaging should be undertaken. When people present they may acknowledge previous bouts of similar headache. A person with a history of repeated bouts of same type of headache which fulfils the criteria for cluster headache does not require routine imaging. Imaging should only be carried out on those people in whom there is a suspicion of an underlying disorder based on additional symptoms and signs that do not fit the clinical diagnosis of primary headache. The background rate of abnormality in the general population is approximately 0.7%[177]. There was no evidence available for people aged 12-15 years. The GDG agreed that a research recommendation should be made for imaging for the first incidence of cluster headache to better inform the evidence base. See appendix M1.

Management

9 Information and support for people with headache disorders

9.1 Introduction

Primary headache disorders and medication overuse headaches are diagnosed clinically. There is no diagnostic test to demonstrate the presence or absence of a headache, or of primary headache disorder. Furthermore, there is no objective measure to use to assess the extent anyone has been helped by headache treatment. As with many other painful disorders, the absence of a diagnostic test can lead to those affected feeling that their symptoms are not believed or the impact on their life has been devalued. Nearly all of the treatments for primary headache are of limited efficacy. There needs to be a dialogue between the person with headaches and their clinician about the comparative benefits and risks of different treatment options. Accurate diagnosis and advice about the nature of headaches might, in itself, be therapeutic independent of any specific treatment being advised. The role of the practitioner in the management of primary headache disorders in providing advice and support is, therefore, critical in achieving good outcomes. Directly addressing the information needs of people with headaches is part of the headache consultation. The data required before advising on information and support is unlikely to found in the quantitative date sought elsewhere in this guidelines. Qualitative data on the sorts of information and support needed was searched for so that we had an appropriate evidence base to produce specific headache recommendations.

9.1.1 Clinical question

What information and support do people with primary headaches say they want?

A review was conducted to determine what information and support people say they want for their primary headaches.

The aim of this review was to provide:

1. Supplementary evidence to clinical questions
2. General overview of peoples' needs for information and support with regard to their headache.

Qualitative research was used as the main source of data. Themes were identified from these studies by two reviewers independently, and then verified jointly. These themes were supplemented with data from surveys where available.

9.2 Literature review

No good quality studies were found directly addressing what people wanted with regard to information and support about their headaches. Consequently, we extracted data from more general qualitative studies on people's views and experience of their headaches. The search strategy included surveys to ensure maximal coverage and three structured surveys of people with headache were found by the search.

Eight qualitative studies were identified[5,14,102,172,175,195,196,158] and three surveys[188,207,215]. The questionnaires used were not validated. One of these surveys addressed adolescents' headaches[207] .

It was considered important if possible to represent this group so this information was presented to the GDG. Two of the surveys asked people about their visit to the doctor and people were asked to rank options presented or to choose their top three[188,207]. These findings were considered complimentary to the qualitative studies.

All themes reported in the included studies are presented in the evidence tables. Only the themes of interest are reported in this section. More details about the qualitative studies are presented in the evidence tables (Appendix section E.2.1). A summary of the study quality for the qualitative literature is presented in Table 30.

Out of the eight qualitative studies, five related to migraine only [5,14,102,172,175], two papers included migraine, tension type headache and chronic daily headache[195,196] (these two papers were reporting different themes from the same data set), and one study examined cluster headaches[158]. We included three surveys, one related to migraine only[215], and two to headaches in general[188,207].

Table 30: Information and support - study quality

Study	Population	Methods	Analysis	Relevance to guideline population
Adelman et al. 2000[5]	Adequately reported	Poorly reported	Poorly reported	US. People with migraine, but diagnosis only by telephone screening.
Belam et al. 2005[14]	Well reported	Adequately reported	Poorly reported	UK. People with migraine attending an intermediate care headache clinic.
Henderson, 1999[102]	Well reported	Well reported	Poorly reported (No quotes or references)	Australia. Females aged 26-45 meeting ICHD criteria for migraine (setting unclear).
Loder, 2005[158]	Poorly reported	Poorly reported	Poorly reported	US. People with cluster headache either current or past patients of Rehabilitation Hospital Headache Management Program.
Meyer, 2002[172]	Well reported	Well reported	Well reported	US. Females with migraine (setting unclear).
Moloney et al. 2006[175]	Well reported	Well reported	Adequately reported.	US. Females (perimenopausal, midlife)
Peters et al. 2003* [195]	Well reported	Well reported	Well reported	UK. Adults with migraine (± TTH and chronic daily headache)
Peters et al. 2004* [196]	Well reported	Well reported	Well reported	UK. Adults with migraine (± TTH and chronic daily headache)

** Same data set - reporting of different section of results analysis*

9.2.1 Common themes

Five themes were identified related to what information and support people with primary headaches wanted. These were identified from studies relating to migraine or primary headaches in general. The only data identified relating to cluster headaches is reported in the section following the fifth theme:

- Having a definite diagnosis
- Knowing the options for management
- Lack of understanding and support by healthcare professionals
- Impact of migraine not understood by non-sufferers
- Talking to other sufferers helped.

Some of these themes overlap.

Theme 1 – Having a definite diagnosis

The first theme describes patients' desire for a definitive diagnosis and/or an understanding of their condition. Five of the qualitative studies[14,102,172,175,195] addressed this theme and this is supplemented by data from two of the surveys[188,207]. Belam et al.[14] described this as 'Making sense of the problem'; patients needed to understand what was happening and to be able to place the problem into the context of their lives. Meyer[172] described this as 'Searching for a name'; women sought a diagnosis that explained the frequency and source of the severity of their headaches. Moloney's theme was [175] 'Looking for an answer'. In this study many women described worrying about whether their headaches related to such causes as a brain tumour, an aneurysm or other causes. Peters et al. [195] reported the diagnosis of headache types and the progressive nature of migraine during attacks and over the years. People in Henderson's study [102] described a desire for the 'recognition of migraine as a biological disorder'. All except two out of the 20 participants reflected a tendency to blame themselves for their headaches. Healthcare professionals and others in the community tended to reinforce this concept.

These data are supplemented with responses from two of the surveys[188,207]. In one of the studies[188] 46 out of 100 participants ranked 'Explanation of cause of pain' as their number one priority out of 12 options, and 77 out of 91 ranked it in the top three. This was the most popular factor. The second most popular factor was 'Pain relief', 31 out of 100 ranked this number 1 and 69 out of 91 ranked it in the top three. The other factors were: medication, explanation of medications (how it works and side effects), treatment other than medications, time to ask doctor questions, a psychiatric evaluation, a doctor willing to follow them for their headache, a complete neurological examination, skull x-rays, talking to other people in a group and a complete eye examination.

The second survey [207] asked adolescents and their mothers to choose 3 items from a list of 9 items what they wanted out of the consultation with a paediatrician for the adolescent's headache. 45 out of 100 adolescents and 62 out of 100 mothers selected 'Find out the causes of headache' and 60 out of 100 adolescents and 47 out of 100 mothers selected 'To be reassured it is not a serious condition'. The study also asked adolescents and their mothers to choose 3 items from a list of 10 items of what they wanted out of the consultation with a headache specialist for the adolescent's headache. 54 out of 100 adolescents and 82 out of 100 mothers selected 'Find out the causes of headache' and 54 out of 100 adolescents and 56 out of 100 mothers selected 'To be reassured it is not a serious condition'.

Theme 2 – Knowing the options for management

Five qualitative studies provided data for this theme (one reported in two papers)[5,14,102,172,195,196]. People expressed a desire to know the options and frustration when information was not available. Meyer[172] described patients using strategies to learn for themselves and from others. They sought information from experts, other people with migraine and the media. People saw this as 'Keeping on top' of the latest developments in treatment. Peters et al.[195,196] identified a similar theme describing knowledge about management strategies acquired through participants' own and other people's experiences through information gathering. As well as actively seeking and/or spontaneously receiving information and advice from other people (healthcare professionals, family and friends) and the media, they identified specialist migraine associations as a source of information.

Adelman et al.[5] provided data directly applicable to our questions. They reported that most people did not think they had the most current information about treating their migraine. The type of information they wished they had known earlier and think other migraine sufferers might find useful to know was most often related to medication. Thirty four percent (n=801) said they would like to have more information on medications, such as what new prescription medication was available and what worked best. Twenty percent felt seeing a physician for a diagnosis and/or treatment was important. Fourteen percent felt that information about other treatments was important, such as how bed rest in a dark room can help a migraine sufferer. Twelve percent believe information related to the cause of migraine is important to know, especially what can trigger a migraine and that migraine can be hereditary.

Henderson [102] reported that all 20 of their participants were frustrated by lack of adequate information and explanation about migraine and its treatment. They stressed there was no attention directed towards coping strategies designed to address the difficulties incurred in living with this disability. All expressed a desire to become more informed about their illness and its management. However, they found it difficult to locate sources of information. Healthcare professionals were described as giving no guidance or direction to sufferers.

Belam et al. [14] identified a theme of participants' advice to other sufferers to read up about their condition before they go to the doctor.

Two surveys provided data on this theme. Both asked what people want from a visit to the doctor. In Packard[188], 29 out of 91 participants ranked 'Explanation about medications (i.e. how it works and side effects)' in the top 3 out of 12 options, although only 3 out of 91 ranked it as the number 1 option. When asked what they wanted from prophylaxis medication in Rosen[215], participants rated the option 'Your physician takes time to explain about possible side effects with prophylactic medication' as 8.5 in importance on a scale of 1 (little importance) to 10 (extremely important), and the option 'You physician involves you in the decision of choosing a headache preventive mediation' as 8.7 in importance. These were the top 2 scores out of 10 options.

Theme 3 - Lack of understanding & support by healthcare professionals

Four qualitative studies reported this as a theme[14,102,175,196]. Belam et al.[14] identified that in many cases, people felt that GPs and other doctors did not take the condition seriously and that they were unhelpful. However, it also reported that talking with healthcare professionals with an interest in the subject was valuable. In Henderson [102] many complained of a lack of understanding and support by health professionals and felt that migraine was not viewed as a valid illness. According to the participants, the influence exerted by healthcare professionals was often experienced negatively. Participants perceived there was a general lack of knowledge and understanding of the biological disorder of migraine and its symptoms, but also the psychosocial and cultural aspects of this illness.

In Moloney et al. [175] healthcare providers received mixed reviews with regard to headache knowledge, treatment and empathy. Many women described caring physicians and nurses who had diagnosed their headaches and supported them, but most also remembered times when they either didn't receive an appropriate diagnosis or help, or when it was apparent that the provider was either too busy to listen to complaints about headaches, or who seemed to think that a headache was not important. Several participants said they suspected the most helpful providers were those who seemed to have migraines themselves.

Peters et al.[196] described that some participants had low expectations and questioned the GP's ability and interest to treat headaches, to the extent that they did not consult for headaches. Participants who had consulted a neurologist described higher expectations and often a preference for specialist consultations, though they were not necessarily more satisfied. Participants thought GP consultations mainly revolved around pharmacological treatments. Little attention was given to issues such as uncovering the causes of headaches, finding a cure and discussing the impact of headaches or non-pharmacological and alternative therapies. These were issues that the participants would have liked to discuss with their GPs. When issues other than medication were discussed, the participants were encouraged to return for further consultations, the GP was perceived as helpful and interested.

Theme 4 – Impact of migraine not understood by non-sufferers

This theme relates to employers, family and friends as well as healthcare professionals. Belam et al. [14] identified a recurring theme that migraine was not understood by non-sufferers. As mentioned previously, Henderson [102] reported a lack of understanding by healthcare professionals. Participants had the view that migraine was not considered a 'valid illness' by healthcare professionals. Moloney [175] reported a theme from their study as described by one person's view of their migraine as 'Having a dirty secret'. A few women in this study noted that they had never appreciated the severity of their mother's headaches, or how they resented how their mother's headache disrupted family and social activities, until they had migraines themselves. In addition to their own feeling of inadequacy about controlling their headaches, the attitude of others (co-workers, healthcare providers and sometimes family) reinforced the stereotype of a midlife woman with migraines being someone who has given in to a headache when she could control it if she had more will power, or of a woman who is using her headaches to avoid responsibilities.

Theme 5 – Talking to other sufferers helped

Two qualitative studies highlighted this theme. Belam et al.[14] reported a recurring theme of the value of talking to others, sharing experiences and exploring meaning. All participants found the opportunity of talking to healthcare professional with an interest in the subject valuable. Peters et al.[196] identified a similar theme. Having people to talk to about headaches, and particularly other people with headache, was considered enjoyable and interesting. Talking to people allowed participants to give and receive support and understanding and to exchange information and gain insights into other management strategies. Getting new information about headaches to better deal with them was considered important.

However, one survey provided supplementary data that appears to show contradictory information. In the survey by Packard[188], investigating what people wanted when seeing a doctor, no participant ranked talking to other people with headache in a group as one of their top 3 options from a list of 12.

9.2.2 Information and support for people with cluster headaches

Only one study was identified for cluster headaches[158]. Participants were asked what they would like to say to their doctor. One of the eight respondents reported a positive view of two helpful specialists. The other eight doctors seen did not treat the person the same way. The person resented the time spent with those doctors. One participant suggested that people take a family member with them to talk to the doctor. She reported that there is an emotional side to dealing with cluster headaches which can be a source of stress at home.

9.2.3 Economic evidence

No economic evidence on the provision of information to people with primary headache was identified.

9.3 Recommendations and link to evidence

Recommendations	**Include the following in discussions with the person with a headache disorder:** • **a positive diagnosis, including an explanation of the diagnosis and reassurance that other pathology has been excluded and** • **the options for management and** • **recognition that headache is a valid medical disorder that can have a significant impact on the person and their family or carers.**
Relative values of different outcomes	The outcomes used in this review were any reported in the papers. The GDG considered any reported opinions of information provision equally important.
Trade off between clinical benefits and harms	There are few, if any, harms from covering areas of likely concern in the consultation
Economic considerations	Providing people with relevant information is not considered to generate significant costs and could lead to a more efficient use of resources (for example people making the most efficient use of treatment) and to an improvement in the person's quality of life.
Quality of evidence	The qualitative studies were of adequate quality and common themes emerged from the studies. No economic evidence was available on this question.
Other considerations	The GDG recognised these are key areas that people value in their consultations. This list is not all inclusive, but a suggestion of the minimum areas that should be included in the discussion with the person.

Recommendations	**Give the person written and oral information about headache disorders, including information about support organisations.**
Relative values of different outcomes	The outcomes used in this review were any reported in the papers. The GDG considered any reported opinions of information provision equally important. This recommendation was based on this information and consensus opinion.
Trade off between clinical benefits and harms	There are few, if any, harms from providing appropriate information.
Economic considerations	Providing people with relevant information is not considered to generate significant costs and could lead to a more efficient use of resources (for example people making the most efficient use of treatment) and to an improvement in the person's quality of life.
Quality of evidence	No economic evidence was available on this question.
Other considerations	Alongside this guideline, a document titled Understanding NICE guidance will be produced. This will provide some information sources for people with headaches. The GDG noted that there are various sources of information available to people, which can be overwhelming and provide misleading information. It is therefore beneficial for the healthcare professional to recommend specific accredited resources.

Recommendations	**Explain the risk of medication overuse headache to people who are using acute treatments for their headache disorder.**
Relative values of different outcomes	This recommendation is based on GDG consensus.
Trade off between clinical benefits and harms	The GDG agreed that the risks of developing medication overuse headache should be explained to people when prescribing acute treatment tension type headache in order to minimise the risk of developing medication overuse headache.
Economic considerations	There might be some costs associated with the time spent by the health care professional in the provision of advice. The GDG considered the potential future cost savings associated with this intervention: less use of medication, fewer visits to health care professional, and they decided this recommendation would lead to health gains and potentially to a net decrease in costs.
Quality of evidence	This recommendation is based on GDG consensus.
Other considerations	Medication overuse headache can develop in people using paracetamol, aspirin or NSAIDs on 15 days per month or more, or opioids for 10 days per month or more (see recommendations for diagnosis, chapter 7). Informal consensus methods were used to form the recommendation.

10 Acute pharmacological treatment of tension type headache

10.1 Introduction

Tension type headache (TTH) is the most common form of headache in the general population. It is common at all ages from children to adults and is diagnosed largely by the lack of clinical symptoms seen in other headache disorders i.e. tension type headache is clinically 'featureless' rather than 'feature-full'. Tension type headache can be episodic or chronic.

In general terms the societal perception of tension type headache is of a reactive head pain disorder secondary to psychological stress. The exact cause and pathophysiological mechanisms underlying pain in TTH is in fact debated. Proposed hypotheses for pain production in TTH include abnormal peripheral pain receptor (nociceptive) functioning from cranial myofascial tissues; abnormal central brain modulatory mechanisms involving both limbic and cortical brain areas that affect stress coping mechanisms coupled with a dysfunctional ability to modulate ascending and descending pain processing pathways and cranial pain sensitisation.

Whilst the exact underlying pathophysiological mechanism for TTH is debated, there is more certainty that increased muscular activity within the scalp i.e. muscle contraction, or indeed muscle inflammation or disturbed metabolism of the scalp muscles is involved.

The lifetime risk of ever suffering episodic tension type headache is about 70-80%. By contrast, the lifetime risk of chronic tension type headache is about 3%. The prevalence of tension type headache appears to vary with age. Prevalence studies of children estimate about 30% (10-72%) are affected at some time[245]. In adults, TTH prevalence seems higher in women than men and a cross-sectional population prevalence study of adults age 40 years identified an episodic TTH population prevalence of nearly 50% compared with just over 2% suffering chronic TTH[86]. Genetic epidemiological studies including twin studies of chronic TTH have suggested an increased genetic risk that likely affects susceptibility for developing TTH.

It is uncommon for episodic TTH sufferers to be seen in secondary care in the UK and it is important to recognise that episodic TTH does not cause significant functional day to day impairment. In fact such individuals usually treat themselves with over the counter analgesics. By comparison, chronic TTH is a more common cause of health impairment with secondary socioeconomic consequences. However, there is a significant overlap between chronic TTH and chronic migraine, and frequently migrainous features are present which suggests a diagnosis of chronic migraine.

The acute treatment of TTH depends not only on an individual's tolerance of pain but also, in part, on the situational context of a TTH attack in addition to the impact of symptoms on day to day functioning. As most individuals may not consult a medical professional and thus use over the counter drugs, it is important to realise what evidence based treatments are available so as to maximise treatment effectiveness as well as minimise any complications from treatment.

The acute treatments that have been advocated for TTH include pharmacological therapies and non-pharmacological therapies e.g. psychological and behavioural therapies, manipulative and physical therapies and complementary therapies.

When deciding to use pharmacological therapies it is important to recognise which type of pharmacological treatment to use, what dose to take and which drugs have evidence for effectiveness in the treatment of acute TTH. Equally it is important for TTH sufferers to realise that overuse of over the counter analgesics can equally transform frequent TTH into medication overuse headache problem. (See diagnosis of medication overuse headache, section 7.1.2, and management section 23.2).

10.1.1 Clinical question

In people with tension type headache, what is the clinical and cost-effectiveness of acute pharmacological treatment with aspirin, NSAIDs, opioids and, paracetamol?

A literature search was conducted for RCTs comparing the clinical effectiveness of different pharmacological interventions for acute treatment of tension type headache. The interventions we included in our search were aspirin, paracetamol, NSAIDs, opioids (weak and strong), and placebo. We looked for any studies that compared the effectiveness of two or more of these treatments (or placebo) (See review protocol in appendix section C.2.2).

When reporting results, available case analysis has been used wherever possible. If it was not possible to determine available case from the data provided by the study, the analysis used is described below. In some studies people were randomised and then only included in the analysis if they suffered from, and treated, a headache attack in the study period. In these cases, the number of people who suffered an attack has been considered as the total number of people for the results.

Randomised crossover studies were included in this, only data from the first intervention people were exposed to were included in the review, unless it was clear that all participants received, and had data from all treatments.

One Cochrane review was identified on the use of dipyrone for the acute treatment of primary headaches but was excluded as the drug is not available in the United Kingdom due to concerns regarding safety and was therefore not a part of this review's protocol[208].

10.2 Matrix of treatment comparisons

Below is a matrix showing where evidence was identified. A box filled with a number represents how many studies were found for that comparison and are reviewed in this chapter. This box will also state the number of studies found. A box filled with - represents where no evidence was found. In this case, no section on this comparison is included in the chapter. The GDG were also interested in the use of opioids for the treatment of tension type headaches but no evidence was identified and therefore there is no section in the chapter.

Paracetamol	2				
NSAIDS	-	6			
Paracetamol + codeine	-	-	-		
Opioids	-	-	-	-	
Placebo	2	8	10	1	-
	Aspirin	**Paracetamol**	**NSAIDS**	**Paracetamol + codeine**	**Opioids**

10.2.1 NSAIDs vs placebo

10.2.1.1 Clinical evidence

See evidence tables in appendix section E.2.2 and forest plots in Figure 20, Appendix G.2.1.

Ten studies were included in this review[47,52,131,169,189,201,205,218,219,239]. One study included people aged 12 years and over[189]. All others were an adult population. The NSAIDs in the included studies were ibuprofen, ketoprofen, naproxen sodium and diclofenac. Doses varied considerably between studies. These were pooled for analysis and only analysed as a subgroup if heterogeneity was present (see protocol, appendix C.2.2).

'Time to freedom from pain' was one of the outcomes in the review protocol for which no evidence was identified. However, the included studies did provide information on 'time to meaningful pain relief'. The GDG discussed this and agreed that the measures provided very similar information and that time to meaningful pain relief could be used as a surrogate outcome for time to freedom from pain.

Headache response at two hours was more commonly reported as pain free at two hours. The GDG agreed this was appropriate to record in the absence of headache response data.

Table 31: NSAIDs vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at 2 hours[47,131,205,239]	4	Randomised trials	Very serious[(a)]	Serious[(b)]	No serious indirectness	Serious [(c)]
Time to meaningful pain relief[52,169,189,205]	4	Randomised trials	Very serious[(a)]	N/A[(d)]	No serious indirectness	N/A[(d)]
Incidence of serious adverse events[52,131,169,201,205,218,219,239]	8	Randomised trials	Very serious[(a)]	N/A[(d)]	No serious indirectness	N/A[(d)]
Headache response at up to 2 hours	0	-	-	-	-	-
Freedom from pain 24 hours after treatment	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-

(a) Unclear randomisation and allocation concealment in all studies; small sample size and unclear blinding of participants and investigators in two studies; difference in baseline characteristics in one study.
(b) Heterogeneity present which was unexplained by different dosages of drugs.
(c) The confidence interval crosses the minimal important difference making the effect size uncertain.
(d) Data could not be meta-analysed as effect sizes were reported in ranges only.
N/A=not applicable.

Table 32: NSAIDs vs placebo – Clinical summary of findings

Outcome	NSAID	Placebo	Relative risk	Absolute effect	Quality
Pain free at 2 hours	235/922 (25.5%)	113/595 (19%)	RR 1.66 (1.13 to 2.44)	125 more per 1000 (from 25 more to 273 more)	VERY LOW
Time to meaningful pain relief	39 -161 min (range)	85 -279 min (range)	N/A*	N/A	VERY LOW
Incidence of serious adverse events	0% -4.7% (range)	0%- 22.5% (range)	N/A*	N/A	VERY LOW

**Data could not be pooled to calculate relative risks.*
N/A=not applicable.

10.2.1.2 Economic evidence

No relevant economic evaluations comparing NSAIDs with placebo were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 33 below).

Table 33: Unit cost of drugs

Drug	Cost per episode (£)	Notes
Aspirin	0.02	Dose: 2*300 mg
Paracetamol	0.02	Dose: 2*500 mg
Paracetamol + codeine	0.01 to 0.08	Dose: 8/500 mg – 15/500 mg – 30/500 mg
NSAID – ibuprofen	0.02	Dose: 400 mg
NSAID – naproxen	0.06	Dose: 500 mg
Opioids - codeine phosphate	0.09	Dose 2 * 30 mg

Source: BNF62[111]

The costs of adverse effects and further events were not estimated.

10.2.1.3 Evidence statements

Clinical:

Four studies with 1580 people with tension type headache suggested that NSAIDs are more clinically effective than placebo in producing freedom from pain at 2 hours, but there is some uncertainty. [Very low quality].

Four studies with 1532 people with tension type headache showed that the range of values for time to meaningful pain relief were lower for NSAIDs than placebo, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

Eight studies with 2653 people with tension type headache showed that the range for the incidence of serious adverse events across studies was lower for NSAIDs than placebo, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

No studies reported outcome data for time to freedom from pain, headache response at up to 2 hours, headache response at 24 hours, freedom from pain at 24 hours or functional health outcomes.

Economic:

No economic evidence was found for this question. A simple cost analysis showed the cost of NSAIDs is between £0.02 and £0.06 per episode.

10.2.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 10.3.

10.2.2 NSAIDs vs paracetamol

10.2.2.1 Clinical evidence

See evidence tables in appendix section E.2.2 and forest plots in Figure 21, Appendix G.2.1.

Six studies were included in this review[47,169,189,201,205,239]. Paracetamol doses considered were 500 mg and 1000 mg. NSAID doses varied from 12.5mg to 550mg, and included ketoprofen, ibuprofen and naproxen sodium. These were pooled for analysis. Heterogeneity was observed for the outcome on freedom from pain at 2 hours. This remained unexplained even when a subgroup analysis by dose was carried out (see forest plots in appendix G.2.1.2).

Table 34: NSAIDs versus paracetamol – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at 2 hours[47,205,239]	3	Randomised trials	Very serious [(a)]	Serious [(b)]	No serious indirectness	No serious imprecision
Time to meaningful pain relief[169,189,205]	4	Randomised trials	Very serious [(a)]	N/A [(c)]	No serious indirectness	N/A [(c)]
Incidence of serious adverse events[169,201,205,240]	4	Randomised trials	Very serious [(a)]	N/A [(c)]	No serious indirectness	N/A [(c)]
Headache response at up to 2 hours	0	-	-	-	-	-
Freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-

(a) Unclear randomisation and allocation concealment in all studies; blinding of participants and investigators unclear in two studies and difference in baseline characteristics in one study; reasons for loss to follow up not provided.
(b) Heterogeneity present which was unexplained by different dosages of drugs used.
(c) Data could not be meta-analysed as effect sizes were reported in ranges only.
N/A=not applicable.

Table 35: NSAIDs versus paracetamol – Clinical summary of findings

Outcome	NSAID	Paracetamol	Relative risk	Absolute effect	Quality
Pain free at 2 hours	138/455 (30.3%)	147/478 (30.8%)	RR 1.12 (0.81 to 1.19)	37 more per 1000 (from 58 fewer to 58 more)	VERY LOW
Time to meaningful pain relief	39-138.5 min (range)	53- 131.5 min (range)	N/A*	N/A*	VERY LOW
Incidence of serious adverse events	0%-2.3% (range)	0%- 1.3% (range)	N/A*	N/A*	VERY LOW

** Data could not be pooled to calculate relative risks.*
N/A=not applicable.

10.2.2.2 Economic evidence

No relevant economic evaluations comparing NSAIDs with paracetamol were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 33 in section 10.2.1.2).

10.2.2.3 Evidence statements

Clinical:

Three studies with 903 people with tension type headache showed that there is no difference between NSAIDs and paracetamol in producing freedom from pain at 2 hours. [Very low quality].

Three studies with 1244 people with tension type headache showed that the range of values for time to meaningful pain relief were slightly lower for NSAIDs than paracetamol , but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

Four studies with 1363 people with tension type headache showed that the range for the incidence of serious adverse events across studies was slightly lower with paracetamol than NSAIDs, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

No studies reported outcome data for time to freedom from pain, headache response at up to 2 hours, headache response at 24 hours, freedom from pain at 24 hours or functional health outcomes.

Economic:

No economic evidence was found for this question. A simple cost analysis showed no difference in drug costs between paracetamol and some NSAIDs such as ibuprofen while there is some difference with other NSAIDs such as naproxen.

10.2.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 10.3.

10.2.3 Aspirin vs placebo

10.2.3.1 Clinical evidence

See evidence tables in appendix section E.2.2 and forest plots in Figure 22, Appendix G.2.1.

Two studies were included in this review [59,240]. The doses of aspirin considered in the studies were 500 and 1000mg. These were pooled for analysis. Both studies were in people with episodic TTH. Steiner et al.[240] included a population aged 16 years and over. The data from Diener et al. 2005[59] could not be pooled for meta-analysis.

Table 36: Aspirin vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at 2 hours[240]	1	Randomised trials	Very serious(a)	No serious inconsistency	No serious indirectness	No serious imprecision
Incidence of serious adverse events[240]	1	Randomised trials	Very serious(a)	N/A(b)	No serious indirectness	N/A(b)
Time to freedom from pain / meaningful pain relief	0	-	-	-	-	-
Headache response at up to 2 hours	0	-	-	-	-	-
Freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-

(a) Unclear randomisation and allocation concealment; blinding of participants and investigators unclear.
(b) Data could not be meta-analysed as effect sizes reported in ranges only.
N/A=not applicable.

Table 37: Aspirin vs placebo – Clinical summary of findings

Outcome	Aspirin	Placebo	Relative risk	Absolute effect	Quality
Pain free at 2 hours	156/214 (72.9%)	49/112 (43.8%)	RR 1.67 (1.33 to 2.09)	293 more per 1000 (from 144 more to 477 more)	LOW
Incidence of serious adverse events	0%	0%	N/A	N/A	VERY LOW

NB. Raw data for incidence of adverse events could not be pooled to calculate relative risks.
N/A=not applicable.

10.2.3.2 Economic evidence

No relevant economic evaluations comparing aspirin with placebo were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 33 in section 10.2.1.2).

10.2.3.3 Evidence statements

Clinical:

One study with 380 people with tension type headache showed that aspirin is more clinically effective than placebo in producing freedom from pain at 2 hours. [Low quality].

One study with 380 people with tension type headache showed that there is no difference in the incidence of adverse events between people treated with aspirin or placebo. [Very low quality].

No studies reported outcome data for time to freedom from pain, headache response at up to 2 hours, headache response at 24 hours, freedom from pain at 24 hours or functional health outcomes.

Economic:

No economic evidence was found for this question. A simple cost analysis showed the cost of aspirin is on average £0.02 per episode.

10.2.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 10.3.

10.2.4 Aspirin vs paracetamol

10.2.4.1 Clinical evidence

See evidence tables in appendix section E.2.2 and forest plots in Figure 23, Appendix G.2.1.

Two studies were included in this review [59,240]. The doses of aspirin considered in the studies were 500 and 1000mg. These were pooled for analysis. Both studies were in people with episodic TTH. Steiner et al.[240] included a population aged 16 years and over. The data from Diener et al. 2005[59] could not be pooled for meta-analysis.

Table 38: Aspirin vs paracetamol– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at 2 hours[240]	1	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Incidence of serious adverse events[59,240]	2	Randomised trials	Very serious [(a)]	N/A [(b)]	No serious indirectness	N/A [(b)]
Time to freedom from pain / meaningful pain relief	0	-	-	-	-	-
Headache response at up to 2 hours	0	-	-	-	-	-
Freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-

(a) Unclear randomisation and allocation concealment; blinding of participants and investigators was unclear.
(b) Data could not be meta-analysed as effect sizes reported in ranges only.
N/A=not applicable.

Table 39: Aspirin vs paracetamol – Clinical summary of findings

Outcome	Aspirin	Paracetamol	Relative risk	Absolute effect	Quality
Pain free at 2 hours	156/214 (72.9%)	146/216 (67.6%)	RR 1.08 (0.95 to 1.22)	54 more per 1000 (from 34 fewer to 149 more)	LOW
Incidence of serious adverse events	0%	0%-0.39% (range)	N/A	N/A	VERY LOW

NB. Raw data for incidence of adverse events could not be pooled to calculate relative risks.
N/A=not applicable.

10.2.4.2 Economic evidence

No relevant economic evaluations comparing aspirin with paracetamol were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 33 in section 10.2.1.2).

10.2.4.3 Evidence statements

Clinical:

One study with 380 people with tension type headache showed that there is no difference between aspirin and paracetamol in producing freedom from pain at 2 hours. [Low quality].

Two studies study with 1088 people with tension type headache suggested that the range of values for incidence of serious adverse events was lower for aspirin than paracetamol, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

No studies reported outcome data for time to freedom from pain, headache response at up to 2 hours, headache response at 24 hours, freedom from pain at 24 hours or functional health outcomes.

Economic:

No economic evidence was found for this question. A simple cost analysis showed no difference in drug costs between aspirin and paracetamol.

10.2.4.4 Recommendations and link to evidence

See recommendations and link to evidence in section 10.3.

10.2.5 Paracetamol vs placebo

10.2.5.1 Clinical evidence

See Evidence tables in appendix section E.2.2 and Forest Plots in Figure 24, Appendix G.2.1.

Eight studies were included in this review[47,59,169,189,201,205,239,240]. The dose of paracetamol was either 500 mg or 1000mg. Doses were pooled for analysis. One study included people aged 12 years and over[189] and another included those aged 16 and over[240], all others were in adult populations.

Table 40: Paracetamol vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at 2 hours[47,205,239,240]	4	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Time to meaningful pain relief[169,189,205]	3	Randomised trials	Very serious [(a)]	N/A [(c)]	No serious indirectness	N/A [(c)]
Incidence of serious adverse events[59,169,201,205,239,240]	5	Randomised trials	Very serious [(a)]	N/A [(c)]	No serious indirectness	N/A [(c)]
Headache response at up	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
to 2 hours						
Freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-

(a) Unclear randomisation in 3 studies; unclear allocation concealment in all studies; blinding of participants and investigators was unclear in all studies; reasons for loss to follow up not provided in 2 studies.
(b) Confidence interval crosses the line of minimally important difference making the effect size uncertain.
(c) Data could not be meta-analysed as effect sizes reported in ranges only.
N/A=not applicable.

Table 41: Paracetamol vs placebo – Clinical summary of findings

Outcome	Paracetamol	Placebo	Relative risk	Absolute effect	Quality
Pain free at 2 hours	293/694 (42.2%)	150/554 (27.1%)	RR 1.44 (1.23 to 1.69)	119 more per 1000 (from 62 more to 187 more)	VERY LOW
Time to meaningful pain relief	53-131.5 min (range)	85- >180 min (range)	N/A*	N/A*	VERY LOW
Incidence of serious adverse events	0%-1.3%	0%-5.8% (range)	N/A*	N/A*	VERY LOW

** Data could not be pooled to calculate relative risks.*
N/A=not applicable.

10.2.5.2 Economic evidence

No relevant economic evaluations comparing paracetamol with placebo were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 33 in section 10.2.1.2).

10.2.5.3 Evidence statements

Clinical:

Four studies with 1294 people with tension type headache suggested that paracetamol may be more clinically effective than placebo in producing freedom from pain at 2 hours, but there is some uncertainty. [Very low quality].

Three studies with 1053 people with tension type headache showed that the range of values for time to meaningful pain relief were shorter for paracetamol than placebo , but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

Six studies with 2107 people with tension type headache showed that the range of values for the incidence of serious adverse events was slightly lower for paracetamol than placebo, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

No studies reported outcome data for time to freedom from pain, headache response at up to 2 hours, headache response at 24 hours, freedom from pain at 24 hours or functional health outcomes.

Economic: No economic evidence was found for this question. A simple cost analysis showed the cost of paracetamol is on average £0.02 per episode.

10.2.5.4 Recommendations and link to evidence

See recommendations and link to evidence in section 10.3.

10.2.6 Paracetamol with codeine vs placebo

10.2.6.1 Clinical evidence

See evidence tables in appendix section E.2.2 and forest plots in Figure 25, Appendix G.2.1.

One study was included in this review[84]. The dose of paracetamol and codeine that was used was not stated.

Table 42: Paracetamol with codeine vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at 2 hours[84]	1	Randomised trials	Very serious[(a)]	No serious inconsistency	No serious indirectness	Serious imprecision[(b)]
Time to freedom from pain	0	-	-	-	-	-
Headache response at up to 2 hours	0	-	-	-	-	-
Freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Incidence of adverse events	0	-	-	-	-	-

(a) Unclear randomisation and allocation concealment; blinding of participants and investigators unclear
(b) Confidence interval crosses the minimally important difference making the effect size uncertain.

Table 43: Paracetamol with codeine vs placebo – Clinical summary of findings

Outcome	Paracetamol + codeine	Placebo	Relative risk	Absolute effect	Quality
Pain free at 2 hours	16/65 (24.6%)	8/67 (11.9%)	RR 2.06 (0.95 to 4.48)	127 more per 1000 (from 6 fewer to 416 more)	VERY LOW

10.2.6.2 Economic evidence

No relevant economic evaluations comparing paracetamol with codeine with placebo were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 33 in section 10.2.1.2).

10.2.6.3 Evidence statements

Clinical:

One study with 132 people with tension type headache suggested that paracetamol with codeine may be more clinically effective than placebo in producing freedom from pain at 2 hours, but there is some uncertainty. [Very low quality].

No studies reported outcome data for time to freedom from pain, headache response at up to 2 hours, headache response at 24 hours, freedom from pain at 24 hours, functional health outcomes, or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed the cost of paracetamol with codeine is between £0.01 and £0.08 per episode depending on the strength of the preparation (8/500mg, 15/500 mg or 30/500 mg) where the most expensive non-proprietary preparation is co-codamol 15/500.

10.3 Recommendations and link to evidence

Recommendations	**Consider aspirin[y], paracetamol or an NSAID for the acute treatment of tension-type headache, taking into account the person's preference, comorbidities and risks of adverse events.**
Relative values of different outcomes	The GDG agreed that pain free at 2 hours was the most important outcome.
Trade off between clinical benefits and harms	Although there may be modest benefits only, the side effects in paracetamol are small when taken in the correct dose. The risk of adverse effects of NSAIDs and aspirin should be considered. Aspirin should not be given to young people under 16 years because of the risk of Reyes syndrome.
Economic considerations	No economic evidence was identified. Based on the acquisition costs, there is a small cost difference between some NSAIDs and aspirin or paracetamol and no cost difference between aspirin and paracetamol.
Quality of evidence	This recommendation is based on low quality evidence for freedom from pain at 2 hours.

[y] Because of an association with Reye's syndrome, preparations containing aspirin should not be offered to people aged under 16 years.

	The economic evidence was based on a limited cost analysis based only on the drug acquisition costs.
Other considerations	The studies included in the review were of a wide range of doses for NSAIDs, varying by drug. Doses of aspirin were 500mg and 1000mg. These doses were pooled for analysis. The GDG considered that dose of treatment should be titrated to effect on headache and did not consider it necessary to make a specific recommendation on dose to medication to use. The healthcare professional treating the person should be aware of the possible overlap with migraine and consider the possibility of low-grade migraine as a diagnosis.

Recommendations	**Do not offer opioids for the acute treatment of tension-type headache.**
Relative values of different outcomes	The GDG agreed that pain free at 2 hours was the most important outcome.
Trade off between clinical benefits and harms	There is no evidence for the effectiveness of opioids in the acute treatment of tension type headache. GDG informal consensus agreed that there are considerable recognised side effects of opioids including an increased risk of medication overuse headache and therefore their use should not be recommended.
Economic considerations	No economic evidence was identified. Based on the acquisition costs, opioids are slightly more expensive than aspirin, paracetamol and NSAIDs. In the absence of evidence of their effectiveness in the acute treatment of tension type headache, the GDG decided they would not constitute an optimal use of NHS resources.
Quality of evidence	There was no evidence identified for the effectiveness of this evidence, the recommendation is based on the absence of evidence and GDG informal consensus. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs.
Other considerations	People should be informed that there is no evidence for the benefit of opioids in acute tension type headache, and there is increased risk of medication overuse headache compared to other painkillers. The GDG considered this risk justified advising people not to use opioids for the treatment of tension type headache. Informal consensus methods were used to form the recommendation.

11 Acute pharmacological treatment of migraine with or without aura

11.1 Introduction

Migraine is common and imposes a substantial burden on the sufferer. The one year period prevalence of migraine in the UK is around 18% of women and 8% of men. On any given day, 190,000 people in the UK have a migraine attack. Furthermore, 25 million days a year are lost from school or work because of migraine.

Migraines can be triggered by a number of internal and external factors. Internal triggers include the menstrual cycle in women, altered sleep and rest patterns, the 'after stress' period or anticipation of an event. Common external triggers are certain food, strong smells, bright light, exercise or inadequate hydration. The aim of acute treatment once an attack has started is to allow rapid but also sustained symptom alleviation.

Acute treatment includes using medicines which act on the different pathways involved in the disorder. The most common medications used for alleviating pain are non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen). NSAIDs exert their anti-inflammatory and analgesic effect by blocking the enzymes that synthesise prostaglandins (COX-1 and COX-2). The mechanism of action of paracetamol is unclear. Initial evidence indicates that it may have some effect on synthesis of endocannibinoids has now been disputed. Nausea in migraine can be treated with anti-emetics/prokinetics and neuroleptic drugs. These antagonise dopamine receptors and act on serotonin receptors. They should be taken at the onset of an attack and it is their varied selectivity for the different receptors which enables these medicines to relieve nausea and vomiting as well as helping to relieve pain in migraine attacks. At the same time, this varied selectivity is also responsible for their differing side effect profiles. The intermittent use of these drugs for acute attacks is thought to be safe and well tolerated.

Triptans are selective agonists at the 5-hydroxytriptamine 1B and 1D receptors. They have a direct effect on sensory neurons reducing neurogenic inflammation and release of vasoactive compounds such as substance-P and Calcitonin Gene Related Protein (CGRP). This leads to a reduction in intracranial vasodilation. There are currently seven drugs within this family licensed for alleviating migraine. They differ in their drug interaction, duration of action and side-effects.

11.1.1 Clinical question

In people with migraine with or without aura, what is the clinical and cost-effectiveness of acute pharmacological treatment with: antiemetics; aspirin; NSAIDs; opioids; paracetamol; triptans; ergots and corticosteroids.

A literature search was conducted for RCTs comparing the clinical effectiveness of different pharmacological interventions for acute migraine. The interventions we included in our search were antiemetics, aspirin, NSAIDs, opioids (weak and strong), paracetamol, triptans, ergots (ergotamine / dihydroergotamine) and corticosteroids. We looked for any studies that compared the effectiveness of two or more of these treatments (or any combinations). We did not include placebo controlled studies since the GDG agreed it was unlikely that people living with migraine would consider no treatment during an acute attack as an option (see protocol C.2.3).The GDG agreed that drugs administered by a clinician should not be directly or indirectly compared to those administered by the individual concerned. Therefore after the evidence was reviewed, it was separated into those administered by healthcare professionals as intravenous, intramuscular or subcutaneous preparations in one meta-analysis, and those potentially self-administered, as oral, nasal or subcutaneous injections, in the second review. Subcutaneous preparations are covered in both sections as they can be self-administered, and they may be used when a migraine sufferer presents at hospital or secondary care for treatment.

When reporting results, available case analysis has been used wherever possible. If it was not possible to determine available case from the data provided by the study, the analysis used is described below. In some studies people were randomised and then only included in the analysis if they suffered from, and treated, a headache attack in the study period. In these cases, the number of people who suffered an attack has been considered as the total number of participants for the results.

Four Cochrane reviews were identified on use of different drugs for the acute treatment of migraine but were excluded as they included trials with a minimum sample size of ten participants per arm, lower than the agreed 25 per arm stated in the protocol for this review (see appendix C.2.3). Any studies included in the review which were relevant to our protocol were identified and included. The reviews evaluated the effectiveness of effectiveness of paracetamol with or without an antiemetic[50], use of oral sumatriptan[167], use of ibuprofen with or without an antiemetic[206] and the use of aspirin with or without an antiemetic for the acute treatment of migraine headaches respectively[126].

One Cochrane review on the use of dipyrone for the acute treatment of primary headaches was identified but was excluded as the drug is not available in the United Kingdom due to concerns regarding safety and was therefore not a part of this review's protocol[208].

11.2 Oral, nasal and self administered subcutaneous treatments

11.2.1 Matrix of treatment comparisons

Below is a matrix showing where clinical evidence was identified for treatments administered as oral, nasal or subcutaneous preparations administered by the individual concerned themselves. Where a box has - studies no evidence was available and the comparison is not discussed further in this chapter.

All routes of administration were oral, unless otherwise stated.

Although most studies only included people in their analyses if they had a migraine attack, very few people did not have an attack. For randomised crossover studies, only data from the first intervention people were exposed to were included in the review, unless it was clear that all participants received, and had data from all treatments.

Paracetamol (PARA)	-								
Antiemetics (AE)	-	-							
Ergots	-	-	-						
NSAIDs	1	1	1	-					
Opioids (OP)	-	-	-	-	-				
Triptans	2	1	-	7	8	-			
Corticosteriod (Steroid)	-	-	-	-	-	-	1		
Combinations (COMB)	1	1	-	1	4	-	12	1	-
	Aspirin	**PARA**	**AE**	**Ergot**	**NSAID**	**OP**	**Triptan**	**Steroid**	**COMB**

This chapter contains three sections:

1. Direct comparisons of treatments from identified trials (starting in 11.2.2)
2. Network meta-analysis comparing all treatments to each other (section 11.4,full details in appendix I)
3. Economic model(section 11.5).

11.2.2 Aspirin vs NSAID

11.2.2.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 26-27, Appendix G.2.2.

One study[54] was identified comparing aspirin (1000mg) with ibuprofen (400mg).

Table 44: Aspirin vs NSAID – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[54]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Pain free at up to 2 hours[54]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Sustained headache response at 24 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Unclear randomisation and allocation concealment; unclear whether both groups received same care; unclear drop outs and missing outcome data.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 45: Aspirin vs NSAID – Clinical summary of findings

Outcome	Aspirin	NSAID	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	116/221 (52.5%)	127/221 (57.5%)	RR 0.91 (0.77 to 1.08)	52 fewer per 1000 (from 132 fewer to 46 more)	LOW
Pain free at up to 2 hours	60/221 (27.1%)	79/221 (35.7%)	RR 0.76 (0.57 to 1)	86 fewer per 1000 (from 154 fewer to 0 more)	VERY LOW

11.2.2.2 Economic evidence

No economic evaluations comparing aspirin with NSAIDs were identified. Aspirin was not included in our cost-effectiveness analysis (see section 11.5) as we had no clinical evidence on its effectiveness at 24 hours.

We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 46 below).

Table 46: Unit cost of drugs

Drug	Cost per episode (£)	Notes
Aspirin	0.02	Dose: 2*300 mg
Paracetamol	0.02	Dose: 2*500 mg
NSAID – ibuprofen	0.02	Dose: 400 mg
NSAID – naproxen	0.06	Dose: 500 mg
NSAID – aceclofenac	0.17	Dose: 100 mg
NSAID – tolfenamic acid	1.65	Dose: 200 mg
Opioids - codeine phosphate	0.09	Dose 2 * 30 mg
Triptans – sumatriptan	0.21	Dose: 50 mg
Triptans (Rizatriptan) – Maxalt	4.46	Dose: 10 mg
Nasal triptans – sumatriptan	5.90	Dose: 10 mg (1 unit)
Subcutaneous triptans – sumatriptan	21.24	1 syringe
Ergot - methysergide (Deseril)	0.22	Dose: 1 mg
Ergotamine + caffeine (Cafergot)	0.33	2 tablets
Antiemetics – metoclopramide	0.04	Dose: 10 mg
Antiemetics – domperidone	0.07	Dose: 2 * 10 mg
Paracetamol + antiemetic (Paramax)	0.46	2 tablets (paracetamol 500 mg + metoclopramide 5 mg/tablet)
Aspirin + antiemetic (Migramax)	1.05	1 sachet (aspirin 900mg, metoclopramide 10mg/sachet)

Source: BNF62[111]

The costs of adverse effects and further events were not estimated.

Some preparations are not included in the BNF62 (oral and nasal dihydroergotamine) and we could not report their costs.

11.2.2.3 Evidence statements

Clinical:

One study with 454 people with migraine showed that there is no difference between aspirin and NSAIDs in producing headache response at up to 2 hours. [Low quality].

One study with 454 people with migraine suggested that NSAIDS may be more clinically effective than aspirin in producing freedom from pain at up to 2 hours, but there is some uncertainty. [Very low quality].

No studies reported outcome data for sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed no difference in drug costs between aspirin and some NSAIDs such as ibuprofen while there is some difference with other NSAIDs such as tolfenamic acid. NSAIDs are on average more costly than aspirin but the cost difference varies with the NSAID product considered (£0.02 to £1.65 vs £0.02 per episode).

11.2.3 Aspirin vs triptan

11.2.3.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 28-29, Appendix G.2.2.

Two studies were identified comparing aspirin (1000mg) with triptans (Sumatriptan 50mg)[54,55].

Table 47: Aspirin vs triptan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[54,55]	2	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Pain free at up to 2 hours[54,55]	2	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Sustained headache response at 24 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Unclear drop outs and missing outcome data.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 48: Aspirin vs triptan – Clinical summary of findings

Outcome	Aspirin	Triptan	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	188/367 (51.2%)	190/359 (52.9%)	RR 0.97 (0.84 to 1.11)	16 fewer per 1000 (from 85 fewer to 58 more)	MODERATE
Pain free at up to 2 hours	97/367 (26.4%)	116/359 (32.3%)	RR 0.84 (0.6 to 1.18)	52 fewer per 1000 (from 129 fewer to 58 more)	LOW

11.2.3.2 Economic evidence

No relevant economic evaluations comparing aspirin with triptans were identified. Aspirin was not included in our cost-effectiveness analysis (see section 11.5) as we had no evidence on its clinical effectiveness at 24 hours.

We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 46 in section 11.2.2.2).

11.2.3.3 Evidence statements

Clinical:

Two studies with 729 people with migraine showed that there was no difference between aspirin and triptans in producing headache response at up to 2 hours. [Moderate quality].

Two studies with 729 people with migraine suggested that triptans may be more clinically effective than aspirin in producing freedom from pain at up to 2 hours, but there is some uncertainty. [Low quality].

No studies reported outcome data for sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a difference in drug costs between triptans and aspirin. Triptans are more costly than aspirin (respectively £0.21 to £21.24 and £0.02 per episode).

11.2.4 Ergot vs triptan

11.2.4.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 30-33, Appendix G.2.2.

Four studies were identified[57,133,254,269]; one comparing subcutaneous dihydroergotamine (1mg) with subcutaneous sumatriptan (6mg); one nasal dihydroergotamine (1mg) with subcutaneous sumatriptan (6mg), one oral cafergot (ergotamine (2mg) plus caffeine (200mg)) with almotriptan (12.5mg) and the last compared oral cafergot (ergotamine tartrate (2mg) plus caffeine(200mg)) with eletriptan (80mg or 40mg). Touchon et al[254] was a randomised crossover trial, the data reported for this includes all participants who treated 2 attacks.

Table 49: Ergot vs triptan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[57,133,269]	3	Randomised trials	Very serious (a)	Very serious (b)	No serious indirectness	Serious (c)
Pain free at up to 2 hours[57,133]	2	Randomised trials	Very serious (d)	Very serious (e)	No serious indirectness	Serious (c)
Sustained headache response at 24 hours[57,254]	2	Randomised trials	Very serious (f)	No serious inconsistency	No serious indirectness	Serious (c)
Sustained pain free at 24 hours[57,133]	2	Randomised trials	Very serious (a)	Serious (g)	No serious indirectness	No serious imprecision
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Unclear randomisation and allocation concealment in two studies, unclear whether groups were comparable at baseline in one study; in 1 study the administering nurse was not blinded to treatment and it is unclear if the investigators of the outcomes were blinded to treatment; unclear drop outs in one study, missing data not reported or unclear in two studies; unclear length of follow-up and investigator blinding in one study.
(b) There is significant statistical unexplained heterogeneity between the studies (I^2=88%, p=0.0002).
(c) The confidence interval crosses one minimal important difference making the effect size uncertain.
(d) Unclear randomisation and allocation concealment in one study, unclear whether groups were comparable at baseline in one study; in 1 study the administering nurse was not blinded to treatment and it is unclear if the investigators of the outcomes were blinded to treatment; unclear drop outs in one study, missing data unclear in one study; unclear length of follow-up and investigator blinding in one study, unclear whether outcome measurement valid and reliable in one study.
(e) There is significant statistical unexplained heterogeneity between the studies (I^2=82%, p=0.02).
(f) Unclear randomisation and allocation concealment in one study; drop outs unclear and missing data not reported in one study; unclear length of follow-up and investigator blinding in one study.
(g) There is significant statistical unexplained heterogeneity between the studies (I^2=60%, p=0.12).

Table 50: Ergot vs triptan – Clinical summary of findings

Outcome	Ergot	Triptan	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	256/524 (48.9%)	486/747 (65.1%)	RR 0.73 (0.54 to 0.98)	176 fewer per 1000 (from 13 fewer to 299 fewer)	VERY LOW
Pain free at up to 2 hours	45/379 (11.9%)	175/597 (29.3%)	RR 0.45 (0.21 to 0.95)	161 fewer per 1000 (from 15 fewer to 232 fewer)	VERY LOW
Sustained headache response at 24	159/467 (34%)	335/685 (48.9%)	RR 0.67 (0.56 to 0.8)	161 fewer per 1000 (from 98 fewer to 215	VERY LOW

Outcome	Ergot	Triptan	Relative risk	Absolute effect	Quality
hours				fewer)	
Sustained pain free at 24 hours	38/383 (9.9%)	145/601 (24.1%)	RR 0.43 (0.25 to 0.74)	138 fewer per 1000 (from 63 fewer to 181 fewer)	VERY LOW

11.2.4.2 Economic evidence

No relevant economic evaluations comparing ergots with triptans were included. However, triptans and ergots were included in the cost-effectiveness analysis developed for this guideline. See section 11.5 for details and results.

One economic study[193] comparing triptans with ergots was excluded due its limited applicability to the NHS UK setting as it was conducted in the USA and QALYs were not calculated. Two cost-utility analyses[76,276], one from Canada one from the USA, were excluded because they were less applicable compared to our original analysis. The results of the Canadian study[76] were in agreement with our findings (triptans are more cost-effective than ergots) while the USA study[276] showed triptans to be both more effective and less costly than ergotamin derivatives; this could be due to the inclusion of indirect costs (i.e. patient travel and waiting time) and emergency rooms and hospitalisation costs for some of the people with no migraine relief. Had we included those costs in our model, less effective treatments such as ergots would have had higher costs and triptans would have been dominant as in the study by Zhang et al (2005)[276].

11.2.4.3 Evidence statements

Clinical:

Three studies with 899 people with migraine suggested that triptans may be more clinically effective than ergots in producing headache response at up to 2 hours, but there is some uncertainty. [Very low quality].

Two studies with 899 people with migraine suggested that triptans may be more clinically effective than ergots in producing freedom from pain at up to 2 hours, but there is some uncertainty. [Very low quality].

Two studies with 944 people with migraine suggested that triptans may be more clinically effective than ergots in sustaining headache response at 24 hours, but there is some uncertainty. [Very low quality].

Two studies with 899 people with migraine showed that triptans are more clinically effective than ergots in sustaining freedom from pain at 24 hours. [Very low quality].

No studies reported outcome data for time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

An original cost-effectiveness analysis developed for this guideline showed that triptans are on average more costly than ergots but they are also more effective. At a willingness to pay of £20,000/QALY triptans are more cost-effective than ergots. When the strategies compared in the model are considered altogether (NSAIDs, paracetamol, ergots, triptans, triptans in combination with NSAIDs and triptans in combination with paracetamol), ergots are likely to be the least cost-effective intervention while triptans in combination with NSAID are the most cost-effective intervention.

11.2.5 NSAID vs triptan

11.2.5.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 34-38, Appendix G.2.2. Six studies comparing orally administered NSAIDs with a triptan were identified[19,54,173,179,237]: three comparing sumatriptan (50 – 80mg) with naproxen (500mg); one sumatriptan (50mg) with ibuprofen (400mg); one sumatriptan (100mg) with tolfenamic acid (200mg); and one rizatriptan (10mg) with ibuprofen (400mg). One of the papers included two studies within it[19].

Table 51: NSAID vs triptan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[19,54,173,179,237]	6	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Pain free at up to 2 hours[19,54,173,179,237]	6	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Sustained headache response at 24 hours[19,237]	3	Randomised trials	Serious [(c)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Sustained pain free at 24 hours[19]	2	Randomised trials	Serious [(d)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Incidence of serious adverse events[19,173,179,237]	5	Randomised trials	Serious [(d)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-

(a) Three studies had unclear randomisation and allocation concealment, two studies had unclear allocation concealment; states it is double blind but the tablets described have different appearances, in one study it is unclear whether both groups received the same care; in one study it is unclear if both groups were followed up for the same length of time, in one study it is unclear whether groups were comparable for treatment completion; in three studies it is unclear whether investigators were blind to participants exposure to the intervention, in five studies it is unclear whether the investigator was blinded to other important confounding and prognostic factors.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) All three studies had unclear randomisation, allocation concealment and investigator blinding.
(d) Unclear randomisation, allocation concealment and investigator blinding in both studies.

Table 52: NSAID vs triptan – Clinical summary of findings

Outcome	NSAID	Triptan	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	617/1285 (48%)	690/1269 (54.4%)	RR 0.88 (0.82 to 0.95)	65 fewer per 1000 (from 27 fewer to 98 fewer)	LOW
Pain free at up to 2 hours	266/1285 (20.7%)	342/1269 (27%)	RR 0.77 (0.67 to 0.88)	62 fewer per 1000 (from 32 fewer to 89 fewer)	VERY LOW
Sustained headache response at 24 hours	271/968 (28%)	314/950 (33.1%)	RR 0.85 (0.74 to 0.97)	50 fewer per 1000 (from 10 fewer to 86 fewer)	LOW
Sustained freedom from pain at 24 hours	74/720 (10.3%)	110/724 (15.2%)	RR 0.68 (0.51 to 0.89)	49 fewer per 1000 (from 17 fewer to 74 fewer)	LOW
Incidence of serious adverse events	3/1084 (0.28%)	1/1080 (0.09%)	RR 1.99 (0.36 to 10.81)	1 more per 1000 (from 1 fewer to 9 more)	LOW

11.2.5.2 Economic evidence

No relevant economic evaluations comparing NSAIDs with triptans were identified. However, NSAIDs and triptans were included in our original cost-effectiveness analysis deveoped for this guideline. See section 11.5 for details and results.

11.2.5.3 Evidence statements

Clinical:

Six studies with 2825 people with migraine showed that triptans are more effective than NSAIDs in producing headache response at up to 2 hours, but the effect size is too small to be clinically important. [Low quality].

Six studies with 2825 people with migraine suggested that triptans may be more effective than NSAIDs in producing freedom from pain at up to 2 hours, but the effect size is too small to be clinically important, and there is some uncertainty. [Very low quality].

Three studies with 2181 people with migraine suggested that triptans may be more effective than NSAIDs in sustaining a headache response at 24 hours, but the effect size is too small to be clinically important, and there is some uncertainty. [Low quality].

Two studies with 1702 people with migraine suggested that triptans may be more clinically effective than NSAIDs in sustaining freedom from pain at 24 hours, but there is some uncertainty. [Low quality].

Five studies with 2387 people with migraine suggest that fewer adverse events occur with triptans than NSAIDs, but there is some uncertainty. [Low quality].

No studies reported outcome data for time to freedom from pain or health related quality of life.

Economic:

An original cost-effectiveness analysis developed for this guideline showed that triptans are on average more costly than NSAIDs but they are also more effective. At a willingness to pay of £20,000/QALY triptans are more cost-effective than NSAIDs. However, when the strategies compared in the model are considered altogether (NSAIDs, paracetamol, ergots, triptans, triptans in combination with NSAIDs and triptans in combination with paracetamol), triptans in combination with NSAIDs are the most cost-effective intervention.

11.2.6 Paracetamol vs triptan

11.2.6.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 39-42, Appendix G.2.2.

One study comparing oral rizatriptan with paracetamol was identified[82].

Table 53: Paracetamol vs triptan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Pain free at up to 2 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (c)
Sustained headache response at 24 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (c)
Sustained freedom from pain at 24 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Unclear allocation concealment and investigator blinding. Unclear outcome data availability.
(b) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.
(c) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 54: Paracetamol vs triptan – Clinical summary of findings

Outcome	Paracetamol	Triptan	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	30/43 (69.8%)	33/43 (76.7%)	RR 0.91 (0.7 to 1.17)	69 fewer per 1000 (from 230 fewer to 130 more)	VERY LOW
Pain free at up to 2 hours	11/43 (25.6%)	17/43 (39.5%)	RR 0.65 (0.34 to 1.21)	138 fewer per 1000 (from 261 fewer to 83 more)	VERY LOW
Sustained headache response at 24 hours	18/43 (41.9%)	23/43 (53.5%)	RR 0.78 (0.5 to 1.23)	118 fewer per 1000 (from 267 fewer to 123 more)	VERY LOW
Sustained freedom from pain at 24 hours	7/43 (16.3%)	10/43 (23.3%)	RR 0.7 (0.29 to 1.67)	70 fewer per 1000 (from 165 fewer to 156 more)	VERY LOW

11.2.6.2 Economic evidence

No relevant economic evaluations comparing paracetamol with triptans were identified. However, paracetamol and triptans were included in our original cost-effectiveness analysis developed for this guideline. See section 11.5 for details and results.

11.2.6.3 Evidence statements

Clinical:

One study with 96 people with migraine suggested that triptans may be more effective than paracetamol in producing headache response at up to 2 hours, but the effect size is too small to be clinically important, and there is some uncertainty. [Very low quality].

One study with 96 people with migraine suggested that triptans may be more clinically effective than paracetamol in producing freedom from pain at up to 2 hours, but there is some uncertainty. [Very low quality].

One study with 96 people with migraine suggested that triptans may be more clinically effective than paracetamol in sustaining headache response at 24 hours, but there is some uncertainty. [Very low quality].

One study with 96 people with migraine suggested that triptans may be more clinically effective than paracetamol in sustaining a freedom from pain at 24 hours, but there is considerable uncertainty. [Very low quality].

No studies reported outcome data for time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

An original cost-effectiveness analysis developed for this guideline showed that triptans are on average more costly than paracetamol but they are also more effective. At a willingness to pay of £20,000/QALY triptans are more cost-effective than paracetamol. However, when the strategies compared in the model are considered altogether (NSAIDs, paracetamol, ergots, triptans, triptans in combination with NSAIDs and triptans in combination with paracetamol), triptans in combination with NSAIDs are the most cost-effective intervention.

11.2.7 Aspirin in combination with antiemetic vs ergot

11.2.7.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 43-44, Appendix G.2.2.

One study was identified comparing oral aspirin (900mg) in combination with metoclopramide (10mg) with ergotamine and caffeine[141].

Table 55: Aspirin + antiemetic vs ergot – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[141]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Pain free at up to 2 hours[141]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Sustained headache response at 24 hours	0	-	-	-	-	-
Sustained freedom pain at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Unclear randomisation and allocation concealment.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 56: Aspirin + antiemetic vs ergot– Clinical summary of findings

Outcome	Aspirin + antiemetic	Ergot	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	73/134 (54.5%)	48/132 (36.4%)	RR 1.5 (1.14 to 1.97)	182 more per 1000 (from 51 more to 353 more)	LOW
Pain free at up to 2 hours	27/134 (20.1%)	11/132 (8.3%)	RR 2.42 (1.25 to 4.67)	118 more per 1000 (from 21 more to 306 more)	LOW

11.2.7.2 Economic evidence

No relevant economic evaluations comparing aspirin in combination with an antiemetic with ergots were identified. Aspirin in combination with an antiemetic was not included in our cost-effectiveness analysis (see section 11.5) as we had no evidence on its clinical effectiveness at 24 hours.

We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 46 in section 11.2.2.2).).

11.2.7.3 Evidence statements

Clinical:

One study with 296 people with migraine suggested that a combination of aspirin plus antiemetics may be more clinically effective than ergots in producing headache response at up to 2 hours, but there is some uncertainty. [Low quality].

One study with 296 people with migraine showed that a combination of aspirin plus antiemetics is more clinically effective than ergots in producing freedom from pain at up to 2 hours. [Low quality].

No studies reported outcome data for sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a difference in drug costs between aspirin in combination with an antiemetic and ergots. Aspirin in combination with an antiemetic is more costly than ergots (respectively £1.05 and £0.22 to £0.33 per episode).

11.2.8 Aspirin in combination with an antiemetic vs triptan

11.2.8.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 45-46, Appendix G.2.2.

Two studies comparing oral aspirin (900mg) in combination with metoclopramide (10mg) versus sumatriptan (100mg) were identified[249,250].

Table 57: Aspirin + antiemetic vs triptan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[249,250]	2	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Pain free at up to 2 hours[249,250]	2	Randomised trials	Very serious [(c)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Sustained headache response at 24 hours	0	-	-	-	-	-
Sustained freedom	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
pain at 24 hours						
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) One study had unclear randomisation and allocation concealment; both studies had unclear dropouts, one study had unclear missing data; in one study it was unclear whether the investigator was blinded to treatment.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) Unclear randomisation, allocation concealment and investigator blinding. Unclear dropouts and missing data.

Table 58: Aspirin + antiemetic vs triptan – Clinical summary of findings

Outcome	Aspirin + antiemetic	Triptan	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	125/257 (48.6%)	150/260 (57.7%)	RR 0.87 (0.73 to 1.02)	75 fewer per 1000 (from 156 fewer to 12 more)	VERY LOW
Pain free at up to 2 hours	48/273 (17.6%)	71/255 (27.8%)	RR 0.64 (0.46 to 0.88)	100 fewer per 1000 (from 33 fewer to 150 more)	VERY LOW

11.2.8.2 Economic evidence

No relevant economic evaluations comparing aspirin in combination with an antiemetic with triptans were identified. Aspirin in combination with an antiemetic was not included in our cost-effectiveness analysis (see section 11.5) as we had no evidence on its clinical effectiveness at 24 hours.

We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 46 in section 11.2.2.2).

11.2.8.3 Evidence statements

Clinical:

Two studies with 666 people with migraine suggested that triptans may be more effective than aspirin plus antiemetics in producing headache response at up to 2 hours, but the effect size is too small to be clinically important, and there is some uncertainty. [Very low quality].

Two studies with 666 people with migraine suggested that triptans may be more clinically effective than aspirin plus antiemetics in producing freedom from pain at up to 2 hours, but there is some uncertainty. [Very low quality].

No studies reported outcome data for sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a difference in drug costs between aspirin in combination with an antiemetic vs triptans. Some triptans (oral sumatriptan) are less costly than aspirin in combination with an antiemetic (respectively £0.21 and £1.05 per episode) while others (rizatriptan or subcutaneous sumatriptan) are more costly (£4.46 and £21.24 per episode).

11.2.9 Paracetamol in combination with an antiemetic vs triptan

11.2.9.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figure 47, Appendix G.2.2.

One study was identified comparing oral paracetamol (500mg) plus domperidone (10mg) with sumatriptan (50mg)[63].

Table 59: Paracetamol + antiemetic vs triptan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[63]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Pain free at up to 2 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Unclear randomisation, allocation concealment and investigator blinding. Unclear if groups were comparable for treatment completion.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 60: Paracetamol + antiemetic vs triptan – Clinical summary of findings

Outcome	Paracetamol + antiemetic	Triptan	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	43/118 (36.4%)	39/117 (33.3%)	RR 1.09 (0.77 to 1.55)	30 more per 1000 (from 77 fewer to 183 more)	VERY LOW

11.2.9.2 Economic evidence

No relevant economic evaluations comparing paracetamol in combination with an antiemetic with triptans were identified. Paracetamol in combination with an antiemetic was not included in our cost-effectiveness analysis (see section 11.5) as we had no evidence on its clinical effectiveness at 24 hours.

We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 46 in section 11.2.2.2).

11.2.9.3 Evidence statements

Clinical:

One study with 235 people with migraine suggested that a combination of paracetamol plus antiemetics may be more effective than triptans in producing a headache response at up to 2 hours but the effect size is too small to be clinically important and there is some uncertainty. [Very low quality].

No studies reported outcome data for freedom from pain at 2 hours, sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a difference in drug costs between a combination of paracetamol plus an antiemetic vs triptans. Some triptans (oral sumatriptan) are less costly than paracetamol in combination with an antiemetic (respectively £ 0.21 and £0.46 per episode) while others (rizatriptan or subcutaneous sumatriptan) are more costly (£4.46 and £21.24 per episode).

11.2.10 Paracetamol in combination with aspirin vs NSAID

11.2.10.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figure 48, Appendix G.2.2.

One study comparing oral paracetamol (500mg) in combination with aspirin (500mg) with ibuprofen (400mg) was identified[92].

Table 61: Paracetamol + aspirin vs NSAID – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[92]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Time to freedom from pain[92]	1	Randomised trials	Serious [(a)]	N/A*	No serious indirectness	N/A*
Pain free at up to 2 hours	0	-	-	-	-	-
Sustained headache	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
response at 24 hours						
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Unclear randomisation, unclear investigator blinding to other important confounding and prognostic factors.
** Data could not be meta-analysed.*
N/A=not applicable.

Table 62: Paracetamol + aspirin vs NSAID – Clinical summary of findings

Outcome	Paracetamol + aspirin	NSAID	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	448/669 (67%)	413/666 (62%)	RR 1.08 (1 to 1.17)	50 more per 1000 (from 0 more to 105 more)	MODERATE
Time to freedom from pain*	128.4 (120,142)	147.9 (135,163)	N/A	N/A	MODERATE

**Time to freedom from pain data was reported as median time to onset of pain relief, in minutes (95% Confidence interval) and could not be meta-analysed.*
N/A=not applicable.

11.2.10.2 Economic evidence

No relevant economic evaluations comparing paracetamol in combination with aspirin with NSAIDs were identified. Paracetamol in combination with aspirin was not included in our cost-effectiveness analysis (see section 11.5) as we had no evidence on its clinical effectiveness at 24 hours.

We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 46 in section 11.2.2.2).

11.2.10.3 Evidence statements

Clinical:

One study with 1335 people with migraine showed that a combination of paracetamol plus aspirin is more effective than NSAIDs in producing a headache response at up to 2 hours but the effect size is too small to be clinically important. [Moderate quality].

One study with 1555 people with migraine showed that the time to freedom from pain was lower for a combination of paracetamol plus aspirin is than NSAIDs, but the difference is uncertain as no comparative analysis could be carried out. [Moderate quality].

No studies reported outcome data for freedom from pain at 2 hours, sustained headache response at 24 hours, sustained freedom from pain at 24 hours, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a small difference in drug costs between a combination of paracetamol plus aspirin vs NSAIDs. Some NSAIDs (ibuprofen) are less costly than paracetamol + aspirin (respectively £0.02 and £0.04 per episode) while others (naproxen or aceclofenac) are more costly (£0.06 and £0.17 per episode).

11.2.11 Paracetamol in combination with aspirin vs triptan

11.2.11.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figure 49, Appendix G.2.2.

One study was identified comparing oral paracetamol (1000mg), aspirin (1000mg) and caffeine (130mg) with sumatriptan (50mg)[91].

Table 63: Paracetamol + aspirin vs triptan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[91]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Pain free up to 2 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Unclear randomisation, unclear investigator blinded to other important confounding and prognostic factors.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 64: Paracetamol + aspirin vs triptan – Clinical summary of findings

Outcome	Paracetamol + aspirin	Triptan	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	42/50 (84%)	30/46 (65.2%)	RR 1.29 (1.01 to 1.64)	189 more per 1000 (from 7 more to 417 more)	LOW

11.2.11.2 Economic evidence

No relevant economic evaluations comparing paracetamol in combination with aspirin vs triptans were identified. Paracetamol in combination with aspirin was not included in our cost-effectiveness analysis (see section 11.5) as we had no evidence on its clinical effectiveness at 24 hours.

We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 46 in section 11.2.2.2).

11.2.11.3 Evidence statements

Clinical:

One study with 96 people with migraine suggested that a combination of paracetamol plus aspirin may be more clinically effective than triptan in producing headache response at up to 2 hours, but there is some uncertainty. [Low quality].

No studies reported outcome data for freedom from pain at 2 hours, sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a difference in drug costs between a combination of paracetamol plus aspirin vs triptans. Triptans are more costly than paracetamol plus aspirin (respectively £0.21 to £21.24 and £0.04 per episode).

11.2.12 Triptan in combination with an NSAID vs NSAID

11.2.12.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 50-53, Appendix G.2.2.

Three studies were identified comparing a combination of oral sumatriptan (50-85mg) and naproxen (500mg) with naproxen (500mg) alone[19,237]. One paper included two studies.

Table 65: Triptan + NSAID vs NSAID – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[19,237]	3	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Pain free at up to 2 hours[19,237]	3	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Sustained headache response at 24 hours[19,237]	3	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Sustained pain free at 24 hours[19,237]	2	Randomised trials	Very serious (b)	No serious inconsistency	No serious indirectness	No serious imprecision
Incidence of serious adverse events[19,237] *	3	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	*

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-

(a) All studies had unclear randomisation, allocation concealment and investigator blinding.
(b) Unclear randomisation, allocation concealment and investigator blinding.
* *data could not be analysed – no serious adverse events were reported by any of the studies.*

Table 66: Triptan + NSAID vs NSAID – Clinical summary of findings

Outcome	Triptan + NSAID	NSAID	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	607/976 (62.2%)	429/968 (44.3%)	RR 1.40 (1.29 to 1.53)	177 more per 1000 (from 129 more to 235 more)	LOW
Pain free at up to 2 hours	317/976 (32.5%)	155/968 (16%)	RR 2.03 (1.71 to 2.4)	165 more per 1000 (from 114 more to 224 more)	LOW
Sustained headache response at 24 hours	447/976 (45.8%)	271/968 (28%)	RR 1.64 (1.45 to 1.85)	179 more per 1000 (from 126 more to 238 more)	LOW
Sustained pain free at 24 hours	173/726 (23.8%)	74/720 (10.3%)	RR 2.32 (1.8 to 2.98)	136 more per 1000 (from 82 more to 204 more)	LOW
Incidence of serious adverse events*	0/976	0/976	-	-	LOW

* *Data could not be meta-analysed – no serious adverse events were reported by any of the studies.*

11.2.12.2 Economic evidence

No relevant economic evaluations comparing triptans in combination with NSAIDs with NSAIDs alone were identified. However triptans in combination with NSAIDs and NSAIDs alone were included in our original cost-effectiveness analysis developed for this guideline. See section 11.5 for details and results.

11.2.12.3 Evidence statements

Clinical:

Three studies with 2205 people with migraine showed that a combination of triptan plus NSAID is more clinically effective than NSAIDs alone in producing headache response at up to 2 hours. [Low quality].

Three studies with 2205 people with migraine showed that a combination of triptan plus NSAID is more clinically effective than NSAIDs alone in producing freedom from pain at up to 2 hours. [Very low quality].

Three studies with 2205 people with migraine showed that a combination of triptan plus NSAID is more clinically effective than NSAIDs alone in sustaining headache response at 24 hours. [Low quality].

Two studies with 1704 people with migraine showed that a combination of triptan plus NSAID is more clinically effective than NSAIDs alone in sustaining freedom from pain at 24 hours. [Low quality].

Two studies with 2815 people with migraine showed that there is no difference in the incidence of serious adverse events between a combination of triptan plus NSAID and NSAID alone. [Low quality].

No studies reported outcome data for freedom from pain at 2 hours, sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain or health related quality of life.

Economic:

An original cost-effectiveness analysis developed for this guideline showed that triptans in combination with NSAIDs are on average more costly than NSAIDs alone but they are also more effective. At a willingness to pay of £20,000/QALY triptans in combination with NSAIDs are more cost-effective than NSAIDs alone. When the strategies compared in the model are considered altogether (NSAIDs, paracetamol, ergots, triptans, triptans in combination with NSAIDs and triptans in combination with paracetamol), triptans in combination with NSAIDs are the most cost-effective intervention.

11.2.13 Triptan in combination with an NSAID vs triptan

11.2.13.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 54-57, Appendix G.2.2. Four studies were identified comparing oral triptan in combination with an NSAID to a triptan alone; three compared sumatriptan (50-85mg) and naproxen (500mg) to sumatriptan (50-85mg) alone and the fourth compared almotriptan (12.5mg) and aclofenac (100mg) with almotriptan (12.5mg) alone [19,220,237]. One paper included two studies.

Table 67: Triptan + NSAID vs triptan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[19,220,237]	4	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Pain free at up to 2 hours[19,220,237]	4	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Sustained headache response at 24 hours[19,237]	3	Randomised trials	Very serious [(c)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Sustained pain free at 24 hours[19,220]	3	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Incidence of serious adverse	4	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
events *[19,220,237]						
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-

(a) All studies had unclear randomisation, allocation concealment and investigator blinding. One study was unclear for treatment completion and event rates had to be calculated by NCGC as only percentages were reported.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) All studies had unclear randomisation, allocation concealment and investigator blinding.
** Data could not be analysed – no serious adverse events reported.*

Table 68: Triptan + NSAID vs triptan – Clinical summary of findings

Outcome	Triptan + NSAID	Triptan	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	639/1066 (59.9%)	527/1039 (50.7%)	RR 1.18 (1.09 to 1.28)	91 more per 1000 (from 46 more to 142 more)	VERY LOW
Pain free at up to 2 hours	354/1066 (33.2%)	244/1039 (23.5%)	RR 1.42 (1.23 to 1.63)	99 more per 1000 (from 54 more to 148 more)	VERY LOW
Sustained headache response at 24 hours	447/976 (45.8%)	314/949 (33.1%)	RR 1.39 (1.24 to 1.55)	129 more per 1000 (from 79 more to 182 more)	VERY LOW
Sustained pain free at 24 hours	201/816 (24.6%)	129/813 (15.9%)	RR 1.55 (1.27 to 1.89)	87 more per 1000 (from 43 more to 141 more)	LOW
Incidence of serious adverse events	0/1033	0/1009	-	-	LOW

11.2.13.2 Economic evidence

No relevant economic evaluations comparing triptans in combination with NSAIDs with triptans alone were identified. However, triptans in combination with NSAIDs and triptans alone were included in our original cost-effectiveness analysis developed for this guideline. See section 11.5 for details and results.

11.2.13.3 Evidence statements

Clinical:

Four studies with 2350 people with migraine suggested that a combination of triptan plus NSAID may be more clinically effective than triptans alone in producing headache response at up to 2 hours, but there is some uncertainty. [Very low quality].

Four studies with 2350 people with migraine suggested that a combination of triptan plus NSAID may be more clinically effective than triptans alone in producing freedom from pain at up to 2 hours, but there is some uncertainty. [Very low quality].

Three studies with 2205 people with migraine suggested that a combination of triptan plus NSAID may be more clinically effective than triptans alone in sustaining headache response at 24 hours, but there is some uncertainty. [Very low quality].

Three studies with 1849 people with migraine showed that a combination of triptan plus NSAID is more clinically effective than triptans alone in sustaining freedom from pain at 24 hours. [Low quality].

Four studies with 2350 people with migraine suggested that there is no difference in the incidence of serious adverse events between a combination of triptan plus NSAID and triptans alone. [Low quality].

No studies reported outcome data for freedom from pain at 2 hours, sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain or health related quality of life.

Economic:

An original cost-effectiveness analysis developed for this guideline showed that triptans in combination with NSAIDs are on average more costly than triptans alone but they are also more effective. At a willingness to pay of £20,000/QALY triptans in combination with NSAIDs are more cost-effective than triptans alone. When the strategies compared in the model are considered altogether (NSAIDs, paracetamol, ergots, triptans, triptans in combination with NSAIDs and triptans in combination with paracetamol), triptans in combination with NSAIDs are the most cost-effective intervention.

11.2.14 Triptan in combination with paracetamol vs triptan

11.2.14.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 58-61, Appendix G.2.2.

One study was identified comparing rizatriptan (10mg) in combination with paracetamol (1000mg) with rizatriptan (10mg) alone[82].

Table 69: Triptan + paracetamol vs triptan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Pain free at up to 2 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Sustained headache response at 24 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Sustained pain free at 24 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Very serious (c)
Incidence of serious adverse events[82] *	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Time to	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
freedom from pain						
Health related quality of life	0	-	-	-	-	-

(a) Unclear allocation concealment and investigator blinding. Unclear outcome data availability.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.
** Data could not be analysed – no serious adverse events reported*

Table 70: Triptan + paracetamol vs triptan – Clinical summary of findings

Outcome	Triptan + paracetamol	Triptan	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	43/48 (89.6%)	33/43 (76.7%)	RR 1.17 (0.96 to 1.41)	130 more per 1000 (from 31 fewer to 315 more)	VERY LOW
Pain free at up to 2 hours	23/48 (47.9%)	17/43 (39.5%)	RR 1.21 (0.76 to 1.94)	83 more per 1000 (from 95 fewer to 372 more)	VERY LOW
Sustained headache response at 24 hours	30/48 (62.5%)	23/43 (53.5%)	RR 1.17 (0.82 to 1.67)	91 more per 1000 (from 96 fewer to 358 more)	VERY LOW
Sustained pain free at 24 hours	15/48 (31.3%)	10/43 (23.3%)	RR 1.34 (0.68 to 2.67)	79 more per 1000 (from 74 fewer to 388 more)	VERY LOW
Incidence of serious adverse events *	0/48	0/43	-	-	LOW

** Data could not be meta-analysed – no serious adverse events reported.*

11.2.14.2 Economic evidence

No relevant economic evaluations comparing triptans in combination with paracetamol with triptans alone were identified. However, triptans in combination with paracetamol and triptans alone were included in our original cost-effectiveness analysis developed for this guideline.See section 11.5 for details and results.

11.2.14.3 Evidence statements

Clinical:

One study with 55 people with migraine suggested that a combination of triptan plus paracetamol may be more clinically effective than triptans alone in producing headache response at up to 2 hours, but there is some uncertainty. [Very low quality].

One study with 55 people with migraine suggested that a combination of triptan plus paracetamol may be more clinically effective than triptans alone in producing freedom from pain at up to 2 hours, but there is some uncertainty. [Very low quality].

One study with 55 people with migraine suggested that a combination of triptan plus paracetamol may be more clinically effective than triptans alone in sustaining headache response at 24 hours, but there is some uncertainty. [Very low quality].

One study with 55 people with migraine suggested that a combination of triptan plus paracetamol may be more clinically effective than triptans alone in sustaining freedom from pain at 24 hours but there is considerable uncertainty. [Very low quality].

One study with 55 people with migraine showed that there is no difference in the incidence of serious adverse events between a combination of triptan plus paracetamol and triptan alone but there is uncertainty. [Low quality].

No studies reported outcome data for freedom from pain at 2 hours, sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain or health related quality of life.

Economic:

An original cost-effectiveness analysis developed for this guideline showed that triptans in combination with paracetamol are on average more costly than triptans alone but they are also more effective. At a willingness to pay of £20,000/QALY triptans in combination with paracetamol are more cost-effective than triptans alone. However, when the strategies compared in the model are considered altogether (NSAIDs, paracetamol, ergots, triptans, triptans in combination with NSAIDs and triptans in combination with paracetamol), triptans in combination with NSAIDs are the most cost-effective intervention.

11.2.15 Triptan in combination with paracetamol vs paracetamol

11.2.15.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 62-65, Appendix G.2.2.

One study was identified comparing rizatriptan (10mg) in combination with paracetamol (1000mg) with paracetamol (1000mg) alone[82].

Table 71: Triptan + paracetamol vs paracetamol – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Pain free at up to 2 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Sustained headache response at 24 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Sustained freedom from pain at 24 hours[82]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Incidence of serious adverse events[82] *	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	N/A*
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-

(a) Unclear allocation concealment and investigator blinding. Unclear outcome data availability.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
** Data could not be meta-analysed – no serious adverse events reported.*

Table 72: Triptan + paracetamol vs paracetamol – Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	43/48 (89.6%)	30/43 (69.8%)	RR 1.28 (1.03 to 1.6)	195 more per 1000 (from 21 more to 419 more)	VERY LOW
Pain free at up to 2 hours	23/48 (47.9%)	11/43 (25.6%)	RR 1.87 (1.04 to 3.38)	223 more per 1000 (from 10 more to 609 more)	VERY LOW
Sustained headache response at 24 hours	30/48 (62.5%)	18/43 (41.9%)	RR 1.49 (0.99 to 2.26)	205 more per 1000 (from 4 fewer to 527 more)	VERY LOW
Sustained pain free at 24 hours	15/48 (31.3%)	7/43 (16.3%)	RR 1.92 (0.86 to 4.26)	150 more per 1000 (from 23 fewer to 531 more)	VERY LOW
Incidence of serious adverse events *	0/48	0/43	N/A	N/A	LOW

* *Data could not be meta-analysed – no serious adverse events reported.*

11.2.15.2 Economic evidence

No relevant economic evaluations comparing triptans in combination with paracetamol with paracetamol alone were identified. However, triptans in combination with paracetamol and paracetamol alone were included in our original cost-effectiveness analysis developed for this guideline. See section 11.5 for details and results.

11.2.15.3 Evidence statements

Clinical:

One study with 55 people with migraine suggested that a combination of triptan plus paracetamol may be more clinically effective than paracetamol alone in producing headache response at up to 2 hours, but there is some uncertainty. [Very low quality].

One study with 55 people with migraine suggested that a combination of triptan plus paracetamol may be more clinically effective than paracetamol alone in producing freedom from pain at up to 2 hours, but there is some uncertainty. [Very low quality].

One study with 55 people with migraine suggested that a combination of triptan plus paracetamol may be more clinically effective than paracetamol alone in sustaining headache response at 24 hours, but there is some uncertainty. [Very low quality].

One study with 51 people with migraine suggested that a combination of triptan plus paracetamol may be more clinically effective than paracetamol alone in sustaining freedom from pain at 24 hours but there is some uncertainty. [Very low quality].

One study with 55 people with migraine showed that there is no difference in the incidence of serious adverse events between a combination of triptan plus paracetamol and paracetamol alone but there is uncertainty. [Low quality].

No studies reported outcome data for freedom from pain at 2 hours, sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain or health related quality of life.

Economic:

An original cost-effectiveness analysis developed for this guideline showed that triptans in combination with paracetamol are on average more costly than paracetamol alone but they are also more effective. At a willingness to pay of £20,000/QALY triptans in combination with paracetamol are more cost-effective than paracetamol. However, when the strategies compared in the model are considered altogether (NSAIDs, paracetamol, ergots, triptans, triptans in combination with NSAIDs and triptans in combination with paracetamol), triptans in combination with NSAIDs are the most cost-effective intervention.

11.2.15.4 Recommendations and link to evidence

See recommendations and link to evidence in section 11.6.

11.3 Intravenous, intramuscular and subcutaneous administered treatments

11.3.1 Matrix of treatment comparisons

Below is a matrix showing the number of studies identified by comparison for treatments administered as intravenous, intramuscular or subcutaneous preparations.

Paracetamol (PARA)	-									
Antiemetics (AE)	-	-								
Ergots (ERG)	-	-	-							
NSAIDs	-	2	1	-						
Lidocaine (LID)	-	-	1	1	-					
Opioids (OP)	-	-	-	-	-	-				
Triptans (TRIP)	1	-	1	2	-	-	-			
Corticosteriods (STER)	-	-	-	-	-	-	-	-		
Opioid + Antiemetic (O+A)	-	-	-	-	-	1	-	-	-	-
	Aspirin	**PARA**	**AE**	**ERG**	**LID**	**NSAID**	**OP**	**TRIP**	**STER**	**O+A**

11.3.2 Antiemetic vs NSAID

11.3.2.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figure 66, Appendix G.2.2.

One study[24] was identified comparing intravenous prochlorperazine to intravenous ketorolac. The population studied was children aged 5 to 18 years (average age 13).

Table 73: Antiemetic vs NSAID – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at up to 2 hours[24]	1	Randomised trials	No serious limitations	No serious inconsistency	Serious [(a)]	Serious imprecision [(b)]
Headache response at up to 2 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) The age of participants ranged from 7 to 18 years (average 13.7 years). The inclusion criteria for this review is age 12 and above.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 74: Antiemetic vs NSAID – Clinical summary of findings

Outcome	Antiemetic	NSAID	Relative risk	Absolute effect	Quality
Pain free at up to 2 hours	11/33 (33%)	2/29 (6.9%)	RR 4.83 (1.17 to 20.03)	264 more per 1000 (from 12 more to 1000 more)	LOW

11.3.2.2 Economic evidence

No economic evaluations comparing antiemetics with NSAIDs administered as intravenous, intramuscular or subcutaneous preparations were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 75 below).

Table 75: Unit cost of drugs

Drug	Cost per episode [a] (£)	Notes
Intravenous NSAID	0.89	Intravenous ketorolac – Dose: 10 mg
Intravenous paracetamol	1.25	Dose: 1g for adults over 50kg.
Intramuscular opioids	2.44	Codeine – Dose: 60mg
Subcutaneous triptans	21.2	Sumatriptan: £42.47 for 2 syringes
Intravenous antiemetics	0.27	Metoclopramide – Dose: 10mg
Intramuscular antiemetics	0.60	Chlorpromazine – Dose: 25mg
Intravenous lidocaine	3.50	Dose: 50 mg
Opioid + antiemetic	1.82	Morphine tartrate 10mg, cyclizine tartrate 50mg/mL. Dose: 1 mL

Source: BNF62[111]

The costs of adverse effects and further events were not estimated.

Some preparations are not included in the BNF62 (intramuscular NSAID, intravenous ergots, intravenous aspirin, intramuscular paracetamol) and we could not report their costs.

11.3.2.3 Evidence statements

Clinical:

One study with 61 people with migraine suggested that intravenous antiemetics may be more clinically effective than intravenous NSAIDs at producing freedom from pain up at 2 hours in young people aged under 18, but there is some uncertainty. [Low quality].

No studies reported outcome data for headache response at up to two hours, sustained freedom from pain at 24 hours, sustained headache response at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a small difference in the cost per episode between intravenous or intramuscular antiemetics (respectively £0.27 and £0.60) and intravenous NSAIDs (£0.89).

11.3.3 Ergots vs antiemetic

11.3.3.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figure 67, Appendix G.2.2.

One study[15] was identified comparing intravenous chlorpromazine to intravenous dihydroergotamine.

Table 76: Ergots vs antiemetic – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at up to 2 hours[15]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)
Headache response at up to 2 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment was unclear. Single blind (only participants were blinded to treatment). Fourteen out of 90 participants randomised dropped out and are not accounted for in the results.
(b) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.

Table 77: Ergots vs antiemetic – Clinical summary of findings

Outcome	Ergot	Antiemetic	Relative risk	Absolute effect	Quality
Pain free at up to 2 hours	6/26 (23.1%)	8/24 (33.3%)	RR 0.69 (0.28 to 1.71)	103 fewer per 1000 (from 240 fewer to 237 more)	VERY LOW
Headache response at up to 2 hours	-	-	-	-	-

Outcome	Ergot	Antiemetic	Relative risk	Absolute effect	Quality
Sustained freedom from pain at 24 hours	-	-	-	-	-
Sustained headache response at 24 hours	-	-	-	-	-
Time to freedom from pain	-	-	-	-	-
Health related quality of life	-	-	-	-	-
Incidence of serious adverse events	-	-	-	-	-

11.3.3.2 Economic evidence

No relevant economic evaluations comparing ergots with antiemetics were identified. Intravenous ergots are not included in the BNF62[111] and their costs could not be estimated.

11.3.3.3 Evidence statements

Clinical:

One study with 50 people with migraine suggested that intravenous antiemetics may be more clinically effective than intravenous ergots at producing freedom from pain at up to 2 hours, but there is considerable uncertainty. [Very low quality].

No studies reported outcome data for headache response at up to two hours, sustained freedom from pain at 24 hours, sustained headache response at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found on this question and a simple cost analysis could not be conducted as ergots are not included in the BNF62[111].

11.3.4 NSAID vs paracetamol

11.3.4.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 68-69, Appendix G.2.2.

Two studies [115,116] were identified comparing intramuscular ketoprofen with intramuscular paracetamol.

Table 78: NSAID vs paracetamol – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at up to 2 hours[115,116]	2	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Time to freedom from pain[115] *	1	Randomised trials	Very serious [(b)]	N/A	No serious indirectness	N/A

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Incidence of serious adverse events[115,116] †	2	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Headache response at up to 2 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment unclear. Unclear if participants and investigators were blinded to treatment in one study. Outcome definition unclear in one study and the method of assessing the outcome was unclear in both studies.
(b) Method of randomisation and allocation concealment unclear. Unclear if participants and investigators were blinded to treatment. Method of assessing the was outcome unclear. Unclear if N values reported for time to freedom from pain relate to those who achieved freedom from pain or the number the sample was recorded from.
** Data couldn't be meta-analysed – only reported as mean number of hours (SD).*
† Data couldn't be meta-analysed – no adverse events reported.
N/A=not applicable.

Table 79: NSAID vs paracetamol – Clinical summary of findings

Outcome	NSAID	Paracetamol	Relative risk	Absolute effect	Quality
Pain free at up to 2 hours	68/79 (86.1%)	12/70 (17.1%)	RR 5.02 (2.98 to 8.47)	689 more per 1000 (from 339 more to 1000 more)	LOW
Time to freedom from pain *	4.9 (5.15)	3.6 (2.4)	-	-	LOW
Incidence of serious adverse events †	0/79	0/70	-	-	LOW

** Data couldn't be meta-analysed – only reported as mean number of hours (SD).*
† Data couldn't be meta-analysed – no adverse events reported.

11.3.4.2 Economic evidence

No relevant economic evaluations comparing intramuscular NSAIDs with intramuscular paracetamol were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 75 in section 11.3.2.2).

11.3.4.3 Evidence statements

Clinical:

Two studies with 149 people with migraine showed that intramuscular NSAIDs are more clinically effective than intramuscular paracetamol at producing freedom from pain at up to 2 hours. [Low quality].

One study with 64 people with migraine showed that the time to freedom from pain was slightly higher for intramuscular NSAIDs compared to intramuscular paracetamol but the difference is uncertain as no comparative analysis could be carried out. [Low quality]

Two studies with 149 people with migraine suggested that there is no difference in the incidence of serious adverse events between intramuscular NSAIDs and intramuscular paracetamol but there is uncertainty. [Low quality]

No studies reported outcome data for headache response at up to two hours, sustained freedom from pain at 24 hours, sustained headache response at 24 hours or health related quality of life.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a small difference in drug costs between intravenous paracetamol and intravenous NSAIDs. Intravenous paracetamol is slightly more costly than intravenous NSAIDs (respectively £1.25 and £0.89 per episode).

11.3.5 Lidocaine vs antiemetic

11.3.5.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figure 70, Appendix G.2.2.

One study[15] comparing intravenous lidocaine with intravenous chlorpromazine was identified.

Table 80: Lidocaine vs antiemetic – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at up to 2 hours[15]	1	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Headache response at up to 2 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health relaed quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment was unclear. Only participants were blinded to treatment. Fourteen out of 90 participants randomised dropped out and are not accounted for in the results.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 81: Lidocaine vs antiemetic – Clinical summary of findings

Outcome	Lidocaine	Antiemetic	Relative risk	Absolute effect	Quality
Pain free at up to 2 hours	2/26 (7.7%)	8/24 (33.3%)	RR 0.23 (0.05 to 0.98)	257 fewer per 1000 (from 7 fewer to 317 fewer)	VERY LOW

11.3.5.2 Economic evidence

No relevant economic evaluations comparing intravenous lidocaine with intravenous antiemetics were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 75 in section 11.3.2.2).

11.3.5.3 Evidence statements

Clinical:

One study with 50 people with migraine suggested that intravenous chlorpromazine may be more clinically effective than intravenous lidocaine at producing freedom from pain at up to 2 hours, but there is some uncertainty. [Very low quality].

No studies reported outcome data for headache response at up to two hours, sustained freedom from pain at 24 hours, sustained headache response at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a difference in drug costs between intravenous lidocaine and intravenous chlorpromazine. Intravenous lidocaine is more costly than intravenous antiemetics (respectively £3.50 and £0.27 per episode)

11.3.6 Lidocaine vs ergot

11.3.6.1 Clinical evidence

Se See Evidence tables in appendix section E.2.3 and Forest Plots in Figure 71, Appendix G.2.2.

One study[15] comparing intravenous lidocaine with intravenous dihydroergotamine was identified.

Table 82: Lidocaine vs ergot – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at up to 2 hours[15]	1	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	Very serious [(b)]
Headache response at up to 2 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment was unclear. Only participants were blinded to treatment. Fourteen out of 90 participants randomised dropped out and are not accounted for in the results.
(b) The upper limit of the confidence intervals cross the minimal important difference in both directions making the effect size very uncertain.

Table 83: Lidocaine vs ergot – Clinical summary of findings

Outcome	Lidocaine	Ergot	Relative risk	Absolute effect	Quality
Pain free at up to 2 hours	2/26 (7.7%)	6/26 (23.1%)	RR 0.33 (0.07 to 1.5)	155 fewer per 1000 (from 215 fewer to 115 more)	VERY LOW

11.3.6.2 Economic evidence

No relevant economic evaluations comparing lidocaine with ergots were identified. Intravenous ergots are not included in the BNF62[111] and their costs could not be estimated.

11.3.6.3 Evidence statements

Clinical:

One study with 52 people with migraine suggested that intravenous ergots may be more clinically effective than intravenous lidocaine in producing freedom from pain at up to 2 hours, but there is considerable uncertainty. [Very low quality].

No studies reported outcome data for headache response at up to two hours, sustained freedom from pain at 24 hours, sustained headache response at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found on this question and a simple cost analysis could not be conducted as intravenous ergots are not included in the BNF62[111].

11.3.7 Triptan vs antiemetic

11.3.7.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 72-73, Appendix G.2.2.

One study[85] comparing subcutaneous sumatriptan with intravenous metoclopramide was identified.

Table 84: Triptan vs antiemetic – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Pain free at up to 2 hours[85]	1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious [(a)]
Sustained freedom from pain at 24 hours[85]	1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious [(b)]
Headache response at up to 2 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) The confidence interval crosses one minimal important difference making the effect size uncertain.
(b) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.

Table 85: Triptan vs antiemetic – Clinical summary of findings

Outcome	Triptan	Antiemetic	Relative risk	Absolute effect	Quality
Pain free at up to 2 hours	13/37 (34.2%)	24/40 (60%)	RR 0.59 (0.35 to 0.97)	246 fewer per 1000 (from 18 fewer to 390 fewer)	MODERATE
Sustained pain free at 24 hours	10/37 (26.3%)	16/40 (40%)	RR 0.68 (0.35 to 1.30)	128 fewer per 1000 (from 260 fewer to 120 more)	LOW

11.3.7.2 Economic evidence

No relevant economic evaluations comparing subcutaneous triptans with intravenous antiemetics were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 75 in section 11.3.2.2).

11.3.7.3 Evidence statements

Clinical:

One study with 78 people with migraine suggested that intravenous antiemetics may be more clinically effective than subcutaneous triptans in producing freedom from pain at up to 2 hours, but there is some uncertainty. [Moderate quality].

One study with 78 people with migraine suggested that intravenous antiemetics may be more clinically effective than subcutaneous triptans in sustaining freedom from pain at 24 hours, but there is considerable uncertainty. [Low quality].

No studies reported outcome data for headache response at up to two hours, sustained headache response at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a large difference in drug costs between intravenous antiemetics and subcutaneous triptans. Subcutaneous triptans are more costly than intravenous antiemetics (respectively £21.2 and £0.27 per episode).

11.3.8 Triptan vs aspirin

11.3.8.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figure 74-76, Appendix G.2.2.

One study[53] comparing subcutaneous sumatriptan with intravenous aspirin was identified.

Table 86: Triptan vs aspirin – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[53]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Pain free at up to 2 hours[53]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Sustained freedom from pain at 24 hours[53]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Very serious (c)
Sustained headache response at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related Quality of Life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment unclear. Unclear if investigators were blinded to treatment.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.

Table 87: Triptan vs aspirin – Clinical summary of findings

Outcome	Triptan	Aspirin	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	104/114 (91.2%)	88/119 (73.9%)	RR 1.23 (1.09 to 1.39)	170 more per 1000 (from 67 more to 288 more)	VERY LOW
Pain free at up to 2 hours	87/114 (76.3%)	52/119 (43.7%)	RR 1.75 (1.39 to 2.19)	328 more per 1000 (from 170 more to 520 more)	LOW

Outcome	Triptan	Aspirin	Relative risk	Absolute effect	Quality
Sustained pain free at 24 hours	80/114 (70.2%)	72/119 (60.5%)	RR 1.16 (0.96 to 1.4)	97 more per 1000 (from 24 fewer to 242 more)	VERY LOW

11.3.8.2 Economic evidence

No relevant economic evaluations comparing subcutaneous triptans with intravenous aspirin were identified. Intravenous aspirin is not included in the BNF62[111] and its cost could not be estimated.

11.3.8.3 Evidence statements

Clinical:

One study with 233 people with migraine suggested that subcutaneous triptans may be more effective than intravenous aspirin in producing a headache response at up to 2 hours, but the effect size is too small to be clinically important, and there is some uncertainty. [Very low quality].

One study with 233 people with migraine showed that subcutaneous triptans are more clinically effective than intravenous aspirin in producing a freedom of pain at up to 2 hours. [Low quality].

One study with 233 people with migraine suggested that subcutaneous triptans may be more effective than intravenous aspirin in sustaining freedom from pain at 24 hours, but the effect size is too small to be clinically important, and there is some uncertainty. [Very low quality].

No studies reported outcome data for sustained headache response at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found on this question and a simple cost analysis could not be conducted as intravenous aspirin is not included in the BNF62[111].

11.3.9 Triptan vs ergot

11.3.9.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figures 77-78, Appendix G.2.2.

Two studies[254,269] comparing subcutaneous sumatriptan with dihydroergotamine administered by nasal spray in one study and subcutaneous in the other were identified.

Table 88: Triptan vs ergot– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours[269]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Sustained headache response at 24 hours[254]	1	Randomised trials	Very serious (c)	No serious inconsistency	No serious indirectness	Serious (b)
Pain free at up to 2 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment unclear. Not reported if groups were comparable at baseline. Nurse administering treatment was not blinded to intervention. Unclear if investigators were blinded to participant characteristics although they were blinded to treatment.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) Method of randomisation and allocation concealment was unclear. The length of follow-up was not reported. Unclear if investigators were blinded to treatment. People taking dihydroergotamine were allowed to take a second dose if it did not work. Although this was placebo controlled people taking triptan were not permitted second dose.

Table 89: Triptan vs ergot – Clinical summary of findings

Outcome	Triptan	Ergot	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours	128/150 (85.3%)	106/152 (69.7%)	RR 1.22 (1.08 to 1.39)	153 more per 1000 (from 56 more to 272 more)	VERY LOW
Sustained headache response at 24 hours	144/266 (54.1%)	104/266 (39.1%)	RR 1.38 (1.15 to 1.67)	149 more per 1000 (from 59 more to 262 more)	VERY LOW

11.3.9.2 Economic evidence

No relevant economic evaluations comparing subcutaneous triptans with subcutaneous or nasal ergots were identified. Subcutaneous or nasal ergots are not included in the BNF62[111] and their cost could not be estimated.

11.3.9.3 Evidence statements

Clinical:

One study with 310 people with migraine suggested that subcutaneous triptans may be more effective than subcutaneous ergots in producing a headache response at up to 2 hours, but the effect size is too small to be clinically important, and there is some uncertainty. [Very low quality].

One study with 317 people with migraine suggested that subcutaneous triptans may be more clinically effective than ergots administered as a nasal spray in sustaining headache response at 24 hours, but there is some uncertainty. [Very low quality].

No studies reported outcome data for freedom from pain at 2 hours, sustained freedom from pain at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found on this question and a simple cost analysis could not be conducted as subcutaneous or nasal ergots are not included in the BNF62 [111].

11.3.10 Opioid in combination with antiemetic vs NSAID

11.3.10.1 Clinical evidence

See evidence tables in appendix section E.2.3 and forest plots in Figure 79, Appendix G.2.2.

One study was identified which compared intramuscular opioid plus an antiemetic with an NSAID[64].

Table 90: Opioid in combination with an antiemetic vs NSAID– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response at up to 2 hours [64]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious [(b)]
Pain free at up to 2 hours	0	-	-	-	-	-
Sustained headache response at 24 hours	0	-	-	-	-	-
Sustained freedom from pain at 24 hours	0	-	-	-	-	-
Time to freedom from pain	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation unclear. Unclear whether groups were comparable at baseline. Three people participated twice in the study.
(b) The confidence intervals cross the minimal important difference in both directions making the effect size very uncertain.

Table 91: Opioid + antiemetic vs NSAID– Clinical summary of findings

Outcome	Opioid	Antiemetic	Relative risk	Absolute effect	Quality
Headache response at up to 2 hours [64]	14/25 (56%)	15/25 (60%)	RR 0.93 (0.58 to 1.5)	42 fewer per 1000 (from 252 fewer to 300 more)	VERY LOW

11.3.10.2 Economic evidence

No economic evaluations comparing opioids in combination with an antiemetic with NSAIDs administered as intravenous, intramuscular or subcutaneous preparations were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 75 in section 11.3.2.2).

11.3.10.3 Evidence statements

Clinical:

In one study with 50 people with migraine there is too much uncertainty to determine whether there is a difference between intramuscular opioids plus antiemetics and intramuscular NSAIDs in producing a headache response at up to 2 hours. [Very low quality].

No studies reported outcome data for freedom from pain at 2 hours, sustained headache response at 24 hours, sustained freedom from pain at 24 hours, time to freedom from pain, health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a small difference in drug costs between intravenous opioids in combination with an antiemetic and an intravenous NSAID. Intravenous opioids in combination with an antiemetic are slightly more costly than intravenous NSAIDs (respectively £1.82 and £0.89 per episode).

11.3.11 Recommendations and link to evidence

See recommendations and link to evidence in section 11.6.

11.4 Network Meta-analysis

A network meta-analysis (NMA) was performed for the treatments administered by oral and subcutaneous routes to help inform the recommendations.

The analyses were based on a total of 19 studies of 10 different interventions (five monotherapy and five different combinations of two agents). These studies formed four networks of evidence for the key outcomes identified by the GDG, i.e. a separate network is developed for each of the four outcomes: headache response at up to two hours, freedom from pain at up to two hours, sustained headache response at 24 hours and sustained freedom from pain at 24 hours. The interventions included in each network are shown in Table 92 below. For more details on these networks, please see appendix I. The baseline risk is defined here as the adult or young person's risk of achieving the outcome of interest (headache response, freedom from pain, sustained headache response, sustained freedom from pain) in the 'control' group. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks.

Table 92: Interventions included in network meta-analysis

Headache response at up to 2 hours	Freedom from pain at up to 2 hours	Sustained headache response at 24 hours	Sustained freedom from pain at 24 hours
Triptan	Triptan	Triptan	Triptan
NSAIDs	NSAIDs	NSAIDs	NSAIDs
Ergot	Ergot	Ergot	Ergot
Paracetamol	Paracetamol	Paracetamol	Paracetamol
Triptan with paracetamol	Triptan with paracetamol	Triptan with paracetamol	Triptan with paracetamol
Triptan with NSAID	Triptan with NSAID	Triptan with NSAID	Triptan with NSAID
Aspirin	Aspirin	-	-
Aspirin with antiemetic	Aspirin with antiemetic	-	-
Paracetamol with aspirin	-	-	-
Paracetamol with antiemetic	-	-	-

11.4.1.1 Evidence statements

First network – headache response at up to two hours

A network meta-analysis of 18 studies comparing ten treatments suggested that triptan in combination with paracetamol is ranked as the best treatment, triptan in combination with an NSAID is ranked second, paracetamol in combination with an anti-emetic third, paracetamol in combination with aspirin 4th, triptan 5th, aspirin in combination with an antiemetic 6th, aspirin 7th, NSAID 8th, paracetamol 9th and ergots ranked least effective at producing headache response at two hours, but there was considerable uncertainty.

A network meta-analysis of 18 studies comparing ten treatments suggested that NSAIDs, triptan in combination with paracetamol, paracetamol in combination with aspirin, triptan in combination with paracetamol, triptan in combination with an NSAID, triptan, aspirin, paracetamol in combination with aspirin and paracetamol in combination with an antiemetic are more effective than ergots in producing headache response at two hours.

A network meta-analysis of 18 studies comparing ten treatments suggested that triptan in combination with paracetamol is more effective than aspirin or paracetamol in producing headache response at two hours.

A network meta-analysis of 18 studies comparing ten treatments suggested that triptan in combination with an NSAID is more effective than triptan, NSAID, aspirin in combination with an antiemetic, aspirin in combination with paracetamol and aspirin as monotherapy in producing headache response at two hours.

A network meta-analysis of 18 studies comparing ten treatments suggested that paracetamol in combination with aspirin is more effective than triptan alone in producing headache response at two hours.

A network meta-analysis of 18 studies comparing ten treatments suggested that aspirin in combination with an antiemetic is more effective than ergots in producing headache response at two hours.

Second network – freedom from pain at up to two hours

A network meta-analysis of 13 studies comparing eight treatments suggested that triptan in combination with NSAID is ranked as the best treatment, paracetamol is ranked second, triptan third, NSAID and aspirin are joint 4th, aspirin in combination with an antiemetic 6th, paracetamol 7th, and ergots were ranked as least effective at producing freedom from pain at two hours, but there was some uncertainty.

A network meta-analysis of 13 studies comparing eight treatments suggested that triptan is more effective than NSAIDs, ergots, aspirin and aspirin in combination with an antiemetic in producing freedom from pain at two hours.

A network meta-analysis of 13 studies comparing eight treatments suggested that NSAIDs, triptan in combination with paracetamol, triptan in combination with an NSIAD, paracetamol, aspirin or aspirin in combination with an antiemetic are more effective than ergots in producing freedom from pain at two hours.

A network meta-analysis of 13 studies comparing eight treatments suggested that triptan in combination with an NSAID are more effective than triptans, NSAIDs, paracetamol, aspirin and aspirin in combination with an antiemetic in producing freedom from pain at two hours.

A network meta-analysis of 13 studies comparing eight treatments suggested that triptan in combination with paracetamol is more effective than paracetamol alone and over ergot in producing freedom from pain at two hours.

Third network – sustained headache response at 24 hours

A network meta-analysis of six studies comparing six treatments suggested that triptan in combination with an NSAID is ranked as the best treatment, triptan in combination with paracetamol second, triptan third, NSAID 4th, paracetamol 5th and ergot as the least effective treatment in producing sustained headache response at 24 hours.

A network meta-analysis of six studies comparing six treatments suggested that triptans are more effective than NSAIDs in producing sustained headache response at 24 hours.

A network meta-analysis of six studies comparing six treatments suggested that triptan in combination with an NSAID are more effective than triptans or NSAIDs in producing sustained headache response at 24 hours.

A network meta-analysis of six studies comparing six treatments suggested that NSAIDs, triptan, triptan in combination with paracetamol and triptan in combination with an NSAID are more effective than ergots in producing sustained headache response at 24 hours.

A network meta-analysis of six studies comparing six treatments suggested that triptan in combination with paracetamol and triptan in combination with an NSAID are more effective than paracetamol in producing sustained headache response at 24 hours.

Fourth network – sustained freedom from pain at 24 hours

A network meta-analysis of six studies comparing six treatments suggested that triptan in combination with an NSAID is the most effective treatment, triptan in combination with paracetamol second, triptan their, NSAID 4th, paracetamol 5th and ergot the least effective treatment at producing sustained freedom from pain at 24 hours.

A network meta-analysis of six studies comparing six treatments suggested that triptans are more effective than NSAIDs in producing sustained freedom from pain at 24 hours.

A network meta-analysis of six studies comparing six treatments suggested that triptan in combination with an NSAID is more effective than triptan or NSAIDs in producing sustained freedom from pain at 24 hours.

A network meta-analysis of six studies comparing six treatments suggested that triptans, NSAIDs, triptan in combination with paracetamol and triptan in combination with an NSAID are more effective than ergots in producing sustained freedom from pain at 24 hours.

For detailed explanation on methodology and results of NMA refer to Appendix I.

11.5 Economic evidence

No economic studies comparing oral treatments for acute migraine attacks were included. One study[193] comparing triptans with ergots was excluded due to its limited applicability to the NHS UK setting as the study was conducted in the USA and QALYs were not calculated. Two cost-utility analyses[76,276], one from Canada one from the USA, were excluded because they were less applicable compared to our original analysis. The results of the Canadian study[76] were in agreement with our findings (triptans more cost-effective than ergots) while the USA study[276] showed triptans to be both more effective and less costly than ergots (ergots were dominated); this could be due to the inclusion of indirect costs (ie participant travel and waiting time) and emergency rooms and hospitalisation costs for some of the people with no migraine relief. If we had included those costs in our model, less effective treatments such as ergots would have had higher costs.

Other economic evaluations[30,31,159,252] were excluded from our literature review as triptans were not compared to any specific treatment strategy but to usual care or to treatment with no triptans.

The topic of oral acute treatment for resolution of headache was chosen by the GDG as one of their top two priorities for original economic analysis, since it is likely to be a consideration for most headaches people at some point. Further details of the original cost-effectiveness analysis can be found in Appendix J.

Health economic modelling

<u>a) Model overview/methods</u>

A cost-utility analysis was undertaken where costs and QALYs are considered from a UK NHS and personal social services perspective. The time horizon considered in the model is 24 hours.

The comparators considered in the model are: NSAIDs, paracetamol, ergotamine tartrate, triptans, triptan+NSAID and triptan+paracetamol. ‘No treatment’ was not an option in the model, since the GDG considered based on usual clinical experiencethat people presenting with migraine are always prescribed some form of acute treatment.

The population entering the model comprises people experiencing an acute migraine attack, indicated for oral treatment, and population characteristics were as in the clinical review: people aged 12 or over, diagnosed with migraine.

Sustained pain free at 24 hours is the intermediate outcome incorporated into the model and is based on our clinical review and network meta-analysis (see 11.4). We did not use the outcome ‘sustained pain free at 2 hours’ and the model assumes that the QALY gain occurs in the 2-24 hour time window only. The model structure is represented in Figure 2.

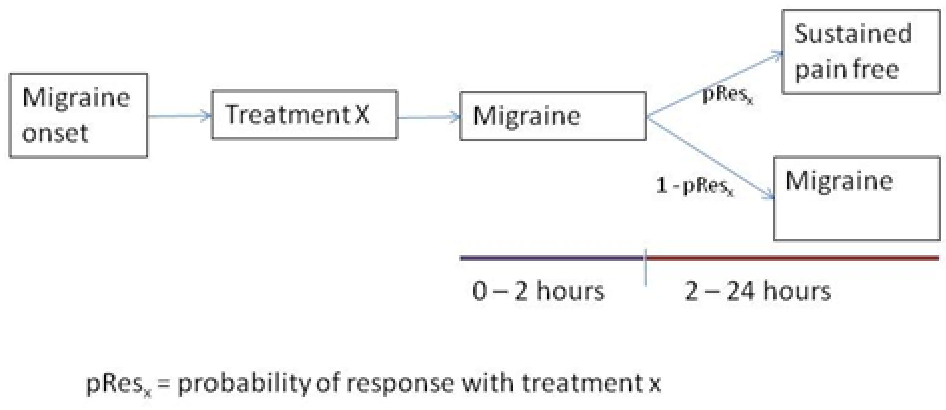

Figure 2: Acute treatment model structure

A utility weight of -0.3 is attached to the migraine state in the model – i.e. the initial 2 hours and the following 22 hours for the proportion of people who do not respond to treatment. The value of the utility weight was obtained from a study[76] which used a previous Canadian prevalence study and the Quality of Wellbeing (QWB) measure to derive a utility weight for an 'average migraine attack'.

Cost components in our model are only the cost of one drug administration, based on the acquisition cost reported in the BNF[112]. Therefore all downstream costs, such as visits to healthcare professionals, tests and rescue medication are omitted from the model.

b) Results

The average cost and QALYs gained with each strategy is reported in Table 93. In this table interventions are ranked according to their mean net benefit, which depends on the costs, QALYs and willingness to pay (set at £20,000/QALY in our analysis).

Table 93: Base case probabilistic results in the model

Rank	Treatment	Average cost	Average QALYs	Net benefit
1	Triptan+NSAID	£2.23	0.000007	-2.099
2	Triptan+Paracetamol	£2.20	-0.000048	-3.156
3	Triptan	£2.17	-0.000280	-7.763
4	Paracetamol	£0.03	-0.000415	-8.334
5	NSAID	£0.06	-0.000447	-8.992
6	Ergot	£0.34	-0.000602	-12.373

Overall, Triptan + NSAID was ranked the most cost effective treatment in the base case analysis. To reflect the uncertainty in model results we produced rank-probability graphs (Figure 3).

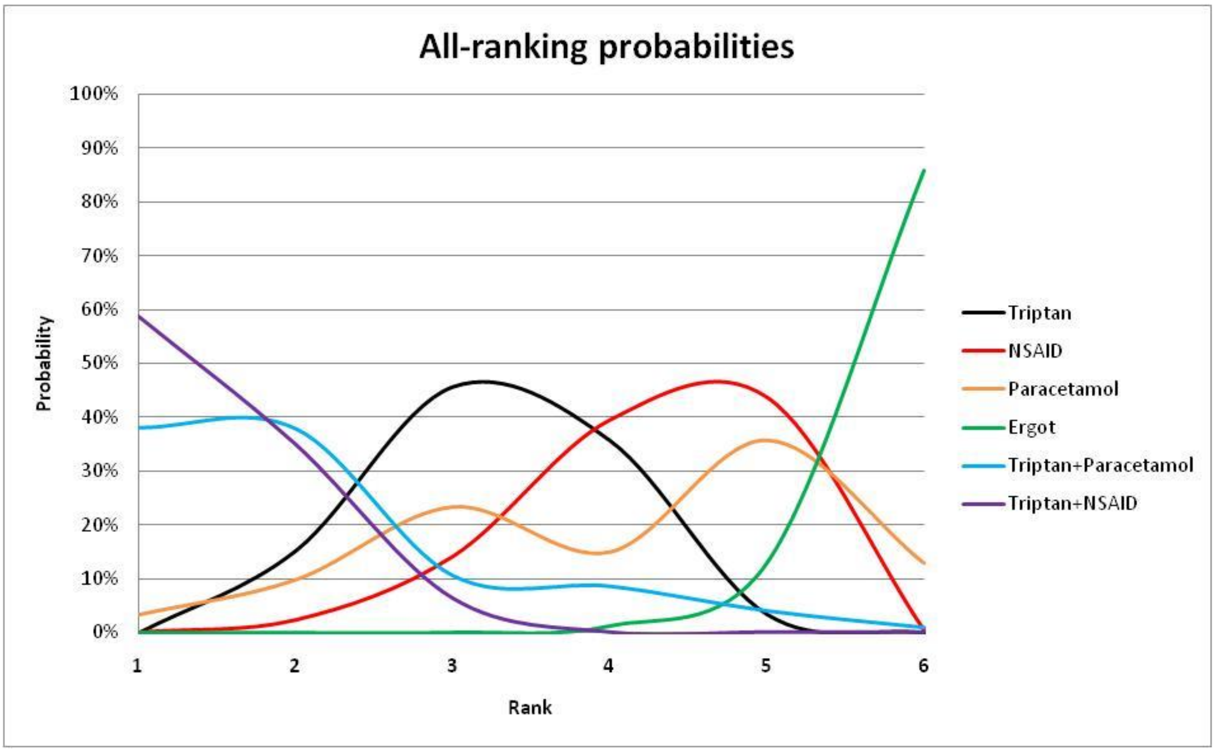

Figure 3: Rank-probability graph. The y-axis shows the rank and the x-axis shows the probability of a given treatment obtaining that rank.

Figure 3 shows that the two treatments with the highest probability of being cost effective are triptan + NSAID and triptan + paracetamol.

One way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters. The following changes were tested:

- Sustained headache response at 24 hours is the intermediate outcome considered (base case was sustained pain relief at 24 hours)
- Utility weight after migraine relief = 0.5 (base case was 0.81)
- Triptan costs were varied using a minimum value (£0.21), or maximum (£7.75) (base case was £2.17).

Throughout these sensitivity analyses, triptan + NSAID remain always the most cost effective treatment.

c) Limitations

This model is based on findings from RCTs and therefore any issues concerning interpretation of the clinical review also apply to interpretation of the economic analysis. One limitation of the model is that it only applies to one-off treatment, therefore downstream costs such as consultations, tests and emergency room visits are not factored in. This is a conservative estimate of cost effectiveness and therefore would not change our conclusions about the optimal treatment (which is the most costly one), but we may have underestimated the cost effectiveness of for example, triptan monotherapy. Furthermore, in modelling one-off treatment only and due to the scarce reporting of adverse events in the RCTs, we are unable to model the disutility of treatment-specific adverse events. This should be considered when interpreting the results of the analysis.

11.6 Recommendations and link to evidence

Recommendations	**Offer combination therapy with an oral triptan[z] and an NSAID, or an oral triptanz and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For young people aged 12–17 years consider a nasal triptan in preference to an oral triptanz.**
Relative values of different outcomes	The GDG considered that the four outcomes included in the network meta-analysis were of equal value for acute migraine: headache response at up to 2 hours, pain free at up to 2 hours, sustained headache response at 24 hours and sustained pain free at 24 hours.
Trade off between clinical benefits and harms	The risk of medication overuse headache with the use of triptans should be considered. However the evidence shows good efficacy of these treatments used in combination. The potential side-effects of non-steroidal drugs, especially gastric ulceration and bleeding and cardiovascular risks should be balanced against the more rapid and prolonged benefit when used in combination with a triptan for treating an acute migraine episode.
Economic considerations	Our original cost-effectiveness analysis showed that a triptan in combination with NSAID is the most cost-effective treatment for the management of acute migraine. Triptan in combination with paracetamol was the second most cost-effective intervention. They were both more costly than other strategies but they were also more effective. In the probabilistic sensitivity analysis, triptan + NSAID was the most cost-effective strategy in about 60% of the simulations while triptan + paracetamol came out the most cost-effective strategy in about 38% of the simulations. While there is some uncertainty when deciding which strategy between the two is the most cost-effective, it is quite certain that both of them are the two most cost-effective options for the acute treatment of migraine.
Quality of evidence	The evidence from the network meta-analysis (based on low and very low quality direct comparison evidence) showed good efficacy of these combinations when compared to singly administered treatments. The evidence suggested that triptan and NSAID was a more effective combination. All evidence is based on oral administered drugs. Only one study of triptan use included people less than 18 years old. The economic evidence Is directly applicable, however it has serious limitations.
Other considerations	The GDG considered that people may prefer to take one drug rather than two. It is likely however that most people consulting a healthcare professional for migraine will take tried over the counter preparations such as paracetamol or NSAIDs before they consult. The GDG considered it important that patients and health professionals are informed of the added efficacy of taking these drugs in combination although patient preference and experience should inform the decision of which treatment to prescribe. The GDG considered the use of triptans for the 12-17 age groups and agreed that triptans were an appropriate option for younger people. Oral triptans are not licensed for use in people aged

[z] At the time of publication (September 2012), triptans (with the exception of nasal sumatriptan) did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

	under 18, sumatriptan is licensed to use as a nasal spray in the under 18 age group and the GDG agreed to indicate this in the recommendation.

Recommendations	**For people who prefer to take only one drug, consider monotherapy with an oral triptan[aa], NSAID, aspirin[bb] (900 mg) or paracetamol for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events.**
Relative values of different outcomes	The GDG considered that the four of the outcomes included in the network meta-analysis were of equal value for acute migraine; headache response at up to 2 hours, pain free at up to 2 hours, sustained headache response at 24 hours and sustained pain free at 24 hours.
Trade off between clinical benefits and harms	The risk of medication overuse headache with acute treatments should be considered. NSAIDs can cause gastric ulceration, reduce renal function and may trigger an anaphylactic reaction in susceptible individuals. Aspirin should not be given to children under 16 years because of potential risk of Reye's syndrome.
Economic considerations	Monotherapy with oral triptans, NSAID, and paracetamol were strategies evaluated in an original cost-utility analysis developed for the guideline. Although in the base case analysis triptan + NSAID and triptan + paracetamol are more effective and cost-effective than monotherapies, results might have been driven by the population included in the RCTs for whom monotherapies had already been tried ineffectively. Aspirin was not included in the original model developed for the guideline due to the absence of RCT reporting the effectiveness at 24 hours. However based on the acquisition cost, aspirin is less costly than other options and from the clinical evidence it is effective at 2 hours. The economic model did not take into account potential adverse events of treatments, therefore these should be considered when deciding the treatment strategy.
Quality of evidence	The direct evidence is of moderate to very low quality. Only one study of triptan use included people less than 18 years. Network meta-analysis of the evidence shows moderate efficacy for these treatments. All evidence is from oral administered drugs and is for the NSAIDs at 400mg minimum, aspirin at 900mg minimum and paracetamol at 1000mg. The economic evidence has direct applicability and potentially serious limitations.
Other considerations	The GDG agreed that there is evidence that compliance may be better with single administrations than dual administration of treatment. Patient preference and experience should inform the decision of which treatment to prescribe. The GDG considered the use of triptans for the 12-17 age groups and agreed that triptans were an appropriate option for younger people. Oral triptans are not licensed for use in people aged under 18 but sumatriptan is licensed to use as a nasal spray in the under 18 age group. GDG consensus opinion was that

[aa] At the time of publication (September 2012), triptans (with the exception of nasal sumatriptan) did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[bb] Because of an association with Reye's syndrome, preparations containing aspirin should not be offered to people aged under 16 years.

	failure to respond to a particular triptan may not be indicative that another triptan will also not work, therefore it may be worth considering an alternative triptan if there's no response to the first one. Studies for aspirin were either 500mg or 1000mg, these were pooled for analysis. GDG consensus opinion was that the higher doses are more effective, therefore agreed to recommend 900mg.

Recommendations	**When prescribing a triptan[cc], start with the one that has the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans.**
Relative values of different outcomes	The GDG considered that the four of the outcomes included in the network meta-analysis were of equal value for acute migraine; headache response at up to 2 hours, pain free at up to 2 hours, sustained headache response at 24 hours and sustained pain free at 24 hours. This recommendation was based on GDG informal consensus.
Trade off between clinical benefits and harms	The risk of medication overuse headache with acute treatments should be considered. The GDG considered that efficacy of triptans can vary between individuals.
Economic considerations	The GDG considered that different triptans were equally effective. Based on this assumption, it is cost effective to try a less costly triptan first because if this is effective, it would save some resources compared to prescribing a more expensive triptan.
Quality of evidence	The direct evidence is of moderate to very low quality. Network meta-analysis of the evidence shows moderate efficacy for triptans. The GDG agreed that triptans should be reviewed as a class (as detailed in the protocol), and therefore no evidence was reviewed comparing different triptans to each other. GDG consensus opinion was that failure to respond to a particular triptan may not be indicative that another triptan will also not work, so this recommendation was formed on informal consensus.
Other considerations	GDG consensus opinion was that failure to respond to a particular triptan may not be indicative that another triptan will also not work, therefore it may be worth considering an alternative triptan if there's no response to the first one. Response should not be judged on one migraine attack alone- the GDG considered that people should be encouraged to use triptan for at least three attacks before considering an alternative triptan. Sumatriptan is licensed to use as a nasal spray in the under 18 age group but other triptans are unlicensed in this age group.

Recommendations	**Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting.**
Relative values of different outcomes	The GDG considered that the four of the outcomes included in the network meta-analysis were of equal value for acute migraine: headache response at up to 2 hours, pain free at up to 2 hours, sustained headache response at 24 hours

[cc] At the time of publication (September 2012), triptans (with the exception of nasal sumatriptan) did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

	and sustained pain free at 24 hours.
Trade off between clinical benefits and harms	There is a small risk that anti-emetic drugs can trigger extra pyramidal side effects; the GDG agreed the risk is higher in those under the age of 20. These reactions which include dystonic reactions can be frightening but are rare and reversible. The GDG also considered the practical difficulty of ingesting three medications together and whether this could trigger more nausea and vomiting.
Economic considerations	Antiemetics in addition to mono or dual therapy were not included in the original model developed for the guideline due to the absence of RCT reporting the effectiveness at 24 hours. However based on the acquisition cost, antiemetics are less costly than other options and from the clinical evidence combinations with antiemetics are effective at 2 hours.
Quality of evidence	The addition of an antiemetic is based on GDG informal consensus. However there was very low quality evidence from one study suggesting paracetamol + anti emetic to more effective than triptans in producing headache response at 2 hours and indirect evidence from non-oral administration of antiemetics showing efficacy at producing freedom from pain at 2 and 24 hours (moderate to very low quality evidence).
Other considerations	The decision to add an antiemetic is likely to depend on patient preference and experience of benefit without anti-emetic. Many people will find it easier and preferable to use fewer drugs, at least initially. The GDG considered it useful for the generalist to be made aware that anti-emetics may have an effect on migraine itself and can be a useful adjunct even if the patient does not have significant nausea and vomiting. The GDG were aware that anti-emetic has historically been included in treatment for effect on nausea and vomiting alone and that for patients with significant nausea and vomiting anti-emetic might be required for those symptoms as well.

Recommendations	**Do not offer ergots or opioids for the acute treatment of migraine.**
Relative values of different outcomes	The GDG considered that the four of the outcomes included in the network meta-analysis were of equal value for acute migraine - headache response at up to 2 hours, pain free at up to 2 hours, sustained headache response at 24 hours and sustained pain free at 24 hours.
Trade off between clinical benefits and harms	The other treatments reviewed in the network meta-analysis were superior to ergots in producing headache response or freedom from pain at up 2 or at 24 hours, with the exception of paracetamol where there is no difference in efficacy. The GDG agreed that the high risk of adverse events associated with the use of ergots, together with the evidence for superiority of comparator treatments, supported this negative recommendation for ergots in the treatment of acute migraine. There was little evidence for effectiveness of opioids in the analyses, but they are known to have addictive properties and the potential to lead to medication overuse headache.
Economic considerations	The original cost-effectiveness analysis showed that ergots are the least cost-effective treatment for the management of acute migraine when compared to triptans + NSAID, triptans + paracetamol, triptans, paracetamol and NSAID. The average acquisition cost of ergots is higher than the cost of NSAID or paracetamol while they are less effective at improving sustained pain-free at 24 hours. Based on the acquisition cost, opioids are more costly than other treatments (e.g. paracetamol, NSAID) for which we have stronger evidence of effectiveness. Opioids are also known to have side effects that have an important impact on the quality of life.

Quality of evidence	The direct evidence for ergots was of very low quality and was in favour of the comparator (triptan). Network meta-analysis of the available evidence did not favour ergots. The GDG agreed that this evidence together with their informal consensus opinion on the high risk of adverse events was sufficient quality evidence for this recommendation. No evidence was identified for opioids and these were therefore not included in the network meta-analysis. The economic evidence for ergots is directly applicable; however it has potentially serious limitations. The economic evidence for opioids was based on a limited cost analysis based only on the drug acquisition cost.
Other considerations	The recommendation against the use of ergots was based on evidence for oral, nasal, subcutaneous and intravenous preparations of ergot derivatives. Opioids may exacerbate nausea and will also increase the risk of medication overuse headache.

Recommendations	**For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:** • **offer a non-oral preparation of metoclopramide or prochlorperazine[dd] and** • **consider adding a non-oral NSAID or triptan[ee] if these have not been tried.**
Relative values of different outcomes	The GDG agreed that pain free at 2 hours and headache response at up to 2 hours were of more importance than 24 hour outcomes for people who had already failed oral treatment or self-administered therapy.
Trade off between clinical benefits and harms	There is a small risk that anti-emetic drugs can trigger extra pyramidal side effects; the GDG agreed the risk is higher in those under the age of 20. These reactions which include dystonic reactions can be frightening but are rare and reversible. The GDG agreed that the benefits of dopamine receptor antagonists (metoclopramide or prochlorperazine) justify their use with consideration of the side-effects in at risk groups. The GDG agreed by informal consensus that additional benefits may be achieved by co-administering an NSAID or triptan.
Economic considerations	A simple cost analysis based on the acquisition cost of drugs showed that intramuscular and intravenous antiemetics and intravenous NSAIDs are associated with small costs and they are deemed to be cost-effective options for people who are unable to take oral treatment.

[dd] At the time of publication (September 2012), prochlorperazine (except for a buccal preparation) did not have a UK marketing authorisation for this indication but is licensed for the relief of nausea and vomiting.The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[ee] At the time of publication (September 2012), triptans (with the exception of nasal sumatriptan) did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

	Subcutaneous triptans are much more costly than the other options considered. The GDG considered this increase in cost justifiable for people not able to take NSAIDs or where they already been used and have been ineffective. The population for whom non-oral medications are being considered are often those with significant nausea and vomiting and healthcare professionals are often reluctant to treat these people with NSAIDs.
Quality of evidence	There is evidence from this systematic review that antiemetics are effective for pain relief, regardless of whether the person has either nausea or vomiting. The evidence review included chlorpromazine, metoclopramide and prochlorpromazine (moderate, low and very low quality evidence). However, parenteral chlorpromazine is not widely used in the UK in the non-palliative setting, therefore the GDG agreed not to make a recommendation for or against its use for migraine treatment. Intravenous or rectal preparations of prochlorperazine are not available the UK and therefore their use by intramuscular administration should be considered. This was agreed by GDG informal consensus. The evidence for prochlorperazine included children in the study population. Although none of the evidence for metoclopramide included in this review was for children and young people aged under 18, the GDG agreed that there were no other considerations for the use of this drug in the 12-17 year old age group (except those stated above in trade offs between clinical benefits and harms) and it could be recommended. There is evidence for good effectiveness of subcutaneous triptans and intravenous NSAIDs given in isolation (low and very low quality). GDG consensus (informal methods) agreed that their use in addition to the antiemetic should be recommended. Intramuscular or rectal administration was based on GDG informal consensus if intravenous administration not available or appropriate. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs.
Other considerations	This recommendation would mainly apply in accident and emergency settings and for out-of-hours GPs. Reasons for oral treatment not being appropriate could include vomiting, previous attempt at oral treatment which has been ineffective and patient choice. The GDG noted that hypotension is more likely when prochlorperazine is given intramuscularly, than by oral administration. If the individual has already taken an NSAID or triptan with unsatisfactory response, do not re-administer the same drug parenterally in addition to the antiemetic.

12 Acute pharmacological treatment of cluster headache

12.1 Introduction

Cluster headache is a strictly unilateral headache that occurs in association with cranial autonomic features (red eye on same side as headache, lacrimation, small pupil, drooping eyelid, eyelid oedema, nasal congestion, watery nose, forehead and facial sweating). It is an excruciating disorder and is probably one of the most painful conditions known to mankind with female sufferers describing each attack as being worse than childbirth. In most people, it has a striking circannual and circadian periodicity.

Cluster headache is a disorder with highly distinctive clinical features. Several of the terms used to describe cluster headache can be confusing so have been defined here. A cluster headache or attack is an individual episode of pain that can last from a few minutes to some hours. A cluster bout or period refers to the duration over which recurrent cluster attacks are occurring; it usually lasts some weeks or months. A remission is the pain-free period between two cluster bouts.

Cluster headache is classified according to the duration of the bout. About 80-90% of sufferers have episodic cluster headache (ECH), which is diagnosed when they experience recurrent bouts. The remaining 10-20% of sufferers have chronic cluster headache (CCH) in which either no remission occurs within one year or the remissions last less than one month. Most people with ECH have one or two annual cluster periods, each lasting between one and three months. Often, a striking periodicity is seen with the cluster periods, with the bouts occurring in the same month of the year.

The prevalence of cluster headache is estimated to be 0.2%. The male:female ratio is 2.5-7.2:1. It can begin at any age though the most common age of onset is the third or fourth decade of life.

Treatment for cluster headache relies on therapy to abort the individual attack, and prophylactic therapy aims to prevent or suppress attacks during the cluster bout (considered in chapter 16 of this guideline). Acute attack therapy must be fast-acting, be easily bioavailable, and provide effective relief from the symptoms. A low adverse-effect profile is also desirable. In routine clinical practice, a wide range of headache abortive treatments including aspirin, paracetamol, oxygen, triptans, ergots, NSAIDs, and opioids are used. The mechanism of action of the effective agents is largely unknown.

12.1.1 Clinical question

In people with cluster headache, what is the clinical evidence and cost-effectiveness for acute pharmacological treatment with: aspirin, paracetamol, oxygen, triptans, ergots, NSAIDs, and opioids?

A literature search was conducted for RCTs comparing the clinical effectiveness of different pharmacological interventions for acute treatment of cluster headache. The interventions we included in our search were paracetamol, NSAIDs, weak and strong opioids, triptans, oxygen, ergotamine and dihydroergotamine and placebo. We looked for any studies that compared the effectiveness of two or more of these treatments (or placebo). The initial protocol did not include placebo comparisons, however due to the limited amount of evidence available the guideline development group decided to amend the protocol to include placebo so that the review did not omit important evidence (see protocol C.2.4).

12.2 Matrix of treatment comparisons

Below is a matrix showing where evidence was identified. A box filled with a number represents the number of studies found, which are reviewed in this chapter. A box filled with - represents where no evidence was found. In this case, no section on this comparison is included in the chapter. The GDG were interested in the use of aspirin, paracetamol, NSAIDs, and opioids for the acute treatment of cluster headaches, but no evidence was identified in the review.

Paracetamol	-						
NSAIDS (including aspirin at appropriate dose)	-	-					
Opioids- weak	-	-	-				
Opioids- strong	-	-	-	-			
Triptans	5	-	-	-	-		
Oxygen	2	-	-	-	-	-	
Ergots	1	-	-	-	-	-	1
	Placebo	**Paracetamol**	**NSAIDs**	**Opioids – weak**	**Opioids – strong**	**Triptans**	**Oxygen**

Two Cochrane reviews were identified on the acute treatment of cluster headaches. One of these on the use of normobaric or hyperbaric oxygen therapy for treatment of cluster headache was excluded as it included studies in children aged less than twelve years of age[16], any studies relevant to our protocol were included. The second Cochrane review[140] did meet the review protocol, however the data were re-analysed to allow addition of new data. One study from the review was not included [11] as both the population and data analysis were unclear.

12.2.1 100% Oxygen vs air

12.2.1.1 Clinical evidence

See evidence tables in appendix section E.2.4 and forest plots in Figures 80-81, appendix G.2.3.

Two studies were identified comparing 100% oxygen to air[40,80]. Populations were recruited from neurology departments, support groups and also from outpatient clinics. Studies analysed included both high flow (12 L/ min) oxygen and low flow (6 L/min) oxygen as interventions.

Both studies reported data on reduction in pain at 30 minutes, however data from one study [80] could not be meta-analysed because the results were not reported in a useable format.

Data on adverse events was reported differently across studies and could not be meta-analysed. None of the studies reported functional health status or health related quality of life data.

Table 94: 100% oxygen vs air – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache response (at 1 hour)[40]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Reduction in pain at 30	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
minutes[40]						
Time to freedom from pain	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Incidence of adverse events	0	-	-	-	-	-

(a) Incomplete accounting of participants and outcome events.

Table 95: 100% oxygen vs air – Clinical summary of findings

Outcome	100% Oxygen	Air	Relative risk	Absolute effect	Quality
Headache response (at 1 hour)	95/103 (92%)	38/64 (59%)	RR 2.25 (1.67 to 3.05)	327 more per 1000 (from 154 more to 546 more)	MODERATE
Reduction in pain at 30 minutes	93/109 (85%)	28/74 (38%)	RR 1.55 (1.26 to 1.92)	473 more per 1000 (from 254 more to 776 more)	MODERATE

Table 96: 100% oxygen vs air – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Reduction in pain at 30 minutes[80]	1	Randomised trials	Serious [(a), (b)]	No serious inconsistency	No serious indirectness	Serious [(c)]
Time to freedom from pain	0	-	-	-	-	-
Headache response (up to 2 hours)	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Incidence of adverse events	0	-	-	-	-	-

(a) The study used unvalidated patient-reported outcomes.
(b) The population was exclusively male.
(c) The confidence interval crosses the minimal important difference making the effect size uncertain.

Table 97: 100% oxygen vs air – Clinical summary of findings

Outcome	100% Oxygen	Air	Relative risk	Absolute effect	Quality
Reduction in pain at 30 minutes (a) (mean [SE])	1.93 (0.22)	0.77 (0.23)	RR 5.99 (1.01 to 35.64) (b)	(c)	LOW

(a) Reduction in pain at 30 minutes was measured using a pain relief score where 0= no relief and 3= complete relief.
(b) Relative risk was calculated from the Log [Risk Ratio] reported in the study.
(c) Result for absolute risk could not be calculated.

12.2.1.2 Economic evidence

No economic evidence for oxygen in the treatment of cluster headache was identified.

Providers of home oxygen therapy vary across England and Wales and it was not possible to obtain any information on the cost of this service from them.

We found some national data from the Primary Care Commissioning publication on Home Oxygen Service[185] where it was estimated that the Home Oxygen Service costs around £175 per new person and around £69 per 6-month check-up, based on the 2008/9 Reference Cost data obtained from 20 submissions for an outpatient 'Oxygen Assessment and Review' service (currency code DZ38Z). These submissions comprised various service setups and the Home Oxygen Service can be expected to have smaller unit costs because of its scale, and the comparatively low resource usage of the half-hour 6-month check-ups.

This information relates to the provision of oxygen for various conditions (e.g. chronic obstructive pulmonary disease) and no specific cost could be determined for people with cluster headache.

12.2.1.3 Evidence statements

Clinical:

One study with 109 people with cluster headache showed that 100% oxygen is more clinically effective than air in reducing pain at 30 minutes. [Moderate quality].

One study with 19 people with cluster headache suggested that 100% oxygen may be more clinically effective than air in reducing pain at 30 minutes, but there is some uncertainty. [Low quality].

One study with 109 people with cluster headache showed that 100% oxygen is more clinically effective than air at producing headache response at one hour. [Moderate quality].

No studies reported outcome data for time to freedom from pain, functional health status and health related quality of life or incidence of serious adverse events.

Economic: No economic evidence was found for this question. The cost of home oxygen service was estimated at £175 per new person and around £69 per 6-month check-up. However, these figures are not specific to people with cluster headache and costs are expected to be smaller due to a better efficient use of resources achieved with the new setup of service provision.

12.2.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 12.3.

12.2.2 100% oxygen vs ergot

12.2.2.1 Clinical evidence

See evidence tables in appendix section E.2.4 and forest plots in Figure 82, appendix G.2.3.

One study was identified comparing 100% oxygen to ergotamine [132,132], this was a crossover trial that looked at an outpatient headache clinic population comparing low flow oxygen (7 L/min) and sublingual ergotamine tartrate (dose not stated). ITT with last observation carried forward only was available for data analysis[132,132].

Table 98: 100% oxygen vs ergot – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Reduction in pain at 30 minutes[132,132]	1	Randomised trials	Very serious[(a), (b), (c)]	No serious inconsistency	No serious indirectness	Serious [(d)]
Time to freedom from pain	0	-	-	-	-	-
Headache response (up to 2 hours)	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Incidence of adverse events	0	-	-	-	-	-

(a) Randomisation, allocation concealment and blinding were not reported
(b) Population and inclusion criteria were unclear
(c) The duration of the trial was unclear
(d)The upper limit of the confidence interval crosses the minimal important difference making the effect size uncertain.

Table 99: 100% oxygen vs ergot – Clinical summary of findings

Outcome	100% oxygen	Ergot	Relative risk	Absolute effect	Quality
Reduction in pain at 30 minutes	41/50 (82%)	35/50 (70%)	RR 1.17 (0.94 to 1.46)	119 more per 1000 (from 42 fewer to 322 more)	VERY LOW

12.2.2.2 Economic evidence

No economic evaluations comparing 100% oxygen with ergotamine were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 100 below). The cost of 100% oxygen is reported in section 12.2.1.2.

Table 100: Unit cost of drugs

Drug	Cost per episode [a] (£)	Notes
Intravenous NSAID	0.89	Intravenous Ketorolac – Dose: 10 mg
Intravenous paracetamol	1.25	Dose: 1g for adults over 50kg.
Intramuscular Opioids	2.44	Codeine – Dose: 60mg
Opioids – oral	0.09	Codeine phosphate - dose 2 x 30 mg
Subcutaneous triptans	21.24	Sumatriptan: £42.47 for 2 syringes
Nasal spray triptans	5.90	Sumatriptan - dose: 20 mg (1 unit)
	6.08	Zolmitriptan – dose: 5 mg (1 unit)
	12.16	Zolmitriptan – dose: 10 mg (2 units)
Aspirin – oral	0.02	Dose: 2x300 mg
Paracetamol – oral	0.02	Dose: 2*500 mg
NSAID – ibuprofen	0.02	Dose: 400 mg
NSAID – naproxen	0.06	Dose: 500 mg
NSAID – aceclofenac	0.17	Dose: 100 mg
NSAID – tolfenamic acid	1.65	Dose: 200 mg
Ergots - Cafergot	0.34	Dose: 2*100 mg

Source: BNF62[111]

The costs of adverse effects and further events were not estimated.

12.2.2.3 Evidence statement

Clinical:

One study with 50 people with cluster headache suggested that 100% oxygen may be more effective than ergotamine in reducing pain at 30 minutes, but the effect size is too small to be clinically important and there is considerable uncertainty. [Very low quality].

No studies reported outcome data for headache response, time to freedom from pain, functional health status and health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed a difference in costs between oxygen and ergotamine but it is difficult to compare the two estimates because the cost of oxygen is a long-term estimate (£175 per new patient and £69 per 6-month check-up for oxygen service) while the cost of ergotamine is a short-term cost (£0.34 per episode).

12.2.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 12.3.

12.2.3 Triptan vs placebo

12.2.3.1 Clinical evidence

See evidence tables in appendix section E.2.4 and forest plots in Figures 83-84, appendix G.2.3.

Five studies were identified comparing triptan to placebo. All studies included were crossover trials that included populations from neurology departments and headache clinics; two studies were carried out on an inpatient population.

The triptans considered in this review were zolmitriptan and sumatriptan which were pooled for analysis; the routes of administration were either nasal or subcutaneous, also pooled for analysis (see protocol C.2.4). No heterogeneity was observed.

Data on adverse events was reported differently across studies and could not be meta-analysed. None of the studies reported functional health status or health related quality of life data. Time to freedom from pain was reported in one study[259]; the data could not be meta-analysed as only the mean time to freedom from pain was reported.

Table 101: Triptan vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Reduction in pain at 30 minutes[36]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Time to freedom from pain	1	Randomised trials	Very serious [(a), (b)]	N/A [(d)]	No serious indirectness	N/A [(d)]
Headache response (at 15 or 30 minutes)[36,67,68,209,259]	5	Randomised trials	Serious [(a), (c)]	No serious inconsistency	No serious indirectness	No serious imprecision
Functional health status and health related quality of life	0	-	-	-	-	-
Incidence of adverse events	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment not reported
(b) Data is reported as mean in the study. It is unclear whether this data reported as mean (SD) or mean (SE)
(c) Incomplete accounting of participants and outcome events
(d) Inconsistency and imprecision could not be assessed as the data could not be meta-analysed.
N/A=not applicable.

Table 102: Triptan vs placebo – Clinical summary of findings

Outcome	Triptan	Placebo	Relative risk	Absolute effect	Quality
Reduction in pain at 30 minutes	65/128 (50.8%)	12/61 (19.7%)	RR 2.58 (1.51 to 4.41)	311 more per 1000 (from 100 more to 671 more)	MODERATE
Time to freedom from pain	12.4 (6) [(a)]	17.6 (12) [(a)]	N/A [(b)]	N/A [(b)]	LOW
Headache response (at 15 or 30 minutes)	336/528 (63.6%)	90/317 (28.4%)	RR 2.22 (1.84 to 2.67)	346 more per 1000 (from 238 more to 474 more)	MODERATE

(a) Data is reported as mean in the study. It is unclear whether this data reported as mean (SD) or mean (SE).
(b) Relative risk and absolute effect could not be calculated as data could not be meta-analysed.
N/A=not applicable.

12.2.3.2 Economic evidence

No relevant economic evaluations comparing triptans with placebo were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 100 in section 12.2.2.2).

12.2.3.3 Evidence statements

Clinical:

One study with 92 people with cluster headache showed that triptans are more clinically effective than placebo at reducing pain at 30 minutes. [Moderate quality].

One study with 118 people with cluster headache showed that the time to freedom from pain was lower with triptans than placebo, but the difference is uncertain as no comparative analysis could be carried out. [Low Quality].

Five studies with 494 people with cluster headache showed that triptans are more clinically effective than placebo in producing headache response at 15 or 30 minutes. [Moderate quality].

No studies reported outcome data for functional health status and health related quality of life or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed the cost per episode is between £5.90 and £12.16 for nasal spray triptans and £21.24 for subcutaneous triptans.

12.2.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 12.3.

12.2.4 Ergots vs placebo

12.2.4.1 Clinical evidence

See evidence tables in appendix section E.2.4.

One study was identified comparing ergots to placebo[228,228]. This was a crossover study reporting intramuscular administration of ergots in inpatients. The only outcome that was reported was the mean time to freedom from pain and data could not be meta-analysed.

Table 103: Ergots vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Time to freedom from pain[228,228] *	1	Randomised trials	Serious [(a)]	N/A	No serious indirectness	N/A
Reduction in pain at 30 minutes	0	-	-	-	-	-
Headache response (up to	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
2 hours)						
Functional health status and health related quality of life	0	-	-	-	-	-
Incidence of adverse events	0	-	-	-	-	-

(a) *Randomisation and allocation concealment was unclear.*
** Data could not be meta-analysed as data only presented as mean number of minutes.*
N/A=not applicable.

Table 104: Ergots vs placebo – Clinical summary of findings

Outcome	Ergots	Placebo	Relative risk	Absolute effect	Quality
Time to freedom from pain (minutes, mean)	55.8	93.3	N/A*	N/A*	MODERATE

**Relative risk and absolute effect not calculated as data only presented as mean number of minutes.*
N/A=not applicable.

12.2.4.2 Economic evidence

No relevant economic evaluations comparing ergots with placebo were identified. We calculated the cost per episode of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 100 in section 12.2.2.2).

12.2.4.3 Evidence statement

Clinical:

One study with 8 people with cluster headache showed that the time to freedom from pain was shorter with ergots than placebo, but the difference is uncertain as no comparative analysis could be carried out. [Moderate quality].

No studies reported outcome data for reduction in pain at 30 minutes, headache response, functional health status and health related quality of life or incidence of serious adverse events.

Economic: No economic evidence was found for this question. A simple cost analysis showed the cost per episode is around £0.22 34 for ergots.

12.3 Recommendations and link to evidence

Recommendations	**Offer oxygen and/or a subcutaneous[ff] or nasal triptan[gg] for the acute treatment of cluster headache.** **When using oxygen for the acute treatment of cluster headache:** • **use 100% oxygen at a flow rate of at least 12 litres per minute with a non-rebreathing mask and a reservoir bag and** • **arrange provision of home and ambulatory oxygen.** **When using a subcutaneous[ff] or nasal triptan[gg], ensure the person is offered an adequate supply of triptans calculated according to their history of cluster bouts, based on the manufacturer's maximum daily dose.**
Relative values of different outcomes	The GDG agreed that pain reduction at 30 minutes was the most important outcome.
Trade off between clinical benefits and harms	**Oxygen:** There is moderate evidence for effectiveness of oxygen compared to air when used at 12 L/min. However the GDG agreed it was important to be aware that use is not advised in people with COPD and it should be used with caution in people with respiratory disease. There was no evidence identified for the effectiveness of ambulatory oxygen, the recommendation is based on GDG informal consensus. **Triptans:** The evidence shows good efficacy of nasal or subcutaneous administered triptans when compared to placebo. The GDG noted that with subcutaneous triptan administration for acute cluster headache, there is often a transient worsening before the improvement. However people with cluster headaches report the improvement gained outweighs the negative aspect. Frequent use of triptans is not of concern in people with cluster headaches. There is no evidence of tachyphylaxis or medication overuse headache. Since there are few concerns about tachyphylaxis in this population and the frequent nature of attacks during a bout of cluster headaches the GDG considered it was important that those affected had an adequate supply of medication to reduce unnecessary pain and disability.
Economic considerations	**Oxygen:** No economic evidence was identified. The cost of home oxygen service was estimated at £175 per new patient and around £69 per 6-month checkup. However, these figures are not specific to people with cluster headache and costs are expected to be lower due to a better efficient use of resources achieved with the new setup of service provision. Therefore these figures are expected to be an overestimate of the current cost of oxygen. Treatment with oxygen is more costly than other treatments. The GDG thought this cost would be justified by the evidence on effectiveness of oxygen; an

[ff] At the time of publication (September 2012), subcutaneous triptans did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[gg] At the time of publication (September 2012), nasal triptans did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

	effective treatment of cluster headache would lead to some cost savings in terms of fewer emergency visits, fewer medications and improved quality of life for people. Early effective treatment may also reduce work loss due to cluster headaches. **Triptans:** The average costs of subcutaneous triptans and nasal triptans are respectively £21.24 and between £5.90 and £12.16 per episode treatment. The GDG agreed that although subcutaneous triptans cost more than oral triptans, the evidence demonstrates that subcutaneous or nasal triptans are the only preparations which are effective for treatment of cluster headache. The higher acquisition cost would be partly offset by the fewer emergency visits and the fewer medications used.
Quality of evidence	**Oxygen:** The evidence for use of oxygen as an acute treatment for cluster headache is based on moderate and low quality evidence. However, all evidence for oxygen at 12 l/min is of moderate quality and demonstrates good efficacy. There was no evidence identified for the effectiveness of ambulatory oxygen, the recommendation is based on GDG informal consensus. The economic evidence was based on national data from the Primary Care Commissioning publication on Home Oxygen Service[185]. **Triptans:** The evidence for use of triptans is of moderate quality and shows good effectiveness. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs.
Other considerations	**Oxygen:** The availability of oxygen and/or time taken to obtain the oxygen cylinders needs to be considered when prescribing. Oxygen supply companies differ by region, see: http://www.homeoxygen.nhs.uk/9.php. It can be obtained by use of the home oxygen order form (HOOF) which is currently available on the following website: http://www.pcc.nhs.uk/home-oxygen-order-form. The GDG were aware that there may be a delay in the provision of oxygen, as oxygen is primarily used in the community for chronic conditions and services are unlikely to be able to provide oxygen on same day basis. The current HOOF includes cluster headache as an indication. The GDG agreed it was important to consider that as cluster headache attacks occur at unpredictable intervals, people may need to have access to an ambulatory cylinder, as well as to home oxygen, in order to treat their attacks at the earliest opportunity The GDG were aware of people with cluster headache being limited to home or ambulatory oxygen therapy but considered this represented a lack of understanding of cluster headache and the use of oxygen in its treatment. People in a bout of cluster headaches should be offered short-burst and/or ambulatory oxygen at 12L/min via a 100% non-rebreathing mask for up to 4 hours daily. The mask should be a cushioned mask, comfortable for the patient. The reservoir bag should be of adequate size. **Triptans:** Although no comparative evidence was reviewed, by informal consensus, the GDG expressed preference for triptans to be administered via a subcutaneous route. Frequent use of triptans is not of concern in people with cluster headaches. There is no triptan licensed for use in under 18 year olds with cluster headache.

Recommendations	**Do not offer paracetamol, NSAIDS, opioids, ergots or oral triptans for the acute treatment of cluster headache.**
Relative values of different outcomes	Pain reduction at 30 minutes was considered to be the most important outcome, however no evidence was found with regards to the use of paracetamol, NSAIDs or opioids for the acute treatment of cluster headache for any of the outcomes assessed.
Trade off between clinical benefits and harms	The GDG agreed that there was no evidence to suggest that paracetamol, NSAIDS or opioids would have any clinical benefit in the treatment of cluster headache. The GDG agreed that ergots have a serious adverse event profile that must be taken into account when considering its use, notably the risk of fibrosis. There was no evidence to suggest that ergots are more effective than oxygen administered at 7 l/min. This is believed to be a sub-optimal level of oxygen therefore there is no evidence for the benefit of ergots in the acute treatment of cluster headache. There is no evidence for the effectiveness of orally administered triptans for the acute treatment of cluster headache. The recommendation is based on the absence of evidence and GDG informal consensus.
Economic considerations	Paracetamol, NSAIDs and opioids are all associated with acquisition costs. Given the lack of evidence on their effectiveness and the availability of evidence on the effectiveness of other treatments, the GDG decided they would not constitute an optimal use of NHS resources. The average cost of ergots is £0.34 per episode. The GDG agreed that although this treatment is less expensive compared to oxygen and other treatments such as subcutaneous or nasal triptans, there were some concerns over their adverse event profile and no evidence on their effectiveness when compared to oxygen. The average cost of a dose of oral triptans is £0.09. The GDG agreed that although this treatment is less expensive compared to oxygen, subcutaneous or nasal triptans, there was no evidence on their effectiveness in cluster headache.
Quality of evidence	There was no evidence identified for the effectiveness of paracetamol, NSAIDs or opioids for the acute treatment of cluster headache. The recommendation is based on the absence of evidence and GDG informal consensus. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs. The recommendation against ergots was based on very low quality evidence and the absence of evidence. The only available evidence was comparing ergotamine to oxygen administered at a sub-optimal flow rate (7 L/min). There is no evidence for the efficacy of ergotamine compared to placebo. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs. No evidence was found for administration of triptans via oral route for acute treatment of cluster headache, the recommendation is based on the absence of evidence and GDG informal consensus. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs.
Other considerations	None.

13 Prophylactic pharmacological treatment of tension type headache

13.1 Introduction

Tension type headache is the most common type of primary headache with life time prevalence quoted of up to 78%. The exact mechanism of tension type headache is unknown. Migraine often co-exists with chronic TTH and analgesic overuse is common. The chronic sub type is invariably associated with disability and high personal and socio-economic costs.

This section describes the pharmacological options for prophylaxis of tension type headache. Non-pharmacological approaches for prophylaxis such as acupuncture, manual therapies and psychological therapies are evaluated in chapters 17, 18 and 19 respectively, and the use of dietary supplements and herbal medicines; exercise and education, self-management are described in chapters 20, 21 and 22 respectively.

13.1.1 Clinical question

In people with tension type headache, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with ACE inhibitors and angiotensin II receptor blockers (ARBs), antidepressants (SNRIs, SSRIs, tricyclics), beta blockers or antiepileptics.

A literature search was conducted for RCTs comparing the clinical effectiveness of different pharmacological interventions for the prophylactic pharmacological treatment of tension type headache. The interventions we included in our search were ACE inhibitors and ARBs, antidepressants (SNRIs, SSRIs or tricyclics), beta blockers, antiepileptics and placebo. We looked for any studies that compared the effectiveness of two or more of these treatments (or placebo). Crossover studies were excluded. See protocol C.2.5.

One Cochrane review on the use of selective serotonin re-uptake inhibitors in prophylaxis of tension type headache was excluded due to inclusion of open label trials and crossover trials[174]. All relevant studies from this review have been included.

Imprecision for the effect size relating to the outcome headache days was assessed using a value agreed by the GDG for the MID: 0.5 days.

13.2 Matrix of treatment comparisons

Below is a matrix showing where evidence was identified. A box filled with a number represents how many studies were found and are reviewed in this chapter. A box filled with - represents where no evidence was found. No evidence was found for; ACE inhibitors and ARBs, SNRIs, SSRIs, beta blockers and antiepileptics.

ACE inhibitors and ARBs	-			
Antidepressants	-	-		
Beta blockers	-	-	-	
Placebo	-	-	1	-
	Antiepileptics	**ACE inhibitors and ARBs**	**Antidepressants**	**Beta blockers**

13.2.1 Tricyclic antidepressants vs placebo

13.2.1.1 Clinical evidence

See evidence table in appendix section E.2.5, forest plots in Figures 85-87, Appendix G.2.4.

One study was identified comparing the effectiveness of amitriptyline and placebo in people with chronic tension type headache[199]. Data were only available analysed as ITT with missing values imputed as last observation carried forward. Therefore, this was used in place of an available case analysis.

Table 105: Tricyclic antidepressants vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported headache days[197,199]	1	Randomised trials	Very serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported headache intensity[197,199]	1	Randomised trials	Very serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Incidence of serious adverse events[197,199] (moderate and serious)	1	Randomised trials	Very serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Responder rate	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-

a) Unclear randomisation and allocation concealment; details of blinding of participants and investigators not provided; the study excluded people with suspected poor compliance.
b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 2: Tricyclic antidepressants vs placebo – Clinical summary of findings

Outcome	Amitriptyline	Placebo	Relative risk	Absolute effect	Quality
Change in patient reported headache days	67	64	-	MD 1 lower (4.26 lower to 2.26 higher)	LOW
Change in patient reported headache intensity	67	64	-	MD 1.1 higher (0.41 to 1.79 higher)	VERY LOW
Incidence of serious adverse events (moderate and serious)	49/67 (73.1%)	37/64 (57.8%)	RR 1.27 (0.98 to 1.63)	156 more per 1000 (from 12 fewer to 364 more)	VERY LOW

13.2.1.2 Economic evidence

No economic evaluations comparing tricyclic antidepressants with placebo were identified. We calculated the cost of a treatment with tricyclic antidepressants based on the unit cost reported in the BNF62[111] and the dosages used in the study[199] included in our clinical review (13.2.1.1).

Based on the drug (amitryptiline) and the dosages used in the study by Pfaffenrath et al (1994), the cost in the first four weeks would be £0.83 then assuming a dosage of 2 tablets per day of 25 mg the cost per month would be £1.80.

The costs of adverse effects and further events such as GP or specialist visits were not estimated.

13.2.1.3 Evidence statements

Clinical:

One study with 131 people with chronic tension type headache suggested that amitriptyline may be more clinically effective than placebo at reducing the number of headache days when assessed at 24 weeks follow up, but there is considerable uncertainty. [Low quality].

One study with 131 people with chronic tension type headache suggested that placebo may be more clinically effective than amitriptyline at reducing the headache intensity when assessed at 24 weeks follow up, but there is some uncertainty. [Very low quality].

One study with 131 people with chronic tension type headache suggested that there are more incidences of moderate and serious adverse events with amitriptyline than placebo when assessed at 24 weeks follow up, but there is some uncertainty. [Low quality].

No studies reported outcome data for responder rate, functional health status or quality of life, resource use or use of acute pharmacological treatment.

Economic:

No economic evidence was found for this question. A simple cost analysis showed that the cost of treatment with tricyclic antidepressants would be £0.83 for the first 4 weeks followed by a monthly cost of £1.80. This cost does not include the cost of treating adverse effects and further events such as GP or specialist visits.

13.3 Recommendations and link to evidence

The GDG decided that there was not enough evidence to make a recommendation for the pharmacological prophylactic treatment of tension type headaches.

Recommendations	
Relative values of different outcomes	The GDG agreed that the most important outcome was change in patient reported headache days.
Trade off between clinical benefits and harms	The GDG agreed that there were some significant side-effects associated with amitriptyline which should be considered. The evidence reviewed reported a high percentage of serious adverse events in both groups. The reviewed evidence did not demonstrate any benefit from amitriptyline that would outweigh these risks.
Economic considerations	Prophylactic treatment with amitriptyline is associated with some costs (£0.83 for the first month followed by a monthly cost of £1.80).In the absence of definite evidence on its benefit, it is impossible to judge whether this treatment represents good value-for-money.
Quality of evidence	The only available clinical evidence was low or very low quality from one relatively small study. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs.
Other considerations	The GDG agreed that there was not enough evidence to recommend pharmacological prophylactic treatment for tension type headaches. The GDG considered that pure tension type headache requiring prophylaxis is rare. Assessment is likely to uncover coexisting migraine symptomatology with a possible diagnosis of chronic migraine. Non-pharmacological treatments could be also be considered (see chapters 17 - 22).

14 Prophylactic pharmacological treatment of migraine with or without aura

14.1 Introduction

Prophylactic treatment aims to reduce the frequency, severity, and duration of migraine attacks. It also aims to avoid medication overuse headache, which is described further in chapter 23.

This section describes the pharmacological options for prophylaxis. Non-pharmacological approaches such as acupuncture, manual therapies and psychological therapies are evaluated in chapters 17, 18 and 19 respectively, and the use of dietary supplements and herbal medicines; exercise and education, self-management are described in chapters 20, 21 and 22 respectively.

Pharmacological prophylaxis falls into three major classes: antiepileptics, antidepressants (including serotonergic modulators) and antihypertensives (which include beta blockers, calcium channel blockers, ACE inhibitors and ARBs). Within each class, response and side effects may differ between people.

Their mechanisms of action in migraine prophylaxis are uncertain. However, antiepileptics are believed to suppress the spreading of cortical depression, which may trigger migraine, by manipulating electrical activity in the brain via blocking voltage-dependent sodium channels, increasing activity of gamma-aminobutyric acid (GABA) receptors and/or antagonising glutamate receptors.

Antidepressants' and serotonergic modulators' usefulness in migraine prophylaxis may stem from their ability to increase the activity and levels of serotonin and noradrenaline – two neurotransmitters where low levels have been implicated in the aetiology of migraine. As well as increasing the flexibility of veins, arteries and capillaries, these neurotransmitters also affect pain perception. Similarly, medicines licensed for use as antihypertensives have been used for migraine prophylaxis due to their activity on ion channels (calcium channel blockers), and on increasing levels of noradrenaline (beta blockers). The mechanism of action of ACE inhibitors and ARBs in preventing migraine is less clear.

If prophylaxis is agreed, then these medicines should be taken every day. While they may not prevent all migraines, they may help to reduce their frequency and severity.

14.1.1 Clinical question

In people with migraine with or without aura, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: ACE inhibitors and ARBs; antidepressants; beta blockers; calcium channel blockers; antiepileptics; and other serotonergic modulators?

A literature search was conducted for RCTs comparing the clinical effectiveness of different pharmacological interventions for the prophylaxis of migraine. The interventions we included in our search were ACE inhibitors and ARBs, antidepressants, beta blockers, calcium channel blockers, antiepileptics (sodium valproate, gabapentin, lamotrigine, oxcarbazepine, topiramate), other serotonergic modulators and placebo. We looked for any studies that compared the effectiveness of two or more of these treatments (or placebo). See protocol C.2.6.

During the development of the Headaches clinical guideline 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 is a relevant treatment option for people with chronic migraine.

The GDG agreed that antiepileptics should be considered by drug and not as a class due to their different modes of action. Therefore after the evidence was reviewed, it was separated into sodium valproate/semisodium valproate, gabapentin, lamotrigine, oxcarbazepine and topiramate.

The GDG agreed that for the short-term outcome reporting period, data reported at 3 and 6 months could be combined for analysis. All data are reported at 3 or 6 months and available case analysis data were used, unless otherwise stated. Most the studies related to people suffering from migraine for less than 15 days per month with an average of around 6 days per month. Imprecision for the effect size relating to the outcome Migraine Specific Quality of Life score (MSQ) was assessed using a value for the MID published in a study by Cole et al[41]. Imprecision for the effect size relating to the outcome headache or migraine days was assessed using a value agreed by the GDG for the MID: 0.5 days.

Four Cochrane reviews were identified for different interventions in the prophylaxis of migraine. One Cochrane review evaluated the effectiveness of anticonvulsants in migraine prophylaxis but was excluded as it included open label trials and some of the included studies had sample sizes of less than 25 participants per arm[35]. Another Cochrane review was excluded as it evaluated drugs for prevention of migraine in children (aged under 12)[262]. One Cochrane review on the use of propranolol was excluded as it evaluated outcomes at four weeks duration and included in its comparisons drugs which were not in this reviews protocol, for example, flunarizine and cyclandelate[152]. The fourth Cochrane review on the use of selective serotonin re-uptake inhibitors in migraine prophylaxis was excluded due to inclusion of open label trails and crossover trials[174]. All relevant studies from these Cochrane reviews were included in this review.

14.2 Matrix of treatment comparisons

Below is a matrix showing the number of studies identified by comparison.

ACE inhibitors	1						
Antidepressants (ADEP)	-	-					
Beta blockers (BB)	4	-	-				
Calcium channel blockers (CCB)	2	-	-	-			
Serotonergic modulators (SM)	-	-	-	-	-		
Antiepileptic (AE)	12	-	-	1	-	-	1
	Placebo	**ACE inhibitors**	**ADEP**	**BB**	**CCB**	**SM**	**AE**

This chapter contains three sections:

1. Direct comparisons of treatments from identified trials (starting in 14.2.1)
2. Network meta-analysis comparing all treatments to each other (section 14.311.4,full details in appendix K)
3. Economic model (section 14.4).

14.2.1 ACE inhibitors/ARBs vs placebo

14.2.1.1 Clinical evidence

See evidence tables in appendix section E.2.6, and forest plots in Figure 88, Appendix G.2.5.

Only one study comparing telmisartan (80mg) with placebo was identified[56].

Table 106: ACE inhibitors/ARBs vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported migraine days [56]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Responder rate	0	-	-	-	-	-
Change inpatient reported migraine frequency	0	-	-	-	-	-
Change in patient reported migraine frequency	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation was unclear; allocation concealment was unclear; groups not comparable at baseline; groups not comparable for availability of outcome data; unclear if investigators were blinded to treatment.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 107: ACE inhibitors/angiotensin receptor blockers vs placebo – Clinical summary of findings

Outcome	Telmisartan	Placebo	Relative risk	Absolute effect	Quality
Change in patient reported migraine days	40	44	-	MD 1.92 lower (3.61 to 0.23 lower)	LOW

14.2.1.2 Economic evidence

No economic evaluations comparing ACE inhibitors/angiotensin II receptor blockers with placebo were identified. However an angiotensin II receptor blocker (telmisartan) was included in our original cost-effectiveness analysis. See section 11.5 for details and results.

14.2.1.3 Evidence statement

Clinical:

One study with 95 people with migraine suggested that telmisartan may be more clinically effective than placebo at reducing the mean number of migraine days per month from baseline when assessed at 12 weeks, but there is considerable uncertainty. [Low quality].

No studies reported outcome data for responder rate, change in patient-reported migraine frequency and intensity, functional health status and health-related quality of life, resource use, use of acute pharmacological treatment or incidence of serious adverse events.

Economic:

An original cost-effectiveness analysis showed that telmisartan is not cost-effective when compared to no treatment as the ICER is above the £20,000/QALY threshold. When compared to other available strategies (topiramate, propranolol and acupuncture), topiramate is the most cost-effective option, followed by propranolol. When the model was run probabilistically, telmisartan was the most cost-effective strategy in 20.7% of the simulations.

14.2.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5.

14.2.2 Antiepileptic - divalproex vs placebo

14.2.2.1 Clinical evidence

See evidence tables in appendix section E.2.6, and forest plots in Figures 89-95, Appendix G.2.5.

Four studies were included in the review, all comparing divalproex with placebo[9,83,127,165]. Divalproex is also known as semisodium valproate (Depakote®).

One study had an exclusively paediatric population (age range 12-17) [9]; the others included both paediatric and adult populations. Two studies compared three doses of Divalproex to placebo: in one they used 250, 500 & 1000mg[9]; in the other they used 500, 1000 and 1500mg[127]. For these studies the results from the three groups of different doses of divalproex were combined together in our analysis. Two studies compared one dose of divalproex (1000mg) to placebo[83,165]. Results for the efficacy analyses of three of the studies [9,83,127] were reported using all data from randomised subjects who received the study drug and provided at least one headache evaluation during the experimental phase. This was described as intention to treat. The fourth study [165] did not describe how they analysed their data though it appears they followed a similar strategy.

In three studies[83,127,165] outcomes for migraine days, migraine frequency and migraine intensity could not be meta-analysed as the standard deviations were not reported with the results.

Table 108: Divalproex vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported migraine days [9]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Responder rate [9,127,165]	3	Randomised trials	Serious (c)	Serious (d)	No serious indirectness	Very serious (e)
Change in patient reported migraine frequency [9]	1	Randomised trials	Very serious (b)	No serious inconsistency	No serious indirectness	No serious imprecision
Incidence of serious adverse events [83]	1	Randomised trials	Serious (f)	No serious inconsistency	No serious indirectness	Very serious (e)
Change in patient reported migraine intensity	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-

(a) Data only available from one of the three studies, the others did not report standard deviations. Method of randomisation and allocation concealment was unclear one study and it was unclear if investigators were kept blind to the intervention.
(b) Data only available from one of the four studies, the others did not report standard deviations. Method of randomisation and allocation concealment was unclear in one study and unclear if investigators were kept blind to the intervention.
(c) Method of randomisation and allocation concealment was unclear in all three studies and it was unclear if investigators were kept blind to the intervention.
(d) There is significant unexplained statistical heterogeneity.
(e) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.
(f) Unclear if investigators were kept blind to the intervention.

Table 109: Divalproex vs placebo – Clinical summary of findings

Outcome	Divalproex	Placebo	Relative risk	Absolute effect	Quality
Change in patient reported migraine days	228	71	-	MD 0.10 higher (-0.72 lower to 0.92 higher)	LOW
Responder rate	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)	VERY LOW

Outcome	Divalproex	Placebo	Relative risk	Absolute effect	Quality
Change in patient reported migraine frequency	228	71	-	MD 0.07 higher (0.49 lower to 0.63 higher)	LOW
Incidence of serious adverse events (follow-up 12 weeks)	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)	VERY LOW

14.2.2.2 Economic evidence

No relevant economic evaluations comparing sodium valproate/semisodium valproate (Divalproex) to placebo were included. One study[273] comparing Divalproex with amitriptyline, beta-blockers, topiramate and no treatment was excluded due to its limited applicability to the NHS UK setting (it was conducted in the USA and a societal perspective was taken).

Sodium valproate/semisodium valproate (Divalproex) was considered in the original cost-effectiveness analysis conducted for this guideline. However, it was excluded from further analysis in our model as it was similarly effective at reducing the number of migraine days compared to placebo/no treatment (see Appendix L). Since sodium valproate/semisodium valproate (Divalproex) is more costly than no treatment, it is dominated by no treatment.

14.2.2.3 Evidence statements

Clinical:

One study with 305 people with migraine showed that there is no difference between divalproex and placebo in reducing the mean number of migraine days per month when assessed at 12 weeks follow-up. [Low quality].

One study with 305 people with migraine showed that there is no difference between divalproex and placebo in reducing the mean number of migraines per month when assessed at 12 weeks follow-up. [Low quality].

Three studies with 588 people with migraine suggested that divalproex may be more clinically effective than placebo at increasing responder rate in people with migraine when assessed at 12 weeks follow-up, but there is some uncertainty. [Very low quality].

One study with 239 people with migraine suggested that fewer serious adverse events occur with divalproex than placebo when assessed at 12 weeks follow-up, but there is considerable uncertainty. [Very low quality].

No studies reported outcome data for change in patient-reported migraine intensity, functional health status and health-related quality of life, resource use or use of acute pharmacological treatment.

Economic:

Sodium valproate/semisodium valproate (Divalproex) is similarly effective at reducing the number of migraine days compared to no treatment, and being more costly, it is dominated by no treatment.

14.2.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5.

14.2.3 Antiepileptic - gabapentin vs placebo

14.2.3.1 Clinical evidence

See evidence tables in appendix section E.2.6, and forest plots in Figures 89-95, Appendix G.2.5.

Only one study was identified[51] which compared gabapentin at a dose of 1200mg/day with placebo. All randomised participants were analysed in the results.

Table 110: Gabapentin vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported migraine frequency [51]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine intensity [51]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Responder rate	0	-	-	-	-	-
Change in patient reported migraine days	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) The method of randomisation and allocation concealment was unclear. It was unclear if participants, the people administering care or the investigators were blinded to the treatments.

Table 111: Gabapentin vs placebo – Clinical summary of findings

Outcome	Gabapentin	Placebo	Relative risk	Absolute effect	Quality
Change in patient reported migraine frequency	35	28	-	MD 1.89 lower (2.37 to 1.41 lower)	MODERATE
Change in patient reported migraine intensity	35	28	-	MD 0.62 lower (0.91 to 0.33 lower)	MODERATE

14.2.3.2 Economic evidence

No economic evaluations comparing gabapentin with placebo were identified. Gabapentin was not included in our cost-effectiveness analysis (see section14.4) as the intermediate outcome used in the model (change in patient reported migraine days) was not available from the clinical evidence (14.2.3.1).

We calculated the cost of a six-month course of different prophylactic treatments based on the unit cost reported in the BNF62[111] (see Table 112 below). Figures are based on the drug acquisiton costs only and do not include monitoring and GP visits.

Table 112: Cost of a six-month course of prophylactic treatment

Drug	Cost per six months (£)	Notes
Beta-blockers (Propranolol)	£16.08	Dosage: 160mg once a day.
Topiramate	£43.73	Dosage: 25 mg initially, then 100 mg three times per day.
ARB (Telmisartan)	£119.00	Dosage: 80 mg once daily.
Gabapentin	£45.72	Dosage: 400 mg three times daily.
Calcium-channel blockers (Nimodipine)	£292.00	Dosage: 30 mg four times a day
Lamotrigine	£26.07	Dosage: 100 mg twice daily.
Sodium valproate/semisodium valproate (Divalproex)	£26.73	Based on the weighted doses used in the clinical studies included in the NMA (see Appendix L and M for details)
Oxcarbazepine	£250.56	Dose: 150 mg per day initially, then escalated by 150 mg every 5 days up to 1200 mg per day.

Source: BNF62[111]

The costs of adverse effects and further events were not estimated.

14.2.3.3 Evidence statements

Clinical:

One study with 63 people with migraine showed that gabapentin is more clinically effective than placebo at reducing migraine frequency when assessed at 12 week follow-up. [Moderate quality].

One study with 63 people with migraine showed that gabapentin is more clinically effective than placebo at reducing migraine intensity when assessed at 12 week follow-up. [Moderate quality].

No studies reported outcome data for responder rate, change in patient-reported migraine days, functional health status and health-related quality of life, resource use, use of acute pharmacological treatment or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed that the cost of treatment with gabapentin is on average £45.72 for a six-month treatment.

14.2.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5.

14.2.4 Antiepileptic - lamotrigine vs placebo

14.2.4.1 Clinical evidence

See evidence tables in appendix section E.2.6.

Only one study comparing lamotrigine (200mg) with placebo was identified[238]. All randomised participants were included in the efficacy and safety analyses.

The only reported outcome, mean migraine days per 28 days, was not able to be meta-analysed as standard deviations were not provided with the results.

14.2.4.2 Economic evidence

No relevant economic evaluations comparing lamotrigine with placebo were identified.

We calculated the cost of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 112 in section 14.2.3.2).

14.2.4.3 Evidence statement

Clinical:

No studies reported outcome data for responder rate, change in patient-reported migraine frequency and intensity, functional health status and health-related quality of life, resource use, use of acute pharmacological treatment or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed that the cost of treatment with lamotrigine is on average £26.07 for a six-month treatment.

14.2.4.4 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5.

14.2.5 Antiepileptic - oxcarbazepine vs placebo

14.2.5.1 Clinical evidence

See evidence tables in appendix section E.2.6, and forest plots in Figures 89-95, Appendix G.2.5.

Only one study comparing oxcarbazepine (1200mg) was identified [229]. Efficacy analyses described as intention to treat where all randomised participants who received at least one dose of double blind study medication were included.

Table 113: Oxcarbazepine vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported migraine days [229]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Responder rate [229]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Very serious [(a)]
Change in patient reported migraine frequency [229]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine intensity [229]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Headache specific quality of life (MIDAS score) [229]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious [(b)]
Use of acute pharmacological treatment [229]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Very serious [(a)]
Incidence of serious adverse events [229]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Very serious [(a)]
Functional health status and health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-

(a) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 114: Oxcarbazepine vs placebo – Clinical summary of findings

Outcome	Oxcarbazepine	Placebo	Relative risk	Absolute effect	Quality
Change in patient reported migraine days	85	85	-	MD 0.37 higher (0.55 lower to 1.29 higher)	HIGH
Responder rate	23/85 (27.1%)	20/85 (23.5%)	RR 1.15 (0.68 to 1.93)	35 more per 1000 (from 75 fewer to 219 more)	LOW
Change in patient reported migraine frequency	85	85	-	MD 0.06 higher (0.52 lower to 0.64 higher)	HIGH
Change in patient reported migraine intensity	85	85	-	MD 0.06 higher (0.1 lower to 0.22 higher)	HIGH

Outcome	Oxcarbazepine	Placebo	Relative risk	Absolute effect	Quality
Headache specific quality of life (MIDAS score)	85	85	-	MD 0.52 lower (0.99 to 0.05 lower)	MODERATE
Use of acute pharmacological treatment	85	85	-	MD 0.55 higher (0.3 lower to 1.4 higher)	LOW
Incidence of serious adverse events	1/85 (1.2%)	2/85 (2.4%)	RR 0.5 (0.05 to 5.41)	12 fewer per 1000 (from 22 fewer to 104 more)	LOW

14.2.5.2 Economic evidence

No relevant economic evaluations comparing oxcarbazepine to placebo were identified.

Oxcarbazepine was considered in the original cost-effectiveness analysis conducted for this guideline. However it was excluded from further analysis in our model (see Appendix L) as it was similarly effective at reducing the number of migraine days compared to placebo/no treatment (see Appendix K). Since oxcarbazepine is more costly than no treatment, it is dominated by no treatment.

14.2.5.3 Evidence statements

Clinical:

One study with 170 people with migraine showed that there was no difference between oxcarbazepine and placebo in reducing the number of migraine days at 15 weeks follow-up. [High quality].

One study with 170 people with migraine showed that oxcarbazepine is more effective than placebo in reducing migraine frequency at 15 weeks follow-up, but the effect size is too small to be clinically important. [High quality].

In one study with 170 people with migraine, there is too much uncertainty to determine whether there is a difference between oxcarbazepine and placebo in responder rate at 15 weeks follow-up. [Low quality].

One study with 170 people with migraine showed that oxcarbazepine and placebo were similarly effective in reducing migraine intensity at 15 week follow-up. [High quality].

One study with 170 people with migraine suggested that there is no difference in the incidence of serious adverse events between than oxcarbazepine and placebo at 15 weeks follow-up, but there is some uncertainty. [Low quality].

One study with 170 people with migraine showed that placebo is more effective than oxcarbazepine in reducing the use of acute pharmacological treatment at 15 weeks follow-up, but the effect size is too small to be clinically important. [Low quality].

One study with 170 people with migraine suggested that there was no difference between oxcarbazepine and placebo in reducing MIDAS score at 15 weeks follow-up. [Moderate quality].

No studies reported outcome data for resource use or use of acute pharmacological treatment.

Economic:

Oxcarbazepine is similarly effective at reducing the number of migraine days compared to no treatment, and being more costly, it is dominated by no treatment.

14.2.5.4 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5.

14.2.6 Antiepileptic - topiramate vs placebo

14.2.6.1 Clinical evidence

See evidence tables in appendix section E.2.6, and forest plots in Figures 89-95, Appendix G.2.5.

Eight studies were identified [20,61,146,157,170,232-234]. Brandes et al. 2004 [20] and Diener et al. 2004[61] had a mixed paediatric and adult populations. Brandes et al. compared three doses of topiramate (50, 100 & 200mg) with each other and placebo whereas Diener compared two doses of topiramate (100 & 200mg) with placebo. Lewis 2009[145,146] looked at two different doses of topiramate (100 & 200mg) in adolescents aged 12-17. Six of the studies [20,61,146,232-234] described their analyses as intention to treat where the intention to treat population was described as the randomised participants who had received at least one dose of the treatment medication and at least one post-baseline efficacy assessment. One study [157] described their analyses as efficacy analyses where the population was described as the randomised participants who had received at least one dose of the treatment medication, at least one post-baseline efficacy assessment and had completed at least 28 days of the double blind phase. For Mei et al. [170] it is unclear whether the analysis is based on numbers randomised or the numbers completing the study.

No evidence was identified for the following outcomes: functional health status and health-related quality of life and resource use.

Two studies [170,233] were not able to be meta-analysed for migraine days as they did not provide standard deviations with the results. Another study [157] was not able to be meta-analysed for serious adverse events as it did not provide standard deviations with the results. Mei et al. [170] reported percentages for the responder rate but it is unclear what the denominators are for the results.

Table 115: Topiramate vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported migraine days (at 26 weeks) [20,61,146,157,232,234]	6	Randomised trials	Serious (c)	No serious inconsistency	No serious indirectness	No serious imprecision
Responder rate [20,61,146,231,232,234]	6	Randomised trials	Serious (a)	Serious (b)	No serious indirectness	No serious imprecision
Change in patient reported migraine frequency (at 26 weeks) [20,61,146,234]	4	Randomised trials	Serious (d)	No serious inconsistency	No serious indirectness	Serious (e)
Change in patient reported migraine intensity [20]	1	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Headache specific quality of life (MIDAS score) [157,232]	2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious [(e)]
Use of acute pharmacological treatment (at 26 weeks) [20,61,232,234]	4	Randomised trials	Serious [(g)]	No serious inconsistency	No serious indirectness	No serious imprecision
Incidence of serious adverse events (at26 weeks) [157,232]	2	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious [(f)]
Functional health status and health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-

(a) The method of randomisation and allocation concealment was not reported for five of the six studies.
(b) There is moderate unexplained heterogeneity in the results.
(c) The method of randomisation and allocation concealment is not reported for five of the seven studies.
(d) The method of randomisation and allocation concealment was not reported for three of the four studies reporting data. One study did not report standard deviations for the mean so the result is not estimable in this analysis.
(e) The confidence interval crosses one minimal important difference making the effect size uncertain.
(f) The confidence interval cross the minimal important difference in both directions making the effect size very uncertain.
(g) The randomisation and allocation concealment was not reported for three of the four studies.

Table 116: Topiramate vs placebo – Clinical summary of findings

Outcome	Topiramate	Placebo	Relative risk	Absolute effect	Quality
Change in patient reported migraine days (at 26 weeks)	1393	802	-	MD 1.03 lower (1.36 to 0.7 lower)	MODERATE
Responder rate	560/1351 (41.5%)	161/631 (25.5%)	RR 1.56 (1.27 to 1.91)	143 more per 1000 (from 69 more to 232 more)	LOW
Change in patient reported migraine frequency (at 26 weeks)	1060	405	-	MD 0.71 lower (1.03 to 0.4 lower)	LOW
Change in patient reported migraine intensity	354	114	-	MD 0.03 lower (0.12 lower to 0.06 higher)	HIGH
Headache specific quality of life (MIDAS score)	312	324	-	MD 8.05 lower (14.42 to 1.68 lower)	MODERATE
Use of acute pharmacological treatment (at 26 weeks)	1026	525	-	MD 0.76 lower (1.1 to 0.43 lower)	MODERATE
Incidence of serious adverse events (at 26 weeks)	3/176 (1.7%)	5/185 (2.7%)	RR 0.63 (0.15 to 2.6)	10 fewer per 1000 (from 23 fewer to 43 more)	LOW

14.2.6.2 Economic evidence

No economic evaluations comparing topiramate with placebo were identified. Four studies[25,26,72,273] comparing topiramate with placebo or no treatment were identified and one [25] included. This is summarised in the economic evidence profile below (Table 117 and Table 118) and in the economic evidence table (Appendix F). The other three studies[26,72,273] were excluded because partially applicable (not UK based).

Topiramate was also included in our original cost-effectiveness analysis. See section 11.5 for details and results.

Table 117: Topiramate vs usual care - Economic study characteristics

Study	Applicability	Limitations	Other Comments
Brown et al (2006)[25]	Directly applicable (a)	Minor limitations (b)	People with moderate-severe migraine. Usual care was 'no treatment'. 1 year time horizon. Decision tree incorporating probabilities of major, moderate and limited clinical response and withdrawal from treatment. Key clinical outcome was reduction in migraine frequency. Estimates were from the same studies used in the clinical review.
NCGC Prophylactic treatment model (Appendix L)	Directly applicable (a)	Minor limitations (c)	Decision tree based on a NMA (Appendix K) with a 6-month time horizon. Key clinical outcome was reduction in migraine days per month.

(a) CUA conducted from the UK NHS perspective.
(b) The key clinical outcome is 'migraines per month' averted. They find this value to be 1.81, while our clinical review found it to be closer to 1.07. However, a value of 0.91 migraines per month averted is explored in sensitivity analysis, so the authors have directly addressed the effects of this limitation No probabilistic sensitivity analysis was conducted.
(c) Limited time horizon. Adverse events were not considered.

Table 118: Topiramate vs usual care - Economic summary of findings

Study	Incremental cost (£)	Incremental effects (QALY)	ICER (£/QALY)	Uncertainty
Brown et al (2006)[25]	248 (a)	0.0384 (b)	6,457	The ICER was found to be under £20,000 per QALY for all deterministic sensitivity analyses. The following parameters were varied: • Baseline number of migraines per month (3-12) • Rate of triptan use per attack (0-100%) • Treatment discontinuation rate (0-50%) • Utility gain (Base case ± 60%) No probabilistic sensitivity analysis was conducted.
NCGC Prophylactic treatment model (Appendix M)	112 (c)	0.01261 (d)	8,882	One-way sensitivity analysis: the utility for a migraine episode was varied; the value at which topiramate was found no longer to be cost-effective compared to no treatment was 0.358, an increase of 0.658 from the base

Study	Incremental cost (£)	Incremental effects (QALY)	ICER (£/QALY)	Uncertainty
				case. Probabilistic sensitivity analysis: topiramate was the most cost-effective strategy in 45.2% of the simulations.

(a) Cost of one-year treatment inflated using PSSRU inflation indices[45]. Costs considered were drugs, consultations, and hospitalisation.
(b) Utility gain was defined by response; 0.0103 for a major response; 0.0087 for a moderate response and 0.0012 for a limited response.
(c) Cost of a six-month treatment. Costs considered were acquisition cost of topiramate and cost of two GP visits.
(d) Utility gain was defined by number of migraine days avoided. The QALY estimates of acute treatment with triptan + NSAID (see acute treatment model, Appendix K) are attached to the prophylactic model to adjust the actual quality of life gain from the avoided attack.

14.2.6.3 Evidence statements

Clinical:

Six studies with 1886 people with migraine showed that topiramate is more clinically effective than placebo at increasing responder rate at 26 week follow-up. [Low quality].

Six studies with 2058 people with migraine showed that topiramate is more effective than placebo in reducing migraine days at 26 weeks follow-up, but the effect size is too small to be clinically important. [Moderate quality].

Four studies with 1345 people with migraine suggested that topiramate may be more effective than placebo in reducing migraine frequency at 26 weeks follow-up, but the effect size is too small to be clinically important, and there is considerable uncertainty. [Low quality].

One study with 107 people with migraine showed that there is no difference between topiramate and placebo in reducing migraine intensity at 26 week follow-up. [High quality].

Two studies with 713 people with migraine suggested that topiramate may be more effective than placebo in reducing MIDAS score at 26 week follow-up, but the effect size is too small to be clinically important and there is some uncertainty. [Moderate quality].

Two studies with 713 people with migraine suggested that fewer adverse events occur with topiramate than placebo, but there is considerable uncertainty. [Low quality].

Four studies with 1497 people with migraine showed that topiramate is more effective than placebo in reducing the use of acute medication at 26 week follow-up, but the effect size is too small to be clinically important. [Low quality].

No studies reported outcome data for functional health status or resource use.

Economic:

An economic study directly applicable and with minor limitations, and our original cost-effectiveness analysis showed that topiramate is cost-effective when compared to no treatment as the ICER is below the £20,000/QALY threshold. When compared to other available strategies (telmisartan, propranolol and acupuncture), topiramate is the most cost-effective option, followed by propranolol. When the model was run probabilistically, topiramate was the most cost-effective strategy in 45.2% of the simulations.

14.2.6.4 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5.

14.2.7 Antiepileptics - topiramate vs sodium valproate

14.2.7.1 Clinical evidence

See evidence tables in appendix section E.2.6, and forest plots in Figures 96-97, Appendix G.2.5.

One study was identified [6] comparing two different anti-epileptics, topiramate (50mg) with sodium valproate (400mg) in people aged 18-65.

Table 119: Topiramate vs sodium valproate – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Patient reported migraine frequency for last weeks (follow up 12 weeks) [6]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Patient reported migraine intensity for last weeks (follow up 12 weeks) [6]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Responder rate	0	-	-	-	-	-
Change in patient reported migraine days	0	-	-	-	-	-
Headache specific quality of life (MIDAS score)	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-

(a) Unclear allocation concealment though the study reported it was double blinded. No data for 30% of topiramate group and 22% of the sodium valproate group.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 120: Topiramate vs sodium valproate – Clinical summary of findings

Outcome	Topiramate	Sodium valproate	Relative risk	Absolute effect	Quality
Mean patient reported migraine frequency for last 4 weeks (follow up 12 weeks)	28	28	-	MD 0.6 lower (1.57 lower to 0.37 higher)	LOW
Mean patient reported migraine intensity for last 4 weeks (follow up 12 weeks)	28	28	-	MD 1.10 lower (2 lower to 0.20 lower)	LOW

14.2.7.2 Economic evidence

No economic evaluations comparing topiramate with sodium valproate/semisodium valproate (Divalproex) were included. Two studies[4,273] comparing topiramate with Divalproex and with other treatments were excluded due to their limited applicability to the NHS UK setting as they were conducted in the USA and QALYs were not calculated nor was a societal perspective was taken.

Sodium valproate/semisodium valproate (Divalproex) was considered in the original cost-effectiveness analysis conducted for this guideline. However it was excluded to further analysis in our model (see Appendix L) as it was similarly effective at reducing the number of migraine days compared to placebo/no treatment (see Appendix K). Since sodium valproate/semisodium valproate (Divalproex) is more costly than no treatment, it is dominated by no treatment and does not represent an appropriate comparator to topiramate.

14.2.7.3 Evidence statements

Clinical:

One study with 76 people suggested that there is no difference between topiramate and sodium valproate in reducing migraine severity at 12 weeks follow-up, but there is considerable uncertainty. [Low quality].

One study with 76 people suggested that topiramate may be more clinically effective than sodium valproate in reducing migraine severity at 12 weeks follow-up, but there is considerable uncertainty. [Low quality].

No studies reported outcome data for responder rate, change in patient-reported migraine days, functional health status and health-related quality of life, resource use, use of acute pharmacological treatment or incidence of serious adverse events.

Economic:

Sodium valproate/semisodium valproate (Divalproex) was excluded to further analysis in our original cost-effectiveness analysis as it was dominated by no treatment (it has similar effectiveness but higher costs). Since it is dominated by no treatment, it does not represent an appropriate comparator to topiramate. When compared to other available strategies (no treatment, telmisartan, propranolol, and acupuncture), topiramate is the most cost-effective option, followed by propranolol. When the model was run probabilistically, topiramate was the most cost-effective strategy in 45.2% of the simulations.

14.2.7.4 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5.

14.2.8 Beta blockers vs placebo

14.2.8.1 Clinical evidence

See evidence tables in appendix section E.2.6, and forest plots in Figures 98-101, Appendix G.2.5.

Four studies comparing beta blockers with placebo were identified [61,104,204,258].In two of these the beta-blocker studied was propranolol (160mg)[61,204], in one study the beta-blocker was propranolol (up to 240mg) or nadolol (up to 120mg) and in the fourth study bioprolol (5 or 10mg) was the beta-blocker [258]. In one study [61] their analyses included randomised participants who had received at least one dose of the treatment medication and at least one post-baseline efficacy assessment. Holroyd [104] used an available case analysis for its results. These are analysed separately in this review as they reported for a longer follow up period than the other three studies. Pradalier[204] stated it followed the intention to treat principle but it is unclear from the paper what is meant.

No evidence was identified for the following outcomes: change in patient-reported migraine intensity, functional health status and health-related quality of life, resource use, use of acute pharmacological treatment and incidence of adverse events.

Table 121: Beta blocker vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported migraine days (follow up 26 weeks) [61]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient reported migraine days (follow up 10 months) [104]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient reported migraine days (follow-up 16 months) [104]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious [(b)]
Responder rate (at 26 weeks) [61]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious [(b)]
Responder rate (at 10 months) [104]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Very serious [(c)]
Change in patient reported migraine	3	Randomised trials	Serious [(a)]	Serious [(d)]	No serious indirectness	No serious imprecision

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
frequency (mean monthly rate at 12 to 26 weeks) [61,204,258]						
Change in patient reported migraine frequency (Mean monthly rate at 10 months) [104]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine frequency (Mean monthly rate at 16 months) [104]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Headache specific quality of life (MSQL Score at 10 months) [104]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Headache specific quality of life (MSQL Score at 16 months) [104]	1	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine intensity	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) *The method of randomisation and allocation concealment is unclear.*
(b) *The confidence interval crosses one minimal important difference making the effect size uncertain.*
(c) *The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.*
(d) *There is significant unexplained statistical heterogeneity.*

Table 122: Beta blocker vs placebo – Clinical summary of findings

Outcome	Beta blocker	Placebo	Relative risk	Absolute effect	Quality
Change in patient reported migraine days (follow up 26 weeks)	143	143	-	MD 0.8 lower (1.48 to 0.12 lower)	LOW
Change in patient reported migraine days (follow up 10 months)	53	55	-	MD 0.6 lower (1.06 to 0.14 lower)	MODERATE
Change in patient reported migraine days (follow-up 16 months)	53	55	-	MD 0.6 lower (1.22 to 0.02 lower)	MODERATE
Responder rate (at 26 weeks)	43/143 (30.1%)	22/143 (15.4%)	RR 1.95 (1.24 to 3.09)	146 more per 1000 (from 37 more to 322 more)	MODERATE
Responder rate (at 10 months)	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)	LOW
Change in patient reported migraine frequency (mean monthly rate at 12 to 26 weeks)	334	252	-	MD 1.37 lower (1.69 to 1.04 lower)	LOW
Change in patient reported migraine frequency (Mean monthly rate at 10 months)	53	55	-	MD 0 higher (0.21 lower to 0.21 higher)	HIGH
Change in patient reported migraine frequency (Mean monthly rate at 16 months)	53	55	-	MD 0 higher (0.33 lower to 0.33 higher)	HIGH
Headache specific quality of life (MSQL Score at 10 months)	53	55	-	MD 0 higher (0.93 lower to 0.93 higher)	HIGH
Headache specific quality of life (MSQL Score at 16 months)	53	55	-	MD 0.3 higher (0.84 lower to 1.44 higher)	HIGH

14.2.8.2 Economic evidence

No relevant economic evaluations comparing beta-blockers to placebo were included. One study[273] comparing beta-blockers with amitriptyline, Divalproex, topiramate and no treatment was excluded due to its limited applicability to the NHS UK setting (it was conducted in the USA and a societal perspective was taken).

However beta-blockers (propranolol) were included in our original cost-effectiveness analysis. See section 14.4 for details and results.

14.2.8.3 Evidence statements

Clinical:

One study with 290 people with migraine suggested that beta blockers may be more clinically effective than placebo at improving responder rate at 26 weeks follow-up, but there is some uncertainty. [Moderate quality]

In one study with 108 people with migraine there is too much uncertainty to determine whether there is a difference between beta blocker and placebo in responder rate at 10 months follow-up. [Low quality].

One study with 290 people with migraine suggested that beta blockers may be more effective than placebo in reducing the number of migraine days at 26 weeks follow-up, but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

One study with 108 people with migraine suggested that beta blockers may be more effective than placebo in reducing the number of migraine days at 10 months follow-up, but the effect size is too small to be clinically important and there is some uncertainty. [Moderate quality].

One study with 108 people with migraine suggested that there is no difference between beta blockers and placebo may in reducing the number of migraine days at 16 months follow-up, but there is some uncertainty. [Moderate quality].

Three studies with 590 people with migraine showed that beta blockers are more effective than placebo in reducing migraine frequency at 12 and 26 weeks follow-up. [Low quality].

One study with 108 people with migraine showed that there is no difference between beta blockers and placebo in reducing migraine frequency at 10 months follow-up. [High quality].

One study with 108 people with migraine showed that there is no difference between beta blockers and placebo in reducing migraine frequency at 16 months follow-up. [High quality].

One study with 108 people with migraine showed that there is no difference between beta blockers and placebo in improving migraine specific quality of life (assessed by MSQL) at 10 months follow-up. [High quality].

One study with 108 people with migraine showed that there is no difference between beta blockers and placebo in improving migraine specific quality of life (assessed by MSQL) at 16 months follow-up. [High quality].

No studies reported outcome data for change in patient reported migraine intensity, resource use, use of acute pharmacological treatment or incidence of serious adverse events.

Economic:

An original cost-effectiveness analysis showed that beta-blockers (propranolol) are cost-effective when compared to no treatment as the ICER is below the £20,000/QALY threshold. When compared to other available strategies (telmisartan, topiramate and acupuncture), topiramate is the most cost-effective option, followed by propranolol. When the model was run probabilistically, propranolol was the most cost-effective strategy in 25.5% of the simulations.

14.2.8.4 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5.

14.2.9 Antiepileptic - topiramate vs beta blocker

14.2.9.1 Clinical evidence

See evidence tables in appendix section E.2.6, and forest plots in Figures 102-105, Appendix G.2.5.

One study was identified[61] which compared two different doses of topiramate (100 & 200mg) with propranolol (160mg) in people aged 12-65. This reported its analyses as randomised participants who had received at least one dose of the treatment medication and at least one post-baseline efficacy assessment.

Table 123: Topiramate vs beta blocker – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported migraine days (at 26 weeks) [61]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Responder rate (at 26 weeks) [61]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient reported migraine frequency (at 26 weeks) [61]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Use of acute pharmacological treatment (at 26 weeks) [61]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine intensity	0	-	-	-	-	-
Headache specific quality of life (MIDAS score)	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) The method of randomisation and allocation concealment was not reported.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 124: Topiramate vs beta-blocker – Clinical summary of findings

Outcome	Topiramate	Beta-blocker	Relative risk	Absolute effect	Quality
Change in patient reported migraine days (follow up 26 weeks)	282	143	-	MD 0.35 higher (0.25 lower to 0.95 higher)	MODERATE
Responder rate (follow up 26 weeks)	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 patient reported migraine frequency (follow up 26 weeks)	282	143	-	MD 0.25 higher (0.26 lower to 0.76 higher)	MODERATE
Use of acute pharmacological treatment (follow up 26 weeks)	282	143	-	MD 0.4 higher (0.1 lower to 0.9 higher)	MODERATE

14.2.9.2 Economic evidence

No relevant economic evaluations comparing topiramate with beta-blockers were included. One study[273] comparing topiramate with amitriptyline, beta-blockers, Divalproex and no treatment was excluded due to its limited applicability to the NHS UK setting (it was conducted in the USA and a societal perspective was taken).

However, topiramate and beta-blockers were included and compared in our original cost-effectiveness analysis. See section 14.4 for details and results.

14.2.9.3 Evidence statements

Clinical:

One study with 575 people with migraine suggested that there is no difference between beta blockers and topiramate at increasing responder rate at 26 weeks follow-up, but there is some uncertainty. [Low quality].

One study with 575 people with migraine showed that there is no difference between beta blockers and topiramate in reducing the number of migraine days at 26 weeks follow-up, but there is some uncertainty. [Moderate quality].

One study with 575 people with migraine showed that there is no difference between beta blockers and topiramate in reducing migraine frequency at 26 weeks follow-up. [Moderate quality].

One study with 575 people with migraine showed that there is no difference between beta blockers and topiramate in reducing the use of rescue medication at 26 weeks follow-up. [Moderate quality].

No studies reported outcome data for change in patient reported migraine intensity, functional health status or health-related quality of life, resource use or incidence of serious adverse events.

Economic:

An original cost-effectiveness analysis showed that topiramate is more cost-effective than beta-blockers (propranolol). Topiramate is more costly but more effective than beta-blockers and the ICER is below the £20,000/QALY threshold. When compared to other available strategies (no treatment, telmisartan, and acupuncture), topiramate is the most cost-effective option, followed by propranolol.

When the model was run probabilistically, topiramate was the most cost-effective strategy in 45.2% of the simulations while propranolol in 25.5% of the simulations.

14.2.9.4 Recommendations and link to evidence

See recommendations and link to evidence in section 14.5.

14.2.10 Calcium channel blockers vs placebo

14.2.10.1 Clinical evidence

See evidence tables in appendix section E.2.6.

The two included studies were by the same authors and looked at nimodipine (120mg) in migraine with, and without aura respectively [87,88].

The two studies were not able to be meta-analysed as standard deviations were not provided with results.

14.2.10.2 Economic evidence

No relevant economic evaluations comparing calcium channel blockers with placebo were identified.

We calculated the cost of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 112 in section 14.2.3.2).

14.2.10.3 Evidence statements

Clinical:

No studies reported outcome data for change in patient-reported migraine frequency and intensity, functional health status and health-related quality of life, responder rate, resource use, use of acute pharmacological treatment or incidence of adverse events.

Economic:

No economic evidence was found on calcium channel blockers vs placebo. A simple cost analysis showed that the cost of treatment with calcium channel blockers (nimodipine) is on average £292 for a six-month treatment.

14.2.10.4 Linking evidence to recommendations

See linking evidence to recommendations in section 14.5.

14.3 Network meta-analysis

A network meta-analysis was performed for the treatments with placebo controlled evidence for change in migraine days to help inform the recommendations.

Our analyses were based on a total of 12 studies [9,20,56,58,61,146,147,153,157,229,232,234] of seven different interventions (six pharmacological and one non-pharmacological – see section 14.2 for direct evidence). These studies formed a network of evidence for change in migraine days, identified by the GDG as the primary outcome of interest. For more detail on this analysis, please see Appendix L. The aim of the NMA was to calculate the change in number of migraine days specific to each treatment. We also calculated the overall ranking of interventions according to their effect size and compared to placebo by counting the proportion of simulations of the Markov chain in which each intervention had the highest reduction in migraine days.

This network meta-analysis does not take into account the adverse effect profile of these treatments, but the known profiles have been taken into account in the development of the associated recommendations.

14.3.1.1 Evidence statements

A network meta-analysis of twelve studies comparing seven interventions suggested that topiramate is ranked as the best treatment, acupuncture, propranolol, and telmisartan as joint second best, divalproex 5th, placebo 6th and oxcarbazepine as the least effective treatment at reducing the number of migraine days.

A network meta-analysis of twelve studies comparing seven interventions showed that topiramate is more effective than placebo in reducing number of migraine days.

A network meta-analysis of twelve studies comparing seven interventions suggested that propranolol, telmisartan and acupuncture are more effective than placebo in reducing number of migraine days, but there is some uncertainty.

A network meta-analysis of twelve studies comparing seven interventions suggested that there is no difference between divalproex and placebo in reducing number of migraine days, but there is some uncertainty.

A network meta-analysis of twelve studies comparing seven interventions suggested that placebo is more effective than oxcarbazepine in reducing number of migraine days, but there is some uncertainty.

For detailed explanation on methodology and results of NMA refer to Appendix K.

14.4 Economic evidence

One economic study[25] comparing topiramate with usual care for prophylaxis of migraine was included while other four studies[4,26,72,273] comparing topiramate or other pharmacological treatments for prophylaxis of migraine were excluded due to their limited applicability to the NHS UK setting (they were conducted in the USA). The results of the included study[25] were in agreement with the findings of our original economic model (see Appendix L).

The topic of prophylactic treatment of headache was chosen by the GDG as one of their top two priorities for original economic analysis. Further details of the original cost-effectiveness analysis can be found in Appendix L.

Health economic modelling

<u>a) Model overview/methods</u>

A cost-utility analysis was undertaken where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services perspective. The time horizon considered in the model was 6 months.

The comparators considered in the model are: oxcarbazepine, sodium valproate, acupuncture, telmisartan, propranolol, topiramate and no treatment. Oxcarbazepine and sodium valproate were associated with an increase in migraine days compared to no treatment (see Appendix K). These two treatments were not considered any further in the analysis since they are dominated by no treatment.

The population entering the model comprises people with a diagnosis of migraine as defined by the inclusion criteria of the RCTs in the clinical review.

'Change in number of migraine days per month' was the intermediate outcome incorporated into the model and was based on our clinical review and network meta-analysis (14.3). The model structure is represented in Figure 4.

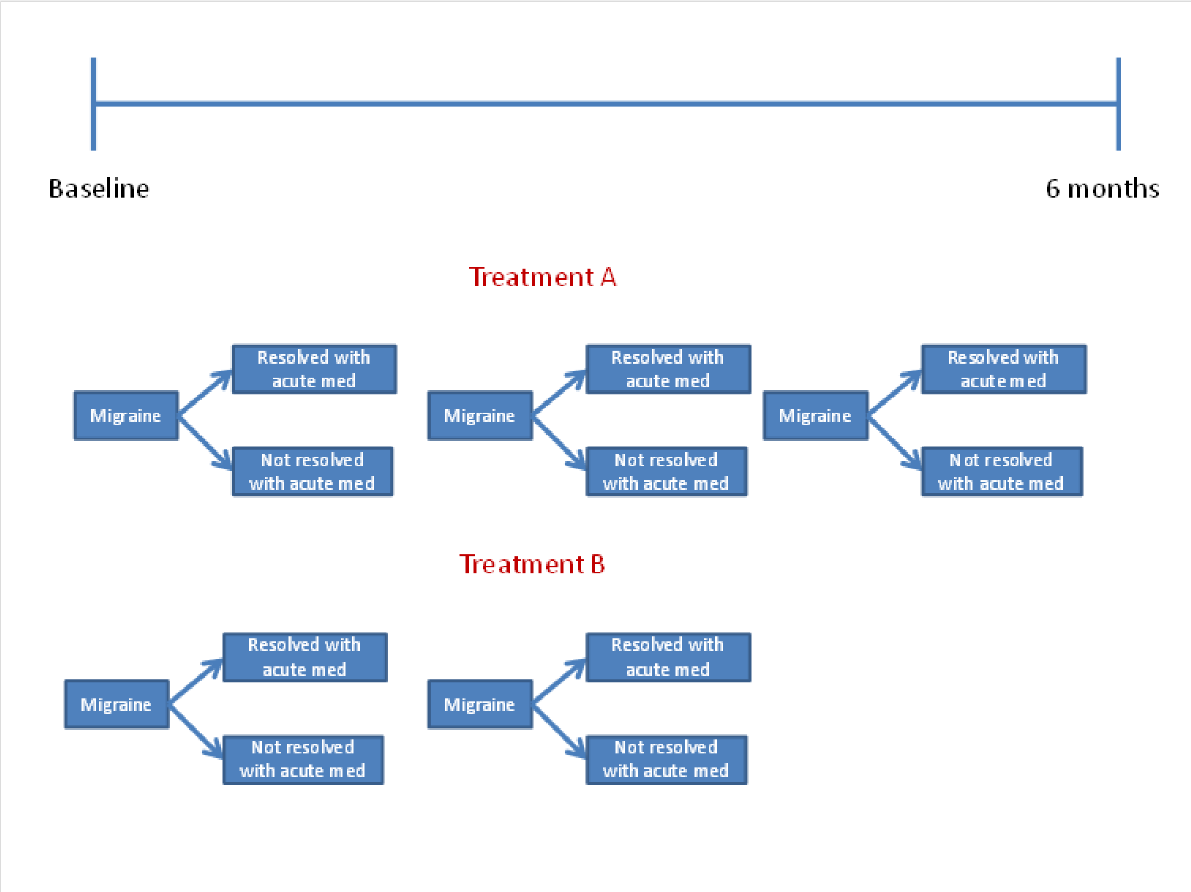

Figure 4: Model overview

From the NMA we obtained the change in number of migraine days per month for every comparator of the model. We then used the costs and QALYs associated with each migraine attack as defined in the acute treatment model (see Appendix J), assuming the most cost-effective acute treatment (triptan + NSAID) would be used in the event of a migraine attack.

Cost components in our model were acquisition costs of drugs and cost of GP visits.

b) Results

The average cost and QALYs gained with each strategy is reported in Table 93. In this table interventions are ranked according to their mean incremental net monetary benefit (INMB), which depends on the costs, QALYs and willingness to pay (set at £20,000/QALY in our analysis). The higher the INMB, the more cost-effective the strategy.

Table 125: Base case probabilistic results in the model

Rank	Strategy	Average cost	Average QALYs gain	INMB [at £20,000/QALY] vs no treatment
1	Topiramate	112	0.01261	139.9
2	Propranolol	90	0.007199	53.63
3	No treatment	0	0	0
4	Telmisartan	194	0.006381	-66.53
5	Acupuncture	228	0.00763	-75.21

Overall, topiramate was ranked the most cost effective treatment in the base case analysis. To reflect the uncertainty in model results we produced rank-probability graphs (Figure 5).

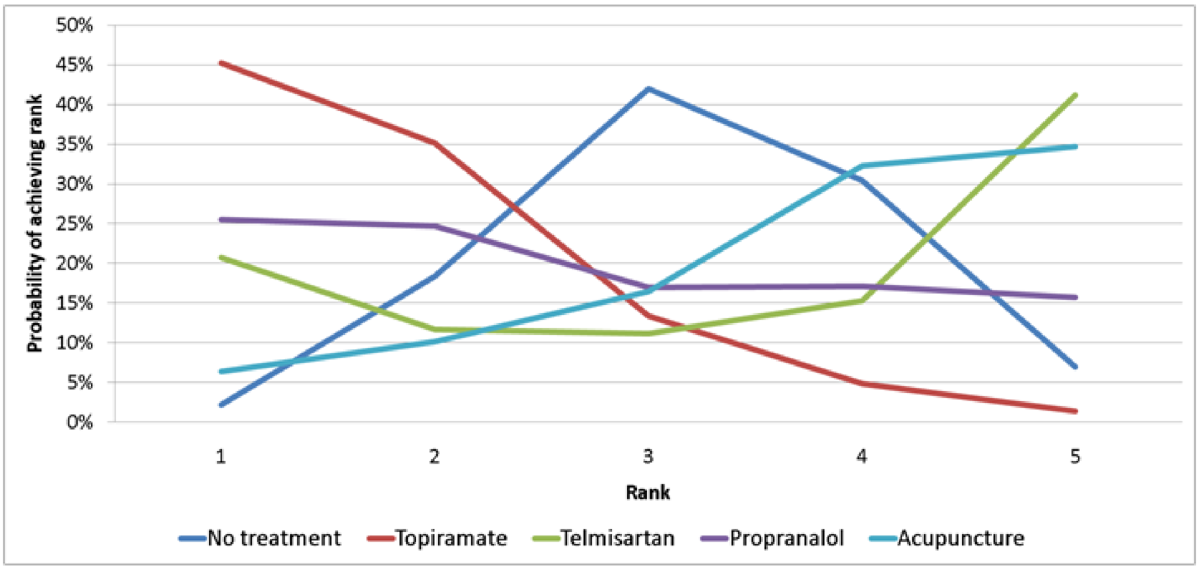

Figure 5: Rank probability plot

One way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters. The following changes were tested:

- A threshold analysis on migraine utility was conducted. The utility value for a migraine episode at which topiramate was found no longer be cost-effective compared to no treatment was 0.358, an increase of 0.658 from the base case, showing that our conclusions were robust to a large change in this parameter.
- In a one-way sensitivity analysis the number of acupuncture visits was assumed to be 9 instead of 15. In this analysis, acupuncture was more cost-effective than no treatment (the INMB was positive) but was still not cost-effective when compared to topiramate or propranolol.
- A threshold analysis was conducted to determine the number of acupuncture sessions above which acupuncture is no longer cost-effective compared to no treatment. When 10 sessions are provided, acupuncture is more cost-effective than no treatment; however above this number (11 sessions onward) acupuncture is not cost-effective. This analysis has some limitations since we are changing the cost of acupuncture according to the number of sessions while the effectiveness is assumed to be similar to that achieved with the number of sessions performed in the RCTs (an average of 15).

<u>c) Limitations</u>

This model is based on findings from RCTs and therefore any issues concerning interpretation of the clinical review also apply to interpretation of the economic analysis. One limitation of the model is that due to the scarce reporting of adverse events in the RCTs, we are unable to model the disutility of treatment specific adverse events. This should be considered when interpreting the results of the analysis. Had we incorporated adverse events, results would have been less in favour of topiramate as the side effect profile of this drug is more pronounced compared to propranolol.

A further limitation is that, due to the treatment durations considered in the clinical trials, we were unable to consider a time horizon longer than 6 months as we could not be sure whether extrapolation of treatment effects was appropriate.

14.5 Recommendations and link to evidence

Recommendations	**Discuss the benefits and risks of prophylactic treatment for migraine with the person, taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life.**
Relative values of different outcomes	This recommendation was based on GDG informal consensus opinion.
Trade off between clinical benefits and harms	The risks and benefits of each of the medicines available should be discussed with the person. By the end of the discussion, the person should understand their risk of migraine recurrence and severity with and without prophylaxis and their risk of adverse effects. If the person is a woman of child-bearing potential, she should be made aware of the teratogenic risks of topiramate, and, if relevant, its potential to reduce the reliability of combined hormonal contraception at doses greater than 200mg/day.
Economic considerations	A discussion with people on prophylactic treatment is not considered to generate significant costs and could lead to a more efficient use of resources (for example people making the best decision whether they would benefit from treatment) and to an improvement in the individual's quality of life.
Quality of evidence	This recommendation was based on GDG informal consensus opinion.
Other considerations	The recommended treatments were supported by the evidence reviewed, however when to start prophylactic treatment was not part of the review question. The GDG agreed this should mainly be determined by patient choice. Informal consensus methods were used to form the recommendation. The GDG noted that there is anecdotal evidence that if someone has medication overuse headache prophylaxis doesn't work. Different people may value the risks and benefits of different choices for prophylaxis. Choices may also be informed by the effectiveness of acute medication for that individual.

Recommendations	**Offer topiramate[hh] or propranolol 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 both topiramate[hh] and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5–8 weeks or gabapentin[ii] (up to 1200 mg per day) according to the person's preference, comorbidities and risk of adverse events.**
Relative values of different outcomes	The GDG agreed that change in patient reported migraine days is the most important outcome for decision making. Responder rate was also considered to be important.
Trade off between clinical benefits and harms	The risks and benefits of topiramate, propranolol and their other options should be discussed with the person. By the end of the discussion, they should understand their risk of migraine recurrence and severity with each option and their risk of adverse effects. Prescribers should consult the summary of product characteristics (SPC) and the latest BNF to familiarise themselves with side effects, contraindications and the availability of once-daily dosage forms. For women of child-bearing age not on appropriate contraceptives beta-blockers should be used in preference to topiramate. **Acupuncture:** There were very little data on serious adverse events reported in the studies included in this review (see chapter 17). Treatment reactions after acupuncture needling are common. Serious adverse events, e.g. pneumothorax can occur. This risk however is small.
Economic considerations	Our original cost-effectiveness analysis, based on a network meta analysis conducted using RCT data, acquisition costs, consultation costs and cost of administering acute medication, showed that a topiramate is the most cost-effective prophylactic treatment of migraine. Propranolol was the second most cost-effective intervention. They were both more costly than no treatment but they were also more effective. Other strategies (telmisartan and acupuncture) were not cost-effective when compared to topiramate and propranolol, and also when compared to no treatment. However the probabilistic sensitivity analysis showed a high level of uncertainty in these results. In the probabilistic sensitivity analysis, topiramate was the most cost-effective strategy in about 45% of the simulations while propranolol came out the most cost-effective strategy in about 26% of the simulations. Our original model did not take into account any adverse events of the treatments being compared. This should be considered when interpreting the results of the analysis. Had we incorporated adverse events, results would

[hh] At the time of publication (September 2012), topiramate did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information..

[ii] At the time of publication (September 2012), gabapentin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

	have been less in favour of topiramate as the side effect profile of this drug is more pronounced compared to propranolol. Potential occurrences of adverse events and their impact on the person's quality of life should be taken into account when considering the treatment options. An economic study was reviewed which compared topiramate to no treatment and found it to be cost effective. The ICERs calculated from this study were slightly lower than those from our analysis, since the efficacy estimates for topiramate were more favourable than those found from our clinical review. However, the authors conducted a sensitivity analysis and topiramate was still cost-effective using efficacy estimates of similar magnitude to those found in our clinical review. While our base case analysis showed that acupuncture is not cost-effective compared to other treatments (topiramate and propranolol) and to no treatment, a previous cost-effectiveness study found that acupuncture is cost-effective compared to usual care. This was a cost-utility analysis conducted alongside an RCT in the UK. Their conclusions, largely different from the findings of our model, can be explained by two factors: on the one hand in our analysis, acupuncture consisted of 15 sessions compared to the 9 used in the RCTs, shifting the cost of the intervention to higher values; on the other hand, the effectiveness estimate of the no treatment intervention in our model was obtained from sham acupuncture rather than 'usual care', which could lead to the overestimation of the effectiveness of no treatment and ultimately to the underestimation of the cost-effectiveness of acupuncture. The conclusions of this study correspond to the findings of our sensitivity analysis on the number of acupuncture visits: when the same estimate was used in our model, acupuncture was cost-effective compared to no treatment. We also conducted a threshold analysis to determine the number of acupuncture sessions above which acupuncture is no longer cost-effective compared to no treatment. When 10 sessions are provided, acupuncture is more cost-effective than no treatment; however above this number (11 sessions onward) acupuncture is not cost-effective.
Quality of evidence	The evidence was based on low to high quality evidence. The trials of topiramate and propranolol included people from age 12 and above. One of the topiramate studies investigated people with chronic migraine defined as having $\geq$15 headaches per month, the rest of the studies included people who had <15 headaches per month, the average being around 6. There was also some evidence for telmisartan from one small study (low quality evidence). The GDG agreed that this evidence wasn't strong enough to form a recommendation for an off-license treatment. The evidence for gabapentin was for change in migraine frequency and intensity and therefore could not be included in the network meta-analysis. However, there was moderate quality evidence for reduction in migraine frequency and intensity compared to placebo. The recommendations are based on studies investigating treatment for between 3 and 6 months. The evidence for longer term use showed no maintained benefit (moderate to high quality). The economic evidence has direct applicability and minor limitations. **Acupuncture:** The evidence reviewed (see chapter 17) was moderate to low quality. All included studies were single blind as the person administering treatment was not blinded to treatment group, however the participants and assessors were blinded. All evidence reviewed was for traditional Chinese medicine approach to acupuncture compared to sham acupuncture. The effect size reported was good, with network meta-analysis showed acupuncture to be ranked joint second most effective treatment for reducing the number of migraine days.

	The economic evidence was based on an original economic model with minor limitations and direct applicability and on a published economic evaluation based on a RCT with minor limitations and partial applicability.
Other considerations	The BNF states details for titration of topiramate when starting treatment. At doses of 200mg or higher, topiramate may induce enzymes responsible for the metabolism of ethinyl estradiol found in combined hormonal contraceptives, thus reducing their levels. Bearing in mind that topiramate is a teratogen and the potentially serious consequences of a pregnancy, the GDG recommends that women of child-bearing potential using topiramate be advised to use a reliable contraceptive method such as medroxyprogesterone acetate depot injection or an intrauterine method (coil or Mirena®) as their metabolism is suggested to be unaffected by topiramate[79]. If she chooses, instead, to use combined hormonal contraception (i.e. combined oral contraception (COC), vaginal ring, the progestogen-only pill (POP) or implant), then she should be advised to additionally use a barrier method and the dose of ethinylestradiol in the COC should be 50mcg or greater[1,79]. Blood monitoring may be needed with some antiepileptics and in order to minimise side effects, it is advisable to start on a low dose and gradually titrate upwards to find the optimal dosage level. Titration may occur over a period of weeks or even months and throughout this period it may be useful to use a diary to record side effects, dose, migraine frequency and severity, and rescue medication. Further detail on contraception for people taking topiramate who require contraception is published in: The diagnosis and management of the epilepsies in adults and children in primary and secondary care, NICE Guideline CG137: http://guidance.nice.org.uk/CG137[2]. This makes several recommendations about contraceptive use and antiepileptic drugs including referring to the BNF (http://www.bnf.org) and Summary of Product Characteristics (SPC) (http://www.medicines.org.uk/emc/) for topiramate for advice. Guidance on drug interactions with hormonal contraception and a statement (2010) on anti-epileptic drugs and contraception are available from the Faculty of Sexual and Reproductive Health Care http://www.fsrh.org/pages/clinical_guidance.asp. Young people were included in the studies of effectiveness of topiramate. Topiramate is not licensed for the use in children for migraine prophylaxis. The evidence for gabapentin came from a study in which participants received 400mg once daily for days one to three, 800mg once daily for days four to six, and 1200mg once daily from day seven. The BNF reports the dose for migraine prophylaxis as initially 300mg then increased according to response up to 2.4g daily in divided doses. The GDG considered it was an appropriate alternative for young people if other options were ineffective, not tolerated or unsuitable. Gabapentin is not licensed for the prophylaxis of migraine in adults or children. The recommended treatments were supported by the evidence reviewed. The GDG noted that there is anecdotal evidence that if someone has medication overuse headache prophylaxis doesn't work. The GDG considered that pharmacological prophylaxis should be reviewed at 6 months and it may be possible to for people to reduce or stop prophylaxis. During the development of the Headaches clinical guideline the NICE technology appraisal programme published guidance on Botox (Botulinum toxin type A for the prevention of headaches in adults with chronic migraine). This is a relevant treatment option for people with chronic migraine. **Acupuncture:** The recommendation for acupuncture was based on the evidence comparing acupuncture with sham acupuncture. It was noted that this review did not look at studies comparing acupuncture with usual care, and there are conflicting views amongst experts in the field as to which is the most valid comparison. However, comparison to sham acupuncture would most

	likely provide a more conservative estimate of the effectiveness of acupuncture and would control for the non-specific effects of the treatment. **Research recommendations:** The GDG agreed that research recommendations should be formed for the use of amitriptyline and pizotifen for the prophylactic treatment of migraine, with a particular focus on people aged under 18 for pizotifen. There was an absence of evidence for these two treatments, but GDG consensus was that they may be of benefit for some people, but research was required to confirm this. See appendix M2 for both research recommendations

Recommendations	**For people who are already having treatment with another form of prophylaxis such as amitriptyline[jj], and whose migraine is well controlled, continue the current treatment as required.**
Relative values of different outcomes	This recommendation was based on GDG consensus opinion.
Trade off between clinical benefits and harms	For risks associated with other forms of prophylaxis for migraine, prescribers should refer to the summary of product characteristics (SPC) or BNF looking at side effects, contraindications, dosage regimens and costs.
Economic considerations	There is some cost saving associated with this recommendation as people on another form of prophylaxis will not have any additional cost for the prophylactic treatment of migraine.
Quality of evidence	This recommendation was based on GDG consensus opinion.
Other considerations	The GDG considered that there may be other prophylactic treatments, such as amitriptyline, pizotifen, sodium valproate, lisinopril and losartan which are in regular use and are effective for some people, although no evidence was identified in this review. Pizotifen is particularly used for prophylaxis in children and young people. This was noted as an absence of evidence, not evidence that such treatments are ineffective. The GDG made research recommendations for trials to evaluate the use of amitriptyline and pizotifen and this is outlined in more detail in Appendix M. During the development of the Headaches clinical guideline the NICE technology appraisal programme has published guidance on Botox (Botulinum toxin type A for the prevention of headaches in adults with chronic migraine). This is a treatment option for people with chronic migraine.

Recommendations	**Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment.**
Relative values of different outcomes	This recommendation was based on GDG consensus opinion.
Trade off between clinical benefits and harms	The aim of prophylaxis is to reduce the frequency and severity of migraine. Continuing to take treatment when it is no longer required puts the patient at risk of side effects and drug interactions.
Economic considerations	In our economic model, the cost of a visit after starting a prophylactic

[jj] At the time of publication (September 2012), amitriptyline did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

	treatment is factored into all the treatment strategies. The strategies recommended in the guideline entail a visit and are cost-effective.
Quality of evidence	All evidence reviewed was for 3-6 months treatment. This recommendation was based on GDG consensus opinion.
Other considerations	The GDG experience is that people are able to stop prophylaxis after 6 months of treatment and have continued benefit from the prophylactic treatment. They considered that all people on prophylactic treatment should have their need to continue treatment reviewed at 6 months.

15 Prophylactic pharmacological treatment of menstrual migraine

15.1 Introduction

Migraine is more than twice as common in women as in men, mostly affecting women during their reproductive years[139,186,210,242,243]. While in most cases management is identical regardless of the person's gender, some additional issues may need consideration in women. This chapter concerns management of pure menstrual and menstrual-related migraine.

Over half of female migraine sufferers report some association between their migraine and menstruation[42,65,94,160,161,163]. Most of these women also have migraine at other times of the month, and are thus defined as having 'menstrual related' migraine. Fewer than 10% of women have 'pure menstrual migraine', when attacks occur exclusively with menstruation[65,94,98,160,161]. Menstrual and menstrual related migraine cause significant morbidity and may cause unnecessary suffering if left untreated[162]. It is important to establish an accurate diagnosis to ensure both types of disorder are appropriately treated, as they are often of greater severity and longer duration than other types of migraine.

The first step in management is to optimise the usual acute medications and avoid any known triggers. The GDG were interested in prophylactic treatment as peri-menstrual prophylaxis may be considered for people who have regular menstrual periods.

Triptans, NSAIDs and hormonal methods such as oestrogen supplements have been used for this purpose.

15.1.1 Clinical question

In people with pure menstrual and menstrual related migraine, what is the clinical evidence and cost effectiveness for prophylactic pharmacological treatment with: ACE inhibitors and angiotensin II receptor antagonists (ARBs), antidepressants (SNRIs, SSRIs, tricyclics), beta blockers, calcium channel blockers, antiepileptics, triptans, other serotonergic modulators, NSAIDs, and hormonal therapy (contraceptives)?

A literature search was conducted for RCTs comparing the clinical effectiveness of different pharmacological interventions for the prophylactic pharmacological treatment of menstrual migraine. The interventions we included in our search were ACE inhibitors and angiotensin II receptor blockers (ARBs), antidepressants (SNRIs, SSRIs, tricyclics), beta blockers, calcium channel blockers, antiepileptics, triptans, other serotonergic modulators, NSAIDs, hormonal therapy (contraceptives) and placebo/no prophylaxis. We looked for any studies that compared the effectiveness of two or more of these treatments (or placebo/no prophylaxis) (see protocol C.2.7). No evidence was found on any of the other comparisons and therefore there is no section in the chapter.

15.2 Matrix of treatment comparisons

Below is a matrix showing where evidence was identified. A box filled with a number represents where evidence was found and how many studies are reviewed in this chapter for that comparison. A box filled with - represents an area the GDG were interested in, but no evidence was found. In this case, no section on this comparison is included in the chapter.

ACE inhibitors /ARBs	-								
Antidepressants (Anti-d)	-	-							
Beta blockers (B-block)	-	-	-						
Calcium channel blockers (CCB)	-	-	-	-					
Antiepileptics (Anti-e)	-	-	-	-	-				
Other serotonergic modulators (sero)	-	-	-	-	-	-			
NSAIDs	-	-	-	-	-	-	-		
Triptans	-	-	-	-	-	-	-	-	
Placebo/no prophylaxis	-	-	-	-	-	-	-	-	3
	Hormonal therapy	**ACE / ARBs**	**Anti-d**	**B-block**	**CCB**	**Anti-e**	**Sero**	**NSAIDs**	**Triptans**

15.2.1 Triptans vs placebo

15.2.1.1 Clinical evidence

See evidence tables in appendix section E.2.7, forest plots in Figures 106-108, appendix G.2.6.

Three studies were included in this review [18,183,257]. The triptans included were frovatriptan, naratriptan and zolmitriptan. Different doses of each of these drugs were used in the trials and were pooled for analysis.

The populations differed between studies. In one study the population included people with 'difficult to treat' menstrual migraine[18], another study included people with pure menstrual migraine but also those who had migraine with aura[257] and the third study included people with migraine with or without aura[183].

The use of acute pharmacological treatment was reported in two different ways in the studies. One study reported the percentage of people requiring acute treatment for breakthrough attacks[18] and another reported the percentage of breakthrough attacks requiring acute treatment[257].

It was not possible to determine the numbers for available case analysis for two of the included studies[18,183]. One study reported outcomes standardised over four peri-menstrual periods but numbers of participants who withdrew along with reasons were reported per peri-menstrual period. In this study, modified intention-to-treat data were used [18]. The modified intention to treat population in this study was defined as all participants who received at least one dose of study medication and provided data for the primary efficacy end-point. An intention-to-treat analysis was used for the second study [183] as no data were provided to carry out an available case analysis. The study did not state whether imputation was used for missing data.

The data for change in headache days and headache intensity could not be meta-analysed as the change values were reported standardised over four peri-menstrual periods. Data for headache specific quality of life were reported in one study as being not significantly different across comparison groups and is presented as such in the evidence tables (See evidence table E.2.7).

Crossover trials were not included in this review. The review protocol can be found in Appendix C.2.7.

Table 126: Triptans vs placebo – Quality assessment

Outcome	No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Responder rate (50% reduction in migraine frequency)[257]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Use of acute pharmacological treatment (% of patients treated)[18]	1	Randomised trials	No serious limitations	No serious inconsistency	Serious[(c)]	Serious[(b)]
Use of acute pharmacological treatment (% of breakthrough attacks treated)[257]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Incidence of serious adverse events[257],[183]	2	Randomised trials	Serious[(d)]	No serious inconsistency[(e)]	Serious	N/A[(f)]
Change in patient reported headache days, frequency and intensity	0	-	-	-	-	-
Functional health status and health-related quality of life	0	-	-	-	-	-
Headache	0	-	-	-	-	-

Outcome	No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
specific QOL						
Resource use	0	-	-	-	-	-

(a) Details of allocation concealment and blinding of investigators not reported.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) Study was conducted among women who were refractory to triptan therapy for acute treatment of tension type headache (difficult to treat).
(d) Both studies did not report details of allocation concealment and blinding of investigators; one study had different proportions of participants in either arm who were on concomitant prophylactic therapy prior to the trial.
(e) One study was conducted in people who were earlier refractory to triptan therapy and the second study was included people with migraine with aura which does not fit the IHS definition of menstrual migraine.
(f) Data could not be meta-analysed.

Table 127: Triptans vs placebo – Clinical summary of findings

Outcome	Triptan	Placebo	Relative risk	Absolute effect	Quality
Responder rate (50% reduction in migraine frequency) [257]	93/163 (57.1%)	31/81 (38.3%)	RR 1.49 (1.1 to 2.03)	188 more per 1000 (from 38 more to 394 more)	LOW
Use of acute pharmacological treatment (% of patients treated)[18]	167/250 (66.8%)	137/160 (85.6%)	RR 0.78 (0.7 to 0.87)	188 fewer per 1000 (from 111 fewer to 257 fewer)	LOW
Use of acute pharmacological treatment (% of breakthrough attacks treated) [257]	100/163 (61.3%)	60/81 (74.1%)	RR 0.83 (0.69 to 0.99)	126 fewer per 1000 (from 7 fewer to 230 fewer)	LOW
Incidence of serious adverse events[257,183]	0/413	0/241	-	0	LOW

15.2.1.2 Economic evidence

No relevant economic evaluations comparing triptans with placebo were identified.

We calculated the cost of treatment with triptans based on the unit cost of drugs reported in the BNF62[111] (see Table 128 below). We assumed the peri-menstrual treatment with triptans is for a six-day period based on the avearage length of treatment in the RCTs included in our clinical review (15.2.1.1).

Table 128: Acquisition cost of triptans

Drug	Cost per peri-menstrual treatment (£)	Notes
Frovatriptan	16.67	Dosage: 2.5 mg once daily
	33.34	Dosage: 2.5 mg twice daily
Naratriptan	49.10	Dosage: 2.5 mg twice daily
Zolmitriptan	36.00	Dosage: 2.5 mg twice daily
	54.00	Dosage: 2.5 mg three times daily

Source: BNF62[111]

The costs of adverse effects and further events such as GP or specialist visits were not estimated.

15.2.1.3 Evidence statements

Clinical:

One study with 244 women with menstrual migraine suggested that triptans may be more clinically effective than placebo at improving responder rate at three months follow up, but there is some uncertainty. [Low quality].

One study with 427 women with refractory menstrual migraine and menstrual related migraine suggested that there is no difference between triptans and placebo in reducing the number of people requiring acute pharmacological treatment at four months follow up, but there is some uncertainty. [Low quality].

One study with 244 women with menstrual migraine suggested that there is no difference between triptans and placebo in reducing the number of attacks requiring acute pharmacological treatment at three months follow up, but there is some uncertainty. [Low quality].

Two studies with 654 women with menstrual migraine showed that there is no difference between triptans and placebo in the incidence of serious adverse events at four months follow up. [Low quality].

No studies reported outcome data for change in patient reported headache days, frequency and intensity, functional health status and health related quality of life, headache specific quality of life and resource use.

Economic:

No economic evidence was found for this question. A simple cost analysis based on acquisition costs showed that the cost of each perimenstrual treatment with triptans is between £16.67 and £54.

15.3 Recommendations and link to evidence

Recommendations	**For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan[kk] (2.5 mg twice a day) or zolmitriptan[ll] (2.5 mg twice or three times a day) on the days migraine is expected.**
Relative values of different outcomes	Responder rate was considered to be the most important outcome. Other evidence considered was based on the reduced use of acute pharmacological treatment.
Trade off between clinical benefits and harms	The risk of medication overuse headache should be considered when triptans are used for prophylaxis of menstrual migraine.
Economic considerations	A simple cost analysis based on acquisition costs showed that the cost of

[kk] At the time of publication (September 2012), frovatriptan did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

[ll] At the time of publication (September 2012), zolmitriptan did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

	perimenstrual treatment with frovatriptan is between £16.67 and £54 and between £36 and £54 with zolmitriptan. The GDG considered this cost too high to recommend the routine use of triptans in women suffering of menstrual-related migraine; however this cost might be justified if conventional treatment has not been effective.
Quality of evidence	This recommendation is based on low quality evidence from two studies[20,257] showing reduced acute medication use and increased responder rate with frovatriptan or zolmitriptan compared to placebo. Only one study reported responder rate[257]. Additional evidence and advice was gained from an expert advisor to inform the recommendations. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs.
Other considerations	Menstrual migraine and menstrual related migraine are treated with the same strategies. One of the important issues in deciding on treatment is frequency of migraine as infrequent migraine is best treated using acute treatments. Studies included in this review have shown a benefit with the use of triptans in doses of 2.5 mg with up to twice daily (with the highest dose of 2.5mg demonstrating better efficacy) dosing for long acting triptans (frovatriptan) and three times a day dosing for short acting triptans (zolmitriptan). The later trials have used longer acting triptans. This treatment is off licence and menstruation needs to be predictable to use this method. The GDG considered that peri menstrual prophylaxis is only required for a small number of people who have regular periods. The co-opted expert considered that oestrogen supplementation e.g. using gels is rarely required even in specialist practice. Women who require contraception and can safely use combined hormonal contraceptives, can manipulate their cycles to reduce the number of periods they have e.g. by tricycling combined hormonal contraception or by reducing the hormone free interval.

16 Prophylactic pharmacological treatment of cluster headache

16.1 Introduction

The majority of people with cluster headache (80-90%) experience daily attacks during an acute bout of cluster headache. These bouts may last for several weeks or months and alternate with pain-free remissions periods that can last for months or years. In 10-20% of people with cluster headache, the pain-free intervals are either absent or last less than one month. The pain experienced during a cluster attack is very severe and recurrent attacks lead to significant disabilities. Prophylactic treatments can be used to improve the symptoms.

The aim of prophylactic therapy is to reduce the frequency, severity and duration of attacks with minimal side effects during a cluster bout and to induce/or lengthen remission periods. Prophylactic therapies are usually started at the onset of a cluster bout and continued until the bout is over. The clinician should bear in mind that cluster headache bouts can be variable and unpredictable. Acute treatments can be used concomitantly with prophylactic therapies, if an individual should experience a cluster attack.

Which prophylactic medication should be used and when it is appropriate is dependent on headache frequency, duration, intensity and presence of co-morbid factors. The person's wishes must also be taken into account.

Prophylactic medications for cluster headaches include verapamil, lithium, corticosteroids, methysergide, melatonin and anti-epileptics agents. Their mechanism of action in cluster headache is poorly understood. The aim of this review was to determine the evidence base for each of these treatments.

16.1.1 Clinical question

In people with cluster headache, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: calcium channel blockers, corticosteroids, lithium, melatonin, antiepileptics and other serotonergic modulators.

A literature search was conducted for RCTs comparing the clinical effectiveness of different pharmacological interventions for prophylactic treatment of cluster headache. The interventions we included in our search were calcium channel blockers, corticosteroids, lithium, melatonin, antiepileptics, methysergide and triptans and placebo. We looked for any studies that compared the effectiveness of two or more of these treatments (or placebo). Unless otherwise stated in the section introduction, all data reported are analysed according to available case analysis (see protocol C.2.8).

16.2 Matrix of treatment comparisons

Below is a matrix showing where evidence was identified. A box filled with a number represents how many studies were identified and are reviewed in this chapter. A box filled with - represents where no evidence was found. In this case, no section on this comparison is included in the chapter.

Methysergide (Meth)	-							
Triptans	2	-						
Antiepileptics (anti-e)	1	-	-					
Melatonin (Mel)	1	-	-	-				
Lithium	-	-	-	-	-			
Corticosteroids (steroid)	-	-	-	-	-	-	-	
Calcium channel blockers (CCB)	1	-	-	-	-	-	-	-
	Placebo	**Meth**	**Triptans**	**Anti-e**	**Mel**	**Lithium**	**Steroid**	**CCB**

16.2.1 Calcium channel blockers vs placebo

16.2.1.1 Clinical evidence

See evidence tables in appendix section E.2.8, forest plots in Figures 109-111, appendix G.2.7.

One study was identified that compared verapamil (360mg per day) with placebo[143]. The study was small (n=30) and carried out in an outpatient setting, with a population of people with episodic cluster headache. People were allowed to use acute treatment throughout the study. Outcomes were reported at two weeks.

Adverse events were reported for this study, but were not classified as serious. This has not been analysed here but data are reported in the evidence table (see appendix E.2.8).

Table 129: Calcium channel blockers vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Responder rate (50% reduction in frequency)[143,144]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported headache frequency[143,144] (attacks per day)	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Use of acute pharmacological treatment[143,144]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in patient-reported headache	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
days						
Change in patient-reported headache intensity	0	-	-	-	-	-
Functional health status and health-related quality of life	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Randomisation and allocation concealment not reported, dropouts not reported, acute treatment allowed throughout the study and baseline characteristics not comparable between groups.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 130: Calcium channel blockers vs placebo – Clinical summary of findings

Outcome	Verapamil	Placebo	Relative Risk	Absolute effect	Quality
Responder rate (50% reduction in frequency)	12/15 (80%)	0/15 (0%)	RR 25 (1.61 to 387.35)	- *	LOW
Change in patient reported headache frequency	0.6 (n=15)	1.65 (n=15)	-	MD 1.05 lower (1.73 to 0.37 lower)	VERY LOW
Use of acute pharmacological treatment	0.5 (n=15)	1.2 (n=15)	-	MD 0.7 lower (1.38 to 0.02 lower)	VERY LOW

**Absolute effect could not be calculated for responder rate as no events occurred in the placebo group.*

16.2.1.2 Economic evidence

No economic evaluations comparing calcium channel blockers with placebo were identified.

We calculated the cost per month of different pharmacological treatments based on the unit cost of drugs reported in the BNF62[111] (see Table 131 below).

Table 131: Acquisition cost of drug treatments

Drug	Cost per month (£)	Notes
Calcium channel blockers (verapamil)	5.21	Dosage: 120mg three times per day
Corticosteroids (prednisolone)	11.84	Dosage: 25 mg four times per day for first 5 days, then 5 mg twice a day every 2 days
Antiepileptics (sodium valproate)	10.49	Dosage: 500 mg twice a day for the first three days, followed by 500 mg three times a day for other 5 days, then 500 mg four times a day.
Triptans (Sumatriptan)	36.96	Dosage: 100 mg three times a day
Triptans (Frovatriptan)	169.02	Dosage: 2.5 mg twice a day

Drug	Cost per month (£)	Notes
Melatonin	78.00	Dosage: 2 mg five times a day

Source: BNF62[111]

The costs of adverse effects and further events such as GP or specialist visits were not estimated.

16.2.1.3 Evidence statements

Clinical:

One study of 30 people showed that calcium channel blockers are more clinically effective than placebo in improving responder rate, measured by 50% reduction in headache frequency, in people with episodic cluster headache at two weeks follow up. [Low quality].

One study of 30 people suggested that calcium channel blockers may be more clinically effective than placebo in reducing headache frequency in people with episodic cluster headache at two weeks follow up but there is some uncertainty. [Very low quality].

One study of 30 people suggested that calcium channel blockers may be more clinically effective than placebo in reducing the number of acute pharmacological treatments used per day in people with cluster headache at two weeks follow up, but there is some uncertainty. [Very low quality].

No studies reported outcome data for change in headache days, change in patient reported headache intensity, functional health status or quality of life, resource use or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed that the cost of treatment with calcium channel blockers is on average £5.21 per month.

16.2.2 Melatonin vs placebo

16.2.2.1 Clinical evidence

See evidence tables in appendix section E.2.8, forest plots in Figures 112-113, appendix G.2.7.

One small study (n=20) was included in this review[144]. Acute pharmacological treatment was allowed throughout the study. Outcomes were reported at two weeks.

Table 132: Melatonin vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient reported headache frequency (attacks per day)[144]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)
Use of acute pharmacological treatment[144]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (c)
Responder rate	0	-	-	-	-	-
Change in patient-reported headache days	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient-reported headache intensity	0	-	-	-	-	-
Functional health status and health-related quality of life	0	-	-	-	-	-
Headache specific QOL	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Small study population, randomisation and allocation concealment not reported, acute treatment allowed throughout duration of the study, number of dropouts from study not reported.
(b) The confidence interval crosses both minimal important differences making the effect size very uncertain.
(c) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 133: Melatonin vs placebo – Clinical summary of findings

Outcome	Melatonin	Placebo	Relative Risk	Absolute effect	Quality
Change in patient reported headache frequency	1.51 (n=10)	2.5 (n=10)	-	MD 0.99 lower (5.36 lower to 3.38 higher)	VERY LOW
Use of acute pharmacological treatment	1.16 (n=10)	2.37 (n=10)	-	MD 1.21 lower (2.24 to 0.18 lower)	VERY LOW

16.2.2.2 Economic evidence

No relevant economic evaluations comparing melatonin with placebo were identified.

We calculated the cost per month of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 131 in section 16.2.1.2).

16.2.2.3 Evidence statements

Clinical:

In one study with 20 people, there is too much uncertainty to determine whether there is a difference between melatonin and placebo in reducing headache frequency (assessed by number of attacks per day) in people with cluster headaches at two weeks follow up. [Very low quality].

One study with 20 people suggested that melatonin may be more clinically effective than placebo at reducing the number of analgesics consumed per day in people with cluster headaches at two weeks follow up, but there is some uncertainty. [Very low quality].

No studies reported outcome data for responder rate, change in headache days, change in patient reported headache intensity, functional health status or quality of life, resource use or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed that the cost of treatment with melatonin is on average £78.00 per month.

16.2.3 Antiepileptics vs placebo

16.2.3.1 Clinical evidence

See evidence tables in appendix section E.2.8, forest plots in Figures 114-117, appendix G.2.7.

One trial was included in this review in which the antiepileptic was sodium valproate[69]; this trial was stopped early due to slow recruitment (n=96). The dose of sodium valproate was increased during the study; participants received 1g per day on days 1 to 3, they received 1.5 g per day on days 4 to 8 and for day 9 onwards they received 2g per day. Outcomes were reported at 2 weeks.

Adverse events were reported, but not classified as serious, so are not analysed here.

Table 134: Sodium valproate vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Responder rate (50% reduction in number of attacks)[69]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in patient-reported headache intensity[69]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Very serious (c)
Use of acute pharmacological treatment (number of people using sumatriptan)[69]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Use of acute	1	Randomised	Very serious	No serious	No serious	Serious (b)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
pharmacological treatment (number of people using oxygen)[69]		trials	(a)	inconsistency	indirectness	
Change in patient-reported headache days	0	-	-	-	-	-
Functional health status and health-related quality of life	0	-	-	-	-	-
Headache specific QOL	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Number of dropouts was unclear, baseline characteristics were not comparable between groups and the trial stopped early due to slow recruitment.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.

Table 135: Sodium valproate vs placebo – Clinical summary of findings

Outcome	Sodium valproate	Placebo	Relative Risk	Absolute effect	Quality
Responder rate (50% reduction in number of attacks)	25/50 (50%)	29/46 (63%)	RR 0.79 (0.56 to 1.13)	132 fewer per 1000 (from 277 fewer to 82 more)	VERY LOW
Mean pain intensity Mean (number of subjects)	4.9 (n=50)	5.3 (n=46)	-	MD 0.4 lower (1.2 lower to 0.4 higher)	VERY LOW
Use of acute pharmacological treatment (sumatriptan)	18/50 (36%)	24/46 (52.2%)	RR 0.69 (0.38 to 1.07)	162 fewer per 100 (from 324 fewer to 37 more)	VERY LOW
Use of acute pharmacological treatment (oxygen)	6/50 (12%)	15/46 (32.6%)	RR 0.37 (0.14 to 0.86)	205 fewer per 1000 (from 46 fewer to 280 fewer)	VERY LOW

16.2.3.2 Economic evidence

No relevant economic evaluations comparing sodium valproate with placebo were identified.

We calculated the cost per month of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 131 in section 16.2.1.2).

16.2.3.3 Evidence statements

Clinical:

One study with 96 peoples suggested that placebo may be more clinically effective than sodium valproate at improving responder rate, assessed by 50% reduction in number of attacks, in people with cluster headaches at two weeks follow up, but there is some uncertainty. [Very low quality].

One study with 96 people suggested that sodium valproate is more effective than placebo in reducing mean pain intensity in people with cluster headache at two weeks follow up, but the effect size is too small to be clinically important and there is some uncertainty. [Very low quality].

One study with 96 people suggested that sodium valproate is more effective than placebo in reducing the use of sumatriptan as rescue medication in people with cluster headache at two weeks follow up, but the effect size is too small to be clinically important and there is some uncertainty. [Very low quality].

One study with 96 people suggested that sodium valproate is more effective than placebo in reducing the use of oxygen as rescue medication in people with cluster headache at two weeks follow up, but the effect size is too small to be clinically important and there is some uncertainty. [Very low quality].

One study with 96 people suggested that there are a greater number of adverse events experienced by people taking sodium valproate than those taking placebo for the prophylactic treatment of cluster headache at two weeks follow up, but there is some uncertainty. [Low quality].

No studies reported outcome data for change in patient reported headache days, functional health status or quality of life or resource use.

Economic:

No economic evidence was found for this question. A simple cost analysis showed that the cost of treatment with sodium valproate is on average £10.49 per month.

16.2.4 Triptan vs placebo

16.2.4.1 Clinical evidence

See evidence tables in appendix section E.2.8, forest plots in Figures 118-119, appendix G.2.7.

Two studies were identified that compared frovatriptan (5 mg per day)[190] and sumatriptan (300mg per day)[176] with placebo. The settings were neurology departments and specialist headache centres. One study reported outcomes at one week[176] and one study reported outcomes at three weeks[190,191].

The study of frovitriptan[190,191] was stopped early due to slow recruitment (n=11), and all participants in the study conducted major protocol violations. Furthermore this study was only reported as a brief communication and therefore was lacking in details such as patient characteristics, however, there was enough information to include the study in the review.

Serious adverse events were not reported, but other adverse events were. This outcome was not analysed here but data are available in the evidence tables (appendix E.2.7).

It was not possible to determine the available case analysis data from either of the papers, therefore the analysis for this review report results on an intention to treat basis with last observation carried forward as reported in the papers.

Table 136: Triptan vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Responder rate (50% reduction in number of attacks)[176]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious [(b)]
Change in patient reported headache frequency (attacks per week)[190,191]	1	Randomised trials	Very serious [(c)]	No serious inconsistency	No serious indirectness	Very serious [(b)]
Use of acute pharmacological treatment (number of attacks per day requiring analgesics)[176]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	N/A [(d)]
Change in patient-reported headache days	0	-	-	-	-	-
Change in patient-reported headache intensity	0	-	-	-	-	-
Functional health status and health-related quality of life	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-

(a) *Allocation concealment not reported, baseline characteristics differ between groups.*
(b) *The confidence interval cross the minimal important difference in both directions making the effect size very uncertain.*
(c) *Study discontinued prematurely due to infeasibility, very small number randomised, all people included conducted major protocol violations.*
(d) *Data could not be meta-analysed therefore imprecision could not be assessed.*
N/A=not applicable.

Table 137: Triptan vs placebo – Clinical summary of findings

Outcome	Triptan	Placebo	Relative Risk	Absolute effect	Quality
Responder rate (50% reduction in number of attacks)	20/89 (22.5%)	17/79 (21.5%)	RR 1.04 (0.59 to 1.85)	9 more per 1000 (from 88 fewer to 183 more)	VERY LOW
Change in headache frequency (attacks per week)	14.1 (n=5)	10.1 (n=6)	-	MD 4 higher (6.04 lower to 14.04 higher)	VERY LOW
Use of acute pharmacological treatment (analgesics)	1	1	N/A	N/A	LOW

N/A=not applicable.

16.2.4.2 Economic evidence

No relevant economic evaluations comparing triptans with placebo were identified.

We calculated the cost per month of different pharmacological treatments based on the unit cost reported in the BNF62[111] (see Table 131 in section 16.2.1.2).

16.2.4.3 Evidence statements

Clinical:

One study with 168 people with cluster headache, suggested that there is no difference between triptans and placebo in improving responder rate assessed by 50% reduction in number of attacks at one week follow up but there is considerable uncertainty. [Low quality].

One study with 11 people with episodic cluster headache suggested that placebo may be more clinically effective than triptans at reducing the number of attacks per week at three weeks follow up, but there is considerable uncertainty. [Very low quality].

In one study with 168 people with cluster headache suggested that triptans and placebo are equally effective in reducing the number of headache attacks requiring acute medication per day at one week follow up, but there is some uncertainty. [Low quality].

No studies reported outcome data for change in patient reported headache days, headache intensity, functional health status and quality of life, resource use or incidence of serious adverse events.

Economic:

No economic evidence was found for this question. A simple cost analysis showed that the cost of treatment is on average £36.96 per month with sumatriptan and £169 per month with frovatriptan.

16.3 Recommendations and link to evidence

Recommendations	**Consider verapamil[mm] for prophylactic treatment during a bout of cluster headache. If unfamiliar with its use for cluster headache, seek specialist advice before starting verapamil, including advice on electrocardiogram monitoring.**
Relative values of different outcomes	The GDG considered that responder rate and number of attacks per day are the most important outcomes.
Trade off between clinical benefits and harms	Verapamil may cause cardiac conduction problems; specialist advice on monitoring and dosing regimens is advised.
Economic considerations	The average cost of treatment with verapamil was £5.21 per month and it is relatively inexpensive when compared to other prophylactic treatments for cluster headache. There is an additional cost associated with specialist telephone advice. The GDG thought the acquisition cost and the specialist time cost would justify the use of verapamil in some people as the clinical evidence showed it has some effect at reducing the number of cluster headache attacks, leading to an improvement in the patient's quality of life.
Quality of evidence	This recommendation is based on low and very low quality evidence from a very small study. There was however a large effect size for responder rate and the GDG agreed that for a clinically devastating condition it was appropriate to recommend the use of verapamil based on this evidence. There are two formulations of verapamil available; fast release and standard release. The formulation of drug that was used in the study that the recommendation is based on was standard release. In the study the dose used was 360mg per day. The economic evidence was based on a limited cost analysis based only on the drug acquisition costs.
Other considerations	The GDG agreed by informal consensus that specialist advice may be required for dosing schedule for verapamil due to potential cardiac conduction problems that verapamil can cause. Electrocardiogram (ECG) monitoring is required before every increase in verapamil dosage and monitoring is also required at intervals if the person remains on verapamil. The consensus of the GDG based on clinical experience is that doses of up to 960 mg verapamil per day have been used for the prophylaxis of cluster headache. Specialist advice should be sought if these higher doses are to be used.

Recommendations	**Seek specialist advice for cluster headache that does not respond to verapamil[mm].**
Relative values of different outcomes	This recommendation was based on GDG consensus opinion alone.
Trade off between clinical benefits and harms	There is a lack of controlled trial evidence to inform prophylactic management of cluster headaches with the exception of verapamil, however the GDG agreed that severity of this condition means that alternative options must be considered for people who do not respond to this and therefore treatment advice should be obtained from a specialist on future management of the person.

[mm] At the time of publication (September 2012), verapamil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

Economic considerations	Referring people to a specialist is associated with the cost of an extra visit. The GDG considered this extra cost to be justified if treatment with verapamil has not been effective.
Quality of evidence	This recommendation was based on GDG consensus opinion alone.
Other considerations	There is a lack of controlled trial evidence to inform prophylactic management of cluster headaches. The GDG considered it is important that the diagnosis of cluster headaches is correct and not migraine misdiagnosed.

17 Prophylactic non-pharmacological management of primary headaches with acupuncture

17.1 Introduction

Therapeutic needling has been used since antiquity. Traditional Chinese Medicine (TCM) does not conform to orthodox clinical diagnosis which makes its translation into western medical practice challenging. The choice of points to needle may appear arbitrary. Western medical acupuncture is an approach to acupuncture that uses orthodox clinical diagnosis to inform selection of points to needle tissues for therapeutic effect possibly via segmental anaesthesia.

There is some evidence that stimulation of acupoints has specific effects in the spinal cord via stimulation of afferent nerve fibres (A-beta, A-delta and C), and that signal molecules and neuromodulators such as opioid peptides, glutamate, 5-hydroxy tryptamine and cholecystokinin octapeptide may modify levels of this variety of stimulation induced analgesia (acupuncture analgesia). Furthermore the characteristic feeling of 'De-Qi' reported by therapists and people treated is reported to improve efficacy of acupuncture analgesia.

Any therapeutic effect from acupuncture may be a combination of both the specific effect of acupuncture, including needling, and the context in which it is given. This leads to the common observation in trials that sham acupuncture may be more effective than no treatment but that there is often little additional benefit from true (verum) acupuncture compared to sham acupuncture.

The GDG decided that only evidence from verum acupuncture compared to a sham procedure would be considered. To be consistent across protocols, wherever a placebo or equivalent existed, this has been used as the comparator for the reviews in this guideline. This also enables indirect comparisons with RCTs of pharmacological treatments (see chapter 14).

17.1.1 Clinical question

For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with acupuncture?

A literature search was conducted for RCTs comparing the clinical effectiveness of verum acupuncture for tension type headache, migraine and cluster headache, plus or minus prophylactic pharmacological treatment (or other non-pharmacological treatment) compared to sham acupuncture. This review does not cover acupuncture compared to usual care (see protocol, C.2.9). A co-opted expert assisted in the development of this recommendation. They attended the meeting where the evidence was presented and informed discussion, but were not present for, or involved in, any discussions about recommendations.

The GDG were interested in searching for evidence for all primary headaches included in the guideline. Evidence was only identified for migraine and tension type headache (no studies were identified that looked at the use of acupuncture for cluster headaches). The evidence has been separated by headache type in this chapter.

17.2 Tension type headache

17.2.1 Verum acupuncture vs sham acupuncture

See evidence tables in appendix section E.3.1, forest plots in Figures 120-128, appendix G.2.8.

Four studies were included in the review. All included studies were single blind and used a Traditional Chinese Medicine approach rather than the Western Medical approach for acupuncture with the exception of one study which compared laser acupuncture to sham laser acupuncture[66]. The results in this study were only reported as median and interquartile range therefore could not be included in the meta-analysis.

One Cochrane review was identified on the use of acupuncture in the prophylaxis of tension type headache but it was excluded as it compared verum acupuncture to usual care or no treatment as well as to sham acupuncture[151]. Any studies which were relevant to our review protocol were included.

Imprecision for the effect size relating to the outcome headache days was assessed using a value agreed by the GDG for the MID: 0.5 days.

Table 138: Verum acupuncture vs sham acupuncture – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient reported headache days[71,118,171]	3	Randomised trials	Very serious (a,b,c)	No serious inconsistency	No serious indirectness	No serious imprecision
Responder rate[71,171]	2	Randomised trials	Very serious (a,b,c)	No serious inconsistency	No serious indirectness	Serious (d)
Change in patient reported headache intensity[118]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (d)
Use of acute pharmacological treatment[118,171]	2	Randomised trials	Serious (a,f)	No serious inconsistency	No serious indirectness	No serious imprecision
SF12 physical health[71]	1	Randomised trials	Very serious (a,e,f)	No serious inconsistency	No serious indirectness	No serious imprecision
SF12 mental health[71]	1	Randomised trials	Very serious (a,f)	No serious inconsistency	No serious indirectness	No serious imprecision
SF36 physical health[171]	1	Randomised trials	Serious (a,e)	No serious inconsistency	No serious indirectness	No serious imprecision
SF36 mental health[171]	1	Randomised trials	Serious (a,e)	No serious inconsistency	No serious indirectness	No serious imprecision
Nottingham Health Profile[118]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (d)
Change in patient reported headache	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
frequency						
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

a) *Single blind (individual administering care was not blinded).*
b) *Baseline differences between groups in two studies.*
c) *Some doubt over maintenance of participant blinding in one study.*
d) *The confidence interval crosses one minimal important difference making the effect size uncertain.*
e) *Baseline differences between groups, greater than effect size.*
f) *Some doubt over maintenance of participant blinding.*

Table 139: Verum acupuncture vs sham acupuncture – Clinical summary of findings

Outcome	Acupuncture	Sham	Relative Risk	Absolute effect	Quality
Change in patient reported headache days	351	284	-	MD 1.92 lower (3.15 to 0.69 lower)	LOW
Responder rate	180/331 (54.4%)	113/255 (44.3%)	RR 1.28 (1.08 to 1.51)	124 more per 1000 (from 35 more to 226 more)	VERY LOW
Change in patient reported headache intensity	34	35	-	MD 0.6 lower (1.45 lower to 0.25 higher)	LOW
Use of acute pharmacological treatment	151	92	-	SMD 0.29 lower (0.55 to 0.03 lower)	MODERATE
SF12 physical health	199	188	-	MD 0.3 higher (1.34 lower to 1.94 higher)	LOW
SF12 mental health	199	188	-	MD 0.2 lower (2 lower to 1.6 higher)	LOW
SF36 physical health	119	57	-	MD 0.8 lower (2.88 lower to 1.28 higher)	MODERATE
SF36 mental health	119	57	-	MD 1.3 higher (2.23 lower to 4.83 higher)	MODERATE
Nottingham Health Profile	34	35	-	MD 2.7 higher (0.36 to 5.04 higher)	LOW

17.2.1.1 Economic evidence

No relevant economic evaluations specifically looking at people with tension type headache were identified. However, in a study[261] comparing acupuncture with usual treatment, people with tension type headache were included in the study population. They represented 5% of the study population while the remaining 95% was represented by people with migraine.

The GDG thought the conclusions of this study could be applicable to the overall study population, including people with tension type headache.

The study is summarised in Table 144 and Table 145 in section 17.3.2). See also the full study evidence tables in Appendix F.

17.2.1.2 Evidence statements

Clinical:

Three studies with 673 people showed that verum acupuncture is more clinically effective than sham acupuncture at reducing the number of headache days at 3 months follow-up in people with tension type headache. [Low quality].

Two studies with 604 people suggested that verum acupuncture may be more clinically effective than sham acupuncture at improving responder rate at 3 months follow-up in people with tension type headache, but there is some uncertainty. [Very low quality].

One study with 69 people suggested that verum acupuncture may be more effective than sham acupuncture in improving headache intensity at 3 months follow up in people with tension type headache, but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

One study with 409 people showed that verum acupuncture and sham acupuncture were similarly effective in improving quality of life (assessed by SF-12 physical health) at 3 months follow up in people with tension type headache. [Low quality].

One study with 409 people showed that there is no difference between verum acupuncture and sham acupuncture in improving quality of life (assessed by SF-12 mental health) at 3 months follow up in people with tension type headache. [Low quality].

One study with 276 people showed that there is no difference between verum acupuncture and sham acupuncture in improving quality of life (assessed by SF-36 physical health) at 3 months follow up in people with tension type headache. [Moderate quality].

One study with 276 people showed that there is no difference between verum acupuncture and sham acupuncture in improving quality of life (assessed by SF-36 mental health) at 3 months follow up in people with tension type headache. [Moderate quality].

One study with 69 people suggested that sham acupuncture may be more clinically effective than verum acupuncture in improving quality of life (assessed by the Nottingham health profile) at 3 months follow up in people with tension type headache, but there is some uncertainty. [Low quality].

Two studies with 243 people suggested that verum acupuncture is more effective than sham acupuncture in reducing acute medication use at 3 months follow up, but the effect size is too small to be clinically important and there is some uncertainty. [Moderate quality].

No studies reported outcome data for headache intensity, quality of life or resource use.

Economic:

An economic study partially applicable and with minor limitations showed that acupuncture is cost-effective when compared to no treatment in people with migraine or tension type headache.

17.2.2 Recommendations and link to evidence

See section recommendations and link to evidence in section 17.4.

17.3 Migraine with or without aura

17.3.1 Verum acupuncture vs sham acupuncture

See evidence tables in appendix section E.3.1, forest plots in Figures 129-143, appendix G.2.8.

Four studies were included in the review. All included studies were single blind and used Traditional Chinese Medicine approach rather than the Western Medical approach for acupuncture. One study compared acupuncture plus placebo tablet to beta-blocker plus sham acupuncture, however the results were only reported as median differences between groups for migraine frequency and intensity and could not be included in the meta-analysis, the only data from that study that could be analysed was incidence of serious adverse events[103].

One Cochrane review was identified on the use of acupuncture in the prophylaxis of migraine but it was excluded as it compared acupuncture to usual care or no treatment as well as to sham acupuncture[150]. All studies relevant to our review protocol were included.

Imprecision for the effect size relating to the outcome Migraine Specific Quality of Life score (MSQ) was assessed using a value for the MID published in a study by Cole et al[41]. Imprecision for the effect size relating to the outcome headache or migraine days was assessed using a value agreed by the GDG for the MID: 0.5 days.

Table 140: Verum acupuncture vs sham acupuncture – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient reported migraine days[58,147,153]	3	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Responder rate[58,153]	2	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine intensity[58,147,153]	3	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine frequency[147]	1	Randomised trial	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
SF12 physical health[58]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
SF12 mental health[58]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
SF36 physical health[153]	1	Randomised trials	Very Serious [(a,c)]	No serious inconsistency	No serious indirectness	No serious imprecision
SF36 mental	1	Randomised	Serious [(a)]	No serious	No serious	No serious

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
health[153]		trials		inconsistency	indirectness	imprecision
MIDAS (i)[77]	1	Randomised trials	Very serious (a,d)	No serious inconsistency	Serious (e)	No serious imprecision
MIDAS (ii)[77]	1	Randomised trials	Very serious (a,d)	No serious inconsistency	Serious (e)	No serious imprecision
MSQ role restrictive subscale[147]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
MSQ role preventive subscale[147]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
MSQ emotional functioning subscale[147]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Use of acute pharmacological treatment (i) [77,153]	2	Randomised trials	Very serious (a,d)	No serious inconsistency	Serious (e)	No serious imprecision
Use of acute pharmacological treatment (ii) [77,153]	2	Randomised trials	Very serious (a,d)	No serious inconsistency	Serious (e)	No serious imprecision
Incidence of serious adverse events[153]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Resource use	0	-	-	-	-	-

a) Single blind (individual administering treatment not blind).
b) The confidence interval crosses one minimal important difference making the effect size uncertain.
c) Baseline differences greater than effect size.
d) Allocation concealment unclear in one study and not all baseline data provided.
e) One study included people with and without tension type symptoms.
Facco et al. has two control arms: (i) compares to ritualized mock acupuncture, (ii) compares to mock acupuncture with western diagnosis.

Table 141: Verum acupuncture vs sham acupuncture – Clinical summary of findings

Outcome	Acupuncture	Sham	Relative Risk	Absolute effect	Quality
Change in patient reported migraine days	786	513	-	MD 0.53 lower (0.89 lower to 0.17 lower)	MODERATE
Responder rate	206/428 (48.1%)	171/395 (43.3%)	RR 1.07 (0.92 to 1.25)	30 more per 1000 (from 35 fewer to 108 more)	MODERATE
Change in patient reported migraine intensity	786	513	-	MD 0.05 higher (0.09 lower to 0.19 higher)	MODERATE
Change in patient reported	358	118	-	SMD 0.04 lower (0.15 lower to 0.08 higher)	MODERATE

Outcome	Acupuncture	Sham	Relative Risk	Absolute effect	Quality
migraine frequency					
SF12 physical	290	317	-	MD 1.6 higher (0.37 to 2.83 higher)	MODERATE
SF12 mental	290	317	-	MD 0.6 higher (0.77 lower to 1.97 higher)	MODERATE
SF36 physical	138	78	-	MD 0.8 lower (2.79 lower to 1.19 higher)	LOW
SF36 mental	138	78	-	MD 1 higher (1.59 lower to 3.59 higher)	MODERATE
MIDAS (i)	32	31	-	MD 2.9 lower (3.64 to 2.16 lower)	VERY LOW
MIDAS (ii)	32	30	-	MD 5.4 lower (6.69 to 4.11 lower)	VERY LOW
MSQ role restrictive subscale	358	118	-	MD 6.32 higher (4.19 to 8.45 higher)	MODERATE
MSQ role preventive subscale	358	118	-	MD 4.92 higher (1.91 to 7.93 higher)	LOW
MSQ emotional functioning subscale	358	118	-	MD 2.16 higher (1 lower to 5.32 higher)	MODERATE
Use of acute pharmacological treatment (i)	170	108	-	SMD 0.33 lower (0.58 to 0.08 lower)	VERY LOW
Use of acute pharmacological treatment (ii)	170	109	-	SMD 0.33 lower (0.58 to 0.08 lower)	VERY LOW
Incidence of serious adverse events	4/145 (2.8%)	1/81 (1.2%)	-	12 fewer per 1000 (from 12 fewer to 12 fewer)	MODERATE

Facco et al. has two control arms: (i) compares to ritualized mock acupuncture, (ii) compares to mock acupuncture with western diagnosis.

Table 142: Verum acupuncture + placebo vs Sham acupuncture + beta-blocker (metoprolol) – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient reported migraine frequency[103]*	1	Randomised trials	Very serious (a,b,c)	No serious inconsistency	No serious indirectness	N/A
Change in patient reported migraine intensity[103]*	1	Randomised trials	Very serious (a,b,c)	No serious inconsistency	No serious indirectness	N/A
Incidence of serious adverse events[103]	1	Randomised trials	Very serious (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine days	0	-	-	-	-	-
Responder rate	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-

a) *Single blind (participant and assessor blinded to treatment only).*
b) *Randomisation and allocation concealment unclear.*
c) *Baseline and final values not reported.*
** Data could not be meta-analysed.*
N/A=not applicable.

Table 143: Verum acupuncture + placebo vs Sham acupuncture + beta-blocker – Clinical summary of findings

Outcome	Acupuncture + placebo	Sham + metoprolol	Relative Risk	Absolute effect	Quality
Change in patient reported migraine frequency	38	39	-	Median 0.7 higher (1.6 lower to 2.7 higher)*	LOW
Change in patient reported migraine	38	39	-	Median 0.3 higher (0.1 to 0.5 higher)*	LOW

Outcome	Acupuncture + placebo	Sham + metoprolol	Relative Risk	Absolute effect	Quality
intensity					
Incidence of serious adverse events	0/38 (0%)	1/39 (2.6%)	RR 0.34 (0.01 to 8.14)	17 fewer per 1000 (from 25 fewer to 183 more)	LOW

** Median between group difference.*

17.3.2 Economic evidence

One study[261] was included that compared acupuncture with usual care. This is summarised in the economic evidence profile below (Table 144 and Table 145). See also the full study evidence tables in Appendix F. Acupuncture was also included in our original cost-effectiveness analysis. See section 14.4 and Appendix M for details and results.

One study[271] was excluded due to its partial applicability to the NHS UK setting as the study was conducted in Germany.

Table 144: Acupuncture versus usual care/no treatment – Economic study characteristics

Study	Applicability	Limitations	Other comments
Vickers et al (2004)[261]	Partially applicable (a)	Minor limitations (b)	Cost-utility analysis based on a RCT. Follow-up: 12 months. Population: people with migraine (95%) or TTH (5%) aged 18-65 with an average of at least 2 headaches per month.
NCGC Prophylaxis model (Appendix M)	Directly applicable (c)	Minor limitations (d)	Decision tree based on a NMA (Appenidx L) with a 6-month time horizon. Key clinical outcome was reduction in migraine days per month.

(a) Acupuncture was compared to usual care instead of a specific treatment strategy or no treatment. The study was conducted in 2003.
(b) Limited time horizon.
(c) CUA conducted from the UK NHS perspective.
(d) Limited time horizon. Adverse events were not considered.

Table 145: Acupuncture versus usual care/no treatment – Economic summary of findings

Study	Incremental cost (£)	Incremental effects (QALYs)	ICER (£/QALY)	Uncertainty
Vickers et al (2004)[261]	260 (a, b)	0.021(c)	12,381	Conclusions did not change when: - alternative unit costs associated with acupuncture were used (e.g. private acupuncture session, GP instead of physiotherapist) - imputation was used to calculate QALYs and costs - productivity costs were included - results were projected into the future up to 10 years. The longer the time horizon, the more cost-effective was acupuncture. At a threshold of £20,000/QALY the probability that acupuncture is cost-

Study	Incremental cost (£)	Incremental effects (QALYs)	ICER (£/QALY)	Uncertainty
				effective is around 80%.
NCGC Prophylaxis model (Appendix M)	228 (d)	0.00763 (e)	29,882	Probabilistic sensitivity analysis: acupuncture was the most cost-effective strategy in 6.4% of the simulations, while no treatment in 2.2%. Threshold analysis: acupuncture is more cost-effective than no treatment when 10 or fewer sessions are provided.

(a) 2002/2003 GBP cost updated using an inflator index = 1.27 (from year 2002/2003) calculated from PSSRU 2010[45] using the Hospital and Community Health Services Pay and Prices Index.
(b) All participants received standard care from GP and participants in the acupuncture group also received up to 12 treatments over 3 months from an advanced member of the Acupuncture Association of Charted Physiotherapists.
(c) Mean difference adjusted for baseline variable. SF-6D algorithm was used to calculate HRQoL data at baseline, 3 months and 1 year from participants' responses to the SF-36 at these time points. No imputation was done for missing HRQoL data.
(d) Cost over six months of an average of 15 acupuncture sessions (according to the average from the included RCTs).
(e) Utility gain was defined by number of migraine days avoided. The QALY estimates of acute treatment with triptan + NSAID (see acute treatment model, Appendix J) are attached to the prophylactic model to adjust the actual quality of life gain from the avoided attack.

17.3.2.1 Evidence statements

Verum acupuncture versus sham acupuncture

Clinical:

Three studies with 1299 people suggested that verum acupuncture is more clinically effective than sham acupuncture in reducing the number of migraine days at three months follow up in people with migraine, but there is some uncertainty. [Low quality].

Two studies with 878 people suggested that verum acupuncture is more effective than sham acupuncture in improving responder rate at three months follow up in people with migraine, but the effect size is too small to be clinically important. [Moderate quality].

Three studies with 1299 people showed that there is no difference between verum acupuncture and sham acupuncture in reducing migraine intensity at three months follow up in people with migraine. [Moderate quality].

One study with 476 people suggested that verum acupuncture is more effective than sham acupuncture in reducing migraine frequency at three months follow up, but there is some uncertainty and the effect size is too small to be clinically important. [Low quality].

One study with 63 people showed that verum acupuncture is more clinically effective than western sham or ritualized sham acupuncture in improving headache specific quality of life (assessed by MIDAS) at three months follow up in people with migraine without aura. [Very low quality].

One study with 476 people showed that verum acupuncture is more clinically effective than sham acupuncture in improving headache specific quality of life assessed by the MSQ role restrictive subscale at 3 months follow up in people with migraine. [Moderate quality].

One study with 476 people suggested that verum acupuncture is more clinically effective than sham acupuncture in improving headache specific quality of life assessed by the MSQ role preventive subscale at 3 months follow up in people with migraine, but there is some uncertainty. [Low quality].

One study with 476 people suggested that there is no difference between verum acupuncture and sham acupuncture in improving headache specific quality of life assessed by the MSQ emotional functioning subscale at 3 months follow up in people with migraine, but the effect size is too small to be clinically important. [Moderate quality].

One study with 652 people showed that verum acupuncture is more effective than sham acupuncture in improving quality of life (assessed by SF-12 physical health) at 3 months follow up in people with migraine, but the effect size is too small to be clinically important. [Moderate quality].

One study with 652 people suggested that there is no difference between verum acupuncture and sham acupuncture in improving quality of life (assessed by SF-12 mental health) at 3 months follow up in people with migraine. [Moderate quality].

One study with 226 people suggested that there is no difference between verum acupuncture and sham acupuncture in improving quality of life (assessed by SF-36 physical health) at 3 months follow up in people with migraine. [Low quality].

One study with 226 people suggested that there is no difference between verum acupuncture and sham acupuncture in improving quality of life (assessed by SF-36 mental health) at 3 months follow up in people with migraine. [Moderate quality].

Two studies with 278 people showed that verum acupuncture is more effective than western sham or ritualised sham acupuncture in reducing acute medication use at 3 months follow up in people with migraine, but the effect size is too small to be clinically effective. [Very low quality].

One study with 226 people suggested that fewer serious adverse events may occur with sham acupuncture than verum acupuncture in people with migraine, but there is considerable uncertainty. [Moderate quality].

No studies reported outcome data for resource use.

Economic:

An original cost-effectiveness analysis showed that acupuncture is not cost-effective when compared to no treatment as acupuncture is more effective but also more costly and the ICER is above the £20,000/QALY threshold. When compared to other available strategies (telmisartan, topiramate and propranolol), topiramate is the most cost-effective option, followed by propranolol. When the model was run probabilistically, acupuncture was the most cost-effective strategy in 6.4% of the simulations. Results are sensitive to the number of acupuncture sessions provided: when the number of sessions is 10 or below, acupuncture is more cost-effective than no treatment.

An economic study partially applicable and with minor limitations showed that acupuncture is cost-effective when compared to no treatment as the ICER is below the £20,000/QALY threshold. In this study the average number of acupuncture sessions was 9. These results are compatible with the findings of our sensitivity analysis on the number of acupuncture visits.

Acupuncture plus placebo vs sham plus beta-blocker

Clinical:

One study with 85 people suggested that there is no difference between verum acupuncture plus placebo and sham acupuncture plus beta-blocker in reducing migraine frequency. [Low quality].

One study with 85 people suggested that verum acupuncture plus placebo is less effective than sham acupuncture plus beta-blocker in reducing migraine intensity. [Low quality].

In one study with 85 people there is too much uncertainty to determine whether there is a difference between acupuncture plus placebo and sham acupuncture plus beta-blocker in the occurrence of adverse events in people with migraine. [Low quality].

Economic:

The original cost-effectiveness model developed for this guideline showed that acupuncture costs on average £273 over 6 months while beta-blockers cost £90. Acupuncture is also less effective than beta-blockers and therefore it is dominated. When all the other strategies compared in the model are considered (oxcarbazepine, valproate, acupuncture, telmisartan, propranolol, topiramate and no treatment), acupuncture is likely to be the least cost-effective intervention.

17.4 Recommendations and link to evidence

Recommendations	**Consider a course of up to 10 sessions of acupuncture over 5–8 weeks for the prophylactic treatment of chronic tension-type headache.**
Relative values of different outcomes	The GDG agreed that change in patient reported headache days and responder rate were the most important outcome measures for decision making.
Trade off between clinical benefits and harms	Serious adverse events were not reported in the included studies. The GDG agreed the risk of serious side effects was low. Treatment reactions after acupuncture needling are common. Serious adverse events, e.g. pneumothorax can occur. This risk, however is small[73,266,270].
Economic considerations	An economic study based on a RCT conducted in the UK showed that acupuncture is cost-effective when compared to no treatment in people with migraine or tension type headache. Although the population in this study was primarily people with migraine (95%), there is a recognised overlap between chronic tension type headache and chronic migraine, which is detailed in the diagnosis tic criteria in recommendation 1.2.1. Therefore chronic migraine results can be extrapolated to chronic tension type headache and (and vice versa) so the GDG considered the findings to be applicable to the overall population included in the RCT.
Quality of evidence	There was some evidence for traditional Chinese acupuncture in two trials versus sham acupuncture for improvements in headache days and responder rate (low and very low quality evidence) from single blind studies. No evidence was found for pharmacological prophylactic treatment of tension type headache, therefore the GDG agreed that this evidence was sufficient. The economic evidence had minor limitations and partial applicability.
Other considerations	The course of treatment was agreed as up to 10 sessions, based on the economic evidence reviewed. The GDG considered that each session should last at least 30 minutes, preferably at a frequency of two sessions a week.

See chapter 14, section 14.5 for acupuncture for prophylactic treatment of migraine recommendation and linking evidence to recommendation.

18 Prophylactic non-pharmacological management of primary headaches with manual therapies

18.1 Introduction

Manual therapy may be defined in several ways often according to the practitioner or profession that is describing it. Generally speaking, manual therapy is a clinical approach which utilises a range of skilled, specific hands-on techniques most commonly to treat soft tissue or joint musculoskeletal structures. Some of these techniques may also be used to aid in diagnosis. Probably the most commonly utilised therapeutic techniques include those aimed specifically at joint mobilisation and manipulation, soft tissue mobilisation and release (e.g. muscle, fascia or neural tissue), trigger point therapies and a variety of soft tissue and joint stretching techniques. Some of these hands-on techniques may be delivered to a person who is passive (inactive) during the procedure (passive therapy). Other techniques may require active participation (e.g. muscle contraction) during the procedure (active therapies). Many practitioners who utilise manual therapies will also include therapeutic exercise as another active therapy to further help with pain modulation, tissue healing/adaptation and restoration of musculoskeletal function. When using manual therapies, practitioners generally do not solely rely on one therapeutic technique but rather use a combination or ‘multi-modal’ approach. The choice of therapies should be tailored to the individual.

Manual therapies are frequently used in the treatment of spinally mediated headache (such as cervicogenic headache) but they are sometimes used to treat primary headache disorders.

In the treatment of a person, a practitioner may need to perform a full assessment of the person (history and physical examination). They would consider all possible contributing factors, in particular whether there is any neck and upper back related component that may be one causative factor in the generation of the headache. When assessing a person, the practitioner must be alert to warning features for serious causes of headache. The presence of these features should lead to an appropriate and timely referral. They must also be vigilant for contraindications to the use of specific manual therapies.

When considering the use of manual therapies for headache disorders, an assessment of the potential risk of side effects or more serious adverse events is fundamental. Some can be regarded as minor side effects of treatment, are relatively common and therefore can be anticipated. Most of these will usually occur within 24 hours of treatment and resolve within 72 hours. They are usually minor in severity and may consist of local joint or muscle soreness or neck stiffness. For a person who is not experiencing a headache at the time of treatment, there is no clear evidence to suggest that cervical spine manual therapies may trigger a migraine headache. The incidence of major adverse events resulting in significant harm (such as stroke from cervical artery dissection) is thought to be low to very low (or rare to very rare).

18.1.1 Clinical question

For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with manual therapies?

A literature search was conducted for RCTs comparing the clinical effectiveness of different manual therapies for the prophylactic treatment of primary headaches. The interventions we included in our search were passive and active manual therapies including manipulation, mobilisation, soft tissue massage therapies, stretching therapies, trigger point therapies and exercise or movement therapies.

The GDG discussed the most appropriate comparator for this review. It was agreed that the same principal should be followed as in all other areas of this guideline, that if a form of active control (or placebo) was possible, that would be the comparator (see protocol C.2.10). Therefore we searched for RCTs that compared the effectiveness of any/all of these treatments with usual care/placebo, pharmacological therapy, acupuncture, psychological therapies, herbal remedies or dietary supplements.

A co-opted expert assisted in the development of this recommendation. They attended the meeting where the evidence was presented and informed discussion, but were not present for, or involved in, any discussions about recommendations.

The GDG were interested in evidence for all primary headaches included in this guideline, but evidence was only identified for tension type headache and migraine. These have been separated in this chapter.

18.2 Tension type headache

One Cochrane review on the use of non-invasive treatments for chronic or recurrent headache was identified but was excluded as it included quasi-randomised studies in addition to randomised controlled trials and reported outcomes at four weeks post treatment (some fewer than 3 months duration in total)[23]. Any studies which were relevant to our review protocol were included.

Imprecision for the effect size relating to the outcome Headache Impact Test (HIT-6) outcome was assessed using a value for the MID published in a study by Coeytaux et al[38]. Imprecision for the effect size relating to the outcome headache days was assessed using a value agreed by the GDG for the MID: 0.5 days.

18.2.1 Manual therapies vs placebo

18.2.1.1 Clinical evidence

See evidence tables in appendix section E.3.2, forest plots in Figures 144-145, appendix G.2.9.

One study was identified comparing spinal manipulation and soft tissue therapy with low power laser placebo and soft-tissue therapy in people with episodic tension type headache[17]. This was a single blind study (only outcome assessors were blinded). No double blind studies were identified.

Table 146: Manual therapies vs placebo– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported headache intensity [17]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Use of acute pharmacological treatment [17]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient-reported headache days	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient-reported headache frequency	0	-	-	-	-	-
Responder rate	0	-	-	-	-	-
Functional health status	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment was unclear; Single blind (only outcome assessors were blinded to treatment).
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 147: Manual therapies vs placebo – Clinical summary of findings

Outcome	Manual therapies	Placebo	Relative risk	Absolute effect	Quality
Change in patient reported headache intensity	37	36	-	MD 4 lower (13.66 lower to 5.66 higher)	LOW
Use of acute pharmacological treatment	37	36	-	MD 0.12 lower (0.47 lower to 0.23 higher)	LOW

18.2.1.2 Economic evidence

No relevant economic evaluations comparing manual therapies with placebo were identified.

18.2.1.3 Evidence statements

Clinical:

One study with 75 people with tension type headache suggested that there is no difference between spinal manipulation with soft tissue therapy and placebo at reducing headache intensity at 3 months follow-up, but there is some uncertainty. [Low quality].

One study of with 75 people with tension type headache suggested that there is no difference between spinal manipulation with soft tissue therapy and placebo at reducing the use of acute pharmacological treatments at 3 months follow-up, but there is some uncertainty. [Low quality].

No studies reported outcome data for change in patient reported headache days or frequency, responder rate, functional health status or quality of life, resource use or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing manual therapies with placebo were identified.

18.2.1.4 Recommendations and link to evidence

See recommendations and link to evidence in section 18.4.

18.2.2 Manual therapies vs acupuncture

18.2.2.1 Clinical evidence

See Evidence tables in appendix section E.3.2, Forest Plots in Figure 146, appendix G.2.9.

One study comparing physiotherapy with acupuncture in people with chronic tension type headache was identified[28]. This was a single blind study (only outcome assessors wee blinded to treatment), no double blind RCTs were identified.

Table 148: Manual therapies vs acupuncture – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported headache intensity [28,29]	1	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient-reported headache days	0	-	-	-	-	-
Change in patient-reported headache frequency	0	-	-	-	-	-
Responder rate	0	-	-	-	-	-
Functional health status	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment was unclear; Single blind study (only outcome assessors were blinded to treatment)
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 149: Manual therapies vs acupuncture – Clinical summary of findings

Outcome	Manual therapies	Acupuncture	Relative risk	Absolute effect	Quality
Change in patient reported headache intensity	23	29	-	MD 0.72 lower (1.22 to 0.22 lower)	VERY LOW

18.2.2.2 Economic evidence

No relevant economic evaluations comparing manual therapies with acupuncture were identified. The cost of a six-month course of acupuncture for the prophylaxis of headache was calculated for the original economic model described in 14.4 and Appendix M. This cost is around £233 per person over six months and includes 15 acupuncture sessions. No data on the cost of manual therapies was found and it is unclear whether manual therapies would be more or less costly than acupuncture.

18.2.2.3 Evidence statements

Clinical:

One study with 62 people with chronic tension type headache suggested that physiotherapy may be more clinically effective than acupuncture at reducing headache intensity at 3 months follow-up, but there is some uncertainty. [Very low quality].

No studies reported outcome data for change in patient reported headache days or frequency, responder rate, functional health status or quality of life, resource use, use of acute pharmacological treatment or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing manual therapies with acupuncture were identified. The cost of a six-month course of acupuncture for the prophylaxis of headache was calculated for the original economic model on prophylactic treatment of migraine and it is around £233 per person over six months and includes 15 acupuncture sessions. No data on the cost of manual therapies was found and it is unclear whether manual therapies would be more or less costly than acupuncture.

18.2.3 Manual therapies vs usual care

18.2.3.1 Clinical evidence

See Evidence tables in appendix section E.3.2, Forest Plots in Figures 147-152, appendix G.2.9.

One study was identified comparing manual therapy with usual care in people with chronic tension type headache[33]. This was a single blind study, no double blind RCTs were identified.

Table 150: Manual therapy vs usual care – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Responder rate[33]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported headache days[33]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported headache intensity [33]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in headache specific QoL (HIT-6) [33]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Resource use (use of additional medical specialists) [33]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Resource use (use of other resources) [33]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in patient reported headache frequency	0	-	-	-	-	-
Functional health status	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation was unclear; Single blind study (only outcome assessors blinded to treatment)
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 151: Manual therapies vs usual care – Clinical summary of findings

Outcome	Manual therapies	Combined treatment	Relative risk	Absolute effect	Quality
Responder rate	31/38 (81.6%)	15/37 (40.5%)	RR 2.01 (1.32 to 3.06)	409 more per 1000 (from 130 more to 835 more)	LOW
Change in patient reported headache days	38	37	-	MD 5 lower (6.95 to 3.05 lower)	LOW
Change in patient reported headache intensity	38	37	-	MD 1.4 lower (2.6 to 0.2 lower)	VERY LOW
Change in headache specific QoL (HIT-6)	38	37	-	MD 4.5 lower (8.35 to 0.65 lower)	VERY LOW
Resource use(use of additional medical specialists)	1/38 (2.6%)	6/37 (16.2%)	RR 0.16 (0.02 to 1.28)	136 fewer per 1000 (from 159 fewer to 45 more)	VERY LOW
Resource use (use of other resources)	3/38 (7.9%)	1/37 (2.7%)	RR 2.92 (0.32 to 26.83)	52 more per 1000 (from 18 fewer to 698 more)	VERY LOW

18.2.3.2 Economic evidence

No relevant economic evaluations comparing manual therapy with usual care were identified.

18.2.3.3 Evidence statements

Clinical:

One study with 82 people with chronic tension type headache showed that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction is more clinically effective than usual care at reducing number of headache days at 26 weeks.[Low quality].

One study with 82 people with chronic tension type headache suggested that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction may be more clinically effective than usual care at reducing headache intensity at 26 weeks, but there is some uncertainty. [Very low quality].

One study with 82 people with chronic tension type headache suggested that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction may be more clinically effective than usual care at improving headache specific quality of life scores (HIT-6) at 26 weeks, but there is some uncertainty. [Very low quality].

One study with 82 people with chronic tension type headache showed that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction is more clinically effective than usual care at increasing responder rate at 26 weeks. [Low quality].

One study with 82 people with chronic tension type headache suggested that there is no difference between manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction, and usual care in reducing the use of additional medical specialists at 26 weeks, but there is some uncertainty. [Very low quality].

One study with 82 people with chronic tension type headache suggested that manual therapy comprising of cervical and thoracic spine mobilisation, exercises and postural correction, and usual care may be similarly effective in reducing the use of additional resources at 26 weeks, but there is some uncertainty. [Very low quality].

No studies reported outcome data for change in patient reported headache frequency, functional health status, use of acute pharmacological treatment or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing manual therapies with usual care were identified.

18.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 18.4.

18.3 Migraine with or without aura

18.3.1 Manual therapies vs placebo

18.3.1.1 Clinical evidence

See evidence tables in appendix section E.3.2, forest plots in Figures 153-155, appendix G.2.9.

One study of people whose migraine was made worse by neck movement, comparing spinal manipulative therapy with detuned inferential therapy as control was included in this review[256].

One Cochrane review on the use of non-invasive treatments for chronic or recurrent headache was identified but was excluded as it included quasi-randomised studies in addition to randomised controlled trials and reported outcomes at four weeks post treatment irrespective of treatment duration (some less than 3 months)[23]. All studies relevant to the protocol were included.

Imprecision for the effect size relating to the outcome headache or migraine days was assessed using a value agreed by the GDG for the MID: 0.5 days.

Table 152: Manual therapies vs placebo – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient-reported migraine frequency[256]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient-reported migraine intensity[256]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Use of acute pharmacological treatment[256]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient reported migraine days	0	-	-	-	-	-
Responder rate	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation and allocation concealment was unclear; blinding of investigators unclear; unclear whether groups were comparable at baseline.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 153: Manual therapies vs placebo– Clinical summary of findings

Outcome	Manual therapies	Placebo	Relative risk	Absolute effect	Quality
Change in patient-reported migraine frequency	83	40	-	MD 2.8 lower (5.28 to 0.32 lower)	LOW
Change in patient-reported migraine intensity	83	40	-	MD 0.7 higher (0.05 to 1.35 higher)	LOW
Use of acute pharmacological treatment	83	40	-	MD 6.4 lower (11.08 to 1.72 lower)	LOW

18.3.1.2 Economic evidence

No relevant economic evaluations comparing manual therapies with placebo were identified.

18.3.1.3 Evidence statements

Clinical:

One study with 127 people with migraine suggested that spinal manipulative therapy may be more clinically effective than placebo at reducing number of migraine days at 3 months follow-up, but there is some uncertainty. [Low quality].

One study with 127 people with migraine suggested that placebo may be more clinically effective than spinal manipulative therapy at reducing migraine intensity at 3 months follow-up, but there is some uncertainty. [Low quality].

One study with 127 people with migraine suggested that spinal manipulative therapy may be more clinically effective than placebo at reducing the average number of acute pharmacological treatments used per month at 3 months follow-up, but there is some uncertainty. [Low quality].

No studies reported outcome data for change in patient reported headache days, responder rate, functional health status or quality of life, resource use or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing manual therapies with placebo were identified.

18.3.2 Manual therapies vs pharmacological treatment

18.3.2.1 Clinical evidence

See evidence tables in appendix section E.3.2, forest plots in Figures 156-159, appendix G.2.9.

One study was identified comparing spinal manipulative therapy with a tricyclic antidepressant (amitriptyline)[182].

Table 154: Manual therapies vs tricyclic antidepressants – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient-reported migraine days[182]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in patient-reported migraine intensity[182]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Functional health status SF-36[182]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Use of acute pharmacological treatment[182]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient-reported migraine frequency	0	-	-	-	-	-
Responder rate	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Open label study; unclear whether both groups were comparable at baseline
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 155: Manual therapies vs tricyclic antidepressants – Clinical summary of findings

Outcome	Manual therapies	Tricyclic antidepressant	Relative risk	Absolute effect	Quality
Change in patient-reported migraine days	58	47	-	MD 3.6 lower (13.66 lower to 6.46 higher)	VERY LOW
Change in patient -reported migraine intensity	56	44	-	MD 0.1 lower (0.69 lower to 0.49 higher)	LOW
Functional health status - SF-36	58	50	-	MD 2.9 higher (2.29 lower to 8.09 higher)	VERY LOW
Use of acute pharmacological treatment	58	47	-	MD 0.1 lower (0.58 lower to 0.38 higher)	LOW

18.3.2.2 Economic evidence

No relevant economic evaluations comparing manual therapies with tricyclic antidepressants were identified.

18.3.2.3 Evidence statements

Clinical:

One study with 147 people with migraine suggested that there is no difference between spinal manipulative therapy and amitriptyline at reducing number of migraine days at 3 months follow-up, but there is some uncertainty. [Very low quality].

One study with 147 people with migraine showed that there is no difference between spinal manipulative therapy and amitriptyline at reducing migraine intensity at 3 months follow-up. [Low quality].

One study with 147 people with migraine suggested that there is no difference between spinal manipulative therapy and amitriptyline at modifying functional health status at 3 months follow-up, but there is some uncertainty. [Very low quality].

One study with 147 people with migraine showed that there is no difference between spinal manipulative therapy and amitriptyline at reducing use of acute pharmacological treatment at 3 months follow-up. [Low quality].

No studies reported outcome data for change in patient reported headache frequency, responder rate, resource use or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing manual therapy with amitriptyline were identified.

18.3.3 Manual therapy vs combined treatment (manual therapy with amitriptyline)

18.3.3.1 Clinical evidence

See evidence tables in appendix section E.3.2, forest plots in Figures 160-163, appendix G.2.9.

One study was identified comparing spinal manipulative therapy with a combination of spinal manipulation and amitriptyline[182].

Table 156: Manual therapy vs combined treatment– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient-reported migraine days[182]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient-reported migraine intensity[182]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Functional health status	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
SF-36[182]						
Use of acute pharmacological treatment[182]	1	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient-reported migraine frequency	0	-	-	-	-	-
Responder rate	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Open label study; unclear whether groups were comparable at baseline.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 157: Manual therapy vs combined treatment – Clinical summary of findings

Outcome	Manual therapy	Combined treatment	Relative risk	Absolute effect	Quality
Change in patient-reported migraine days	58	54	-	MD 3 lower (13.35 lower to 7.35 higher)	LOW
Change in patient-reported migraine intensity	56	50	-	MD 0.1 higher (0.49 lower to 0.69 higher)	LOW
Functional health status - SF-36	58	55	-	MD 2.5 higher (2.88 lower to 7.88 higher)	VERY LOW
Use of acute pharmacological treatment	58	54	-	MD 0.5 lower (1.01 lower to 0.01 higher)	VERY LOW

18.3.3.2 Economic evidence

No relevant economic evaluations comparing manual therapy with combined treatment (spinal manipulation with amitriptyline) were identified.

18.3.3.3 Evidence statements

Clinical:

One study with 148 people with migraine showed that there is no difference between spinal manipulative therapy and combined treatment (spinal manipulation with amitriptyline) at reducing the number of migraine days when assessed at 3 months follow-up. [Low quality].

One study with 148 people with migraine showed that there is no difference between spinal manipulative therapy and combined treatment (manual therapies with tricyclic antidepressants) at reducing migraine intensity when assessed at 3 months follow-up. [Low quality].

One study with 148 people with migraine suggested that there is no difference between spinal manipulative therapy and combined treatment (spinal manipulation with amitriptyline) at modifying functional health status when assessed at 3 months follow-up, but there is some uncertainty. [Very low quality].

One study with 148 people with migraine suggested that there is no difference between spinal manipulative therapy and combined treatment (spinal manipulation with amitriptyline) at reducing use of acute pharmacological treatments when assessed at 3 months follow-up, but there is some uncertainty. [Very low quality].

No studies reported outcome data for change in patient reported headache frequency, responder rate, resource use or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing manual therapy with combined treatment (spinal manipulation with amitriptyline) were identified.

18.3.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 18.4.

18.3.4 Pharmacological treatment vs combined treatment (manual therapies + tricyclic antidepressants)

18.3.4.1 Clinical evidence

See evidence tables in appendix section E.3.2, forest plots in Figures 164-167, appendix G.2.9.

One study was identified comparing amitriptyline to spinal manipulation in combination with amitriptyline[182].

18.3.4.2 Clinical evidence

Table 158: Pharmacological treatment vs combined treatment – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient-reported migraine days[182]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient-reported migraine intensity[182]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Functional health status - SF-36[182]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Use of acute	1	Randomised	Very serious	No serious	No serious	Serious (b)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
pharmacological treatment[182]		trials	(a)	inconsistency	indirectness	
Change in patient-reported migraine frequency	0	-	-	-	-	-
Responder rate	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Open label study; unclear whether groups were comparable at baseline.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 159: Pharmacological treatment vs combined treatment – Clinical summary of findings

Outcome	Amitriptyline	Combined treatment	Relative risk	Absolute effect	Quality
Change in patient-reported migraine days	47	54	-	MD 0.6 higher (9.13 lower to 10.33 higher)	LOW
Change in patient-reported migraine intensity	44	50	-	MD 0.2 higher (0.35 lower to 0.75 higher)	VERY LOW
Functional health status -SF-36	50	55	-	MD 0.4 lower (5.47 lower to 4.67 higher)	LOW
Use of acute pharmacological treatment	47	54	-	MD 0.4 lower (0.95 lower to 0.15 higher)	VERY LOW

18.3.4.3 Economic evidence

No relevant economic evaluations comparing amitriptyline with combined treatment (spinal manipulation with amitriptyline) were identified.

18.3.4.4 Evidence statements

Clinical:

One study with 141 people with migraine showed that there is no difference between amitriptyline and combined treatment (spinal manipulation with amitriptyline) at reducing number of migraine days at 3 months follow-up. [Low quality].

One study with 141 people with migraine suggested that there is no difference between amitriptyline and combined treatment (spinal manipulation with amitriptyline) at reducing migraine intensity at 3 months follow-up, but there is some uncertainty. [Very low quality].

One study with 141 people with migraine showed that there is no difference between amitriptyline and combined treatment (spinal manipulation with amitriptyline) at modifying functional health status at 3 months follow-up. [Low quality].

One study with 141 people with migraine suggested that there is no difference between amitriptyline and combined treatment (spinal manipulation with amitriptyline) at reducing use of acute pharmacological treatment at 3 months follow-up, but there is some uncertainty [Very low quality].

No studies reported outcome data for change in patient reported headache frequency, responder rate, resource use or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing amitriptyline with combined treatment (spinal manipulation with amitriptyline) were identified.

18.4 Recommendations and link to evidence

Although there is some preliminary evidence to suggest that seeing a practitioner who utilises manual therapies may be of benefit, the GDG decided there was not enough evidence to make a recommendation for or against the use of manual therapies for the prophylactic treatment of tension type headache or migraine.

Recommendation	
Relative values of different outcomes	The GDG agreed that responder rate, was the most important outcomes for decision making. Patient reported headache frequency and intensity were also considered for decision making.
Trade off between clinical benefits and harms	There may be a risk of cervical artery dissection and possible neurological compromise resulting in stroke associated with manual therapies of the neck. However, the evidence for this risk is based mainly on case reports and cases series which by design cannot determine causality. Many of the studies are of poor quality with high risk of reporting bias. However one high quality case control study found no evidence of excess risk of vertebro-basilar artery stroke associated with chiropractic care compared to primary (GP) care[32]. Overall the evidence indicates that the risk of a major adverse event (such as stroke) is low to very low, although minor short-lived side effects (e.g. soreness) are relatively common. Practitioners are taught to be alert to the risk factors for cervical artery dissection, the presenting features of cervical artery dissection, and the need for appropriate and timely referral. The chiropractic profession in the UK have set up a reporting service for adverse events (www.cpirls.org).'
Economic considerations	Manual therapies are associated with some costs. In the absence of good evidence on the effectiveness of manual therapies it is difficult to judge whether their costs would be offset by their effectiveness.
Quality of evidence	The evidence reviewed was low to very low quality. Two studies were single blind studies (outcome assessors were blinded), but since the outcomes were patient reported, it did not decrease the risk of outcome assessor bias. Two other studies were open label studies. No economic evidence was available on this topic.
Other considerations	The GDG agreed that there was not enough evidence to form a recommendation for or against manual therapies for prophylaxis of tension type headache or migraine from the evidence reviewed. For tension type headache the study states that the population was of chronic tension type headache, however there is a recognised overlap between chronic tension type headache and chronic migraine, which is detailed in the diagnostic

Recommendation	
	criteria in section 7.1.2 of this guideline. The GDG agreed that chronic TTH is rare and is more commonly in fact chronic migraine. In the case of this study, the GDG considered that it was possible that many of these people actually had migraine and therefore these data may not be directly applicable to the specific headache type. For migraine, there was one study showing some benefit. The GDG were concerned that the evidence reviewed was of low to very low quality with a lot of uncertainty in the effect estimates, and that rare adverse events may be severe when they do occur. It was agreed that better evidence was required to make a recommendation. **Research recommendations:** The GDG agreed to make a research recommendation for the use of manual therapies for people with chronic headache disorders to strengthen the evidence base. See appendix M.

19 Prophylactic non-pharmacological management of primary headaches with psychological therapies

19.1 Introduction

Migraine and tension type headache are associated with high levels of psychological distress. Migraine in particular is frequently co-morbid with depression and anxiety. It is likely that treatment using a bio-psychosocial perspective would allow the multiple social, environmental and psychological factors contributing to these primary headaches to be addressed. Psychological therapies include relaxation training, biofeedback training, and cognitive behavioural therapies amongst others. Such treatments may address factors such as self-efficacy, catastrophising, help enable coping strategies to better manage their pain and associated headache symptoms, or they can play a prophylactic role, depending on the focus of the specific therapy. Such non-drug treatments may be preferable to regular drug treatments for some people or a beneficial adjunct.

19.1.1 Clinical question

For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with psychological therapies?

The GDG discussed the most appropriate comparator for this review. It was agreed that the same principal should be followed as in all other areas of this guideline, that if a form of active control (or placebo) was possible, that would be the comparator (see protocol C.2.11). Therefore a literature search was conducted for RCTs comparing the clinical effectiveness of psychological therapies for tension type headache compared to an active control or pharmacological therapy, acupuncture, manual therapy, herbal remedies or dietary supplements.

A co-opted expert assisted in the development of this recommendation. They attended the meeting where the evidence was presented and informed discussion, but were not present for, or involved in, any discussions about recommendations.

The GDG were interested in the evidence for the use of psychological therapies for tension type headache and migraine. Psychological therapies are not commonly used to treat pain in people with cluster headaches, therefore these were not included in this review. The evidence that was identified for tension headaches and migraine has been separated in this chapter.

19.2 Tension type headache

19.2.1 Psychological therapy vs active control

See evidence tables in appendix section E.3.3, forest plots in Figures 168-170, appendix G.2.10.

Two studies were identified. One study which compared at relaxation training with information contact[136] in adolescents with tension type headache and mixed tension type headache and migraine was not able to be meta-analysed as standard deviations were not provided with results. The other study[46] compared written emotional disclosure to a neutral writing control in undergraduate psychology students. Available case data were available for both studies. Imprecision for the effect size relating to the outcome Migraine Specific Quality of Life score (MSQ) was assessed using a value for the MID published in a study by Cole et al[41]. Imprecision for the effect size relating to the outcome Headache Impact Test (HIT-6) outcome was assessed using a value for the MID published in a study by Coeytaux et al[38]. Imprecision for the effect size relating to the outcome headache days was assessed using a value agreed by the GDG for the MID: 0.5 days.

Table 160: Written emotional disclosure vs neutral writing – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient reported headache frequency [46]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious [(b)]
Change in patient reported headache intensity[46]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious [(b)]
Change in headache specific QoL[46]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious [(b)]
Chang in patient reported headache days	0	-	-	-	-	-
Responder rate	0	-	-	-	-	-
Functional health status and health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Blinding of participants and assessors was unclear; students were given course credit or money for participating.
(b) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.

Table 161: Written emotional disclosure v neutral writing – Clinical summary of findings

Outcome	Written emotional disclosure	Neutral writing	Relative Risk	Absolute effect	Quality
Change in patient reported headache frequency	17	17	-	MD 1 higher (4.7 lower to 6.7 higher)	VERY LOW
Change in patient reported headache intensity	17	17	-	MD 0.29 higher (0.86 lower to 1.44 higher)	VERY LOW
Change in headache specific QoL	17	17	-	MD 1.06 higher (4.57 lower to 6.69 higher)	VERY LOW

Table 162: Relaxation therapy vs information contact – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient reported headache frequency [137]	1	Randomised trials	Very serious [(a)]	No serious inconsistency	Serious [(b)]	N/A *
Change in patient reported headache intensity [137]	1	Randomised trials	Very serious [(a)]	No serious inconsistency	Serious [(b)]	N/A *
Responder rate	0	-	-	-	-	-
Change in patient reported migraine days	0	-	-	-	-	-
Change in headache specific QoL (MIDAS)	0	-	-	-	-	-
Functional health status and health-related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

a) Method of randomisation and allocation concealment unclear. Single blind (investigator not blind to treatment, unclear if assessor was). Participants were paid for their involvement.
b) Mixed tension type headache and migraine, defined as chronic headaches. Groups not separated for analysis.
** Data could not be meta-analysed, no SD provided.*
N/A=not applicable.

Table 163: Relaxation therapy vs information contact – Clinical summary of findings

Outcome	Relaxation therapy	Information contact	Change from baseline at 6 months	Absolute effect	Quality
Change in patient reported headache frequency	11	13	Relaxation: -3.4 Information: -0.9	-	VERY LOW
Change in patient reported headache intensity	11	13	Relaxation: -0.3 Information: -0.3	-	VERY LOW

19.2.1.1 Economic evidence

No relevant economic evaluations on psychological therapies in people with tension type headache were identified.

19.2.1.2 Evidence statements

Clinical:

One study with 34 people suggested that there is no difference between written emotional disclosure and neutral writing in reducing headache frequency in the prophylactic treatment tension type headache but there is considerable uncertainty. [Very low quality].

One study with 34 people suggested that there is no difference between written emotional disclosure and neutral writing in reducing headache intensity in the prophylactic treatment of tension type headache, but there is considerable uncertainty. [Very low quality].

One study with 34 people suggested that there is no difference between written emotional disclosure and neutral writing in improving headache related quality of life in the prophylactic treatment of tension type headache but there is considerable uncertainty. [Very low quality].

One study with 24 adolescents with chronic tension type headache and combined tension type headache and migraine showed that there was a greater reduction in headache frequency at six months with relaxation therapy is than active control, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

One study with 24 adolescents with chronic tension type headache and combined tension type headache and migraine showed no difference in headache intensity at six months between relaxation therapy and active control, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

No studies reported outcome data for change in patient reported headache days, responder rate, functional health status or quality of life, resource use, use of acute pharmacological treatment or incidence of serious adverse events.

Economic:

No relevant economic evaluations on psychological therapies in people with tension type headache were identified.

19.2.1.3 Recommendations and link to evidence

See recommendations and link to evidence in section 19.4.

19.3 Migraine with and without aura

19.3.1 Psychological therapy vs active control

See evidence tables in appendix section E.3.3, forest plots in Figures 171-173, appendix G.2.10.

Three studies were identified. They could not be combined for analysis as the therapies, comparisons and populations differed. One compared written emotional disclosure and a neutral writing control in undergraduate psychology students[46]. The other looked at relaxation training and cognitive coping compared to an active control in children and adolescents aged between 9 and 18 years[211] and the third was a three arm study comparing relaxation, exercise and topiramate in adults with migraine.

Only the relaxation and topiramate arms are considered here – see chapter x for the other comparisons[260].

Richter et al.[211] and Varkey et al. were analysed using available case data, however in D'Souza et al.[46] the number of dropouts per group could not be determined from the paper and therefore ITT with last observation carried forward was used as reported in the paper. Imprecision for the effect size relating to the outcome Migraine Specific Quality of Life score (MSQ) was assessed using a value for the MID published in a study by Cole et al[41]. Imprecision for the effect size relating to the outcome headache or migraine days was assessed using a value agreed by the GDG for the MID of 0.5 days.

Table 164: Written emotional disclosure vs neutral writing – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported migraine frequency [46]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(b)]
Change in patient reported migraine intensity[46]	1	Randomised trials	Serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(d)]
Change in headache specific QoL (MIDAS)[46]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious[(d)]
Responder rate	0	-	-	-	-	-
Change in patient reported migraine days	0	-	-	-	-	-
Functional health status and health-related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Blinding of participants and assessors was unclear; students were given course credit or money for participating; groups not comparable at baseline.
(b) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.
(c) Blinding of participants and assessors was unclear; students were given course credit or money for participating.
(d) The confidence interval crosses one minimal important difference making the effect size uncertain.
MIDAS = Migraine disability assessment.

Table 165: Written emotional disclosure vs neutral writing – Clinical summary of findings

Outcome	Written emotional disclosure	Neutral writing	Relative Risk	Absolute effect	Quality
Change in patient reported migraine frequency	29	27	-	MD 0.03 higher (3.11 lower to 3.17 higher)	VERY LOW
Change in patient reported migraine intensity	29	27	-	MD 0.32 lower (1.37 lower to 0.73 higher)	LOW
Change in headache specific QoL (MIDAS)	29	27	-	MD 0.26 lower (5.65 lower to 5.13 higher)	LOW

19.3.1.1 Economic evidence

No relevant economic evaluations on psychological therapies in people with migraine were identified.

19.3.1.2 Evidence Statements

Clinical:

One study with 56 people with migraine showed that there is no difference between written emotional disclosure and neutral writing in reducing headache frequency. [Very low quality].

One study with 56 people with migraine suggested that there is no difference between written emotional disclosure and neutral writing in reducing headache intensity in, but there is some uncertainty. [Low quality].

One study with 56 people with migraine suggested that there is no difference between written emotional disclosure and neutral writing in improving headache related quality of life, assessed by MIDAS, but there is some uncertainty. [Low quality].

No studies reported outcome data for responder rate, change in patient reported migraine days, health related quality of life (not headache specific), resource use, use of acute pharmacological treatment or incidence of serious adverse events.

Economic:

No relevant economic evaluations on psychological therapies in people with migraine were identified.

19.3.2 Relaxation training vs attention control

Table 166: Relaxation training vs attention control – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient reported migraine frequency [211]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Change in patient reported migraine intensity [211]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]
Responder rate	0	-	-	-	-	-
Change in patient reported migraine days	0	-	-	-	-	-
Change in headache specific QoL (MIDAS)	0	-	-	-	-	-
Functional health status and health-related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation was unclear.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 167: Relaxation training vs attention control – Clinical summary of findings

Outcome	Relaxation training	Attention control	Relative Risk	Absolute effect	Quality
Change in patient reported migraine frequency[211]	15	12	-	MD 1.77 lower (5.49 lower to 1.95 higher	LOW
Change in migraine intensity [211]	15	12	-	MD 0.02 higher (0.68 lower to 0.72 higher)	VERY LOW

19.3.2.1 Economic evidence

No relevant economic evaluations comparing relaxation training with attention control in people with migraine were identified.

19.3.2.2 Evidence statements

Clinical:

One study with 27 people with migraine suggested that relaxation training may be more effective than active control in reducing migraine frequency but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

In one study with 27 people with migraine, there is too much uncertainty to determine whether there is a difference between relaxation training and attention control in reducing migraine intensity. [Very low quality].

No studies reported outcome data for responder rate, migraine days, functional health status or quality of life, resource use, use of acute medication or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing relaxation training with attention control in people with migraine were identified.

19.3.3 Cognitive coping vs attention control

Table 168: Cognitive coping vs attention control – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient reported migraine frequency[211]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient reported migraine intensity[211]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious [(c)]
Responder rate	0	-	-	-	-	-
Change in patient reported migraine days	0	-	-	-	-	-
Change in headache specific QoL (MIDAS)	0	-	-	-	-	-
Functional health status and health-related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacologic	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
al treatment						
Incidence of serious adverse events	0	-	-	-	-	-

(a) Method of randomisation was unclear.
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.

Table 169: Cognitive coping vs attention control – Clinical summary of findings

Outcome	Cognitive coping	Information contact	Relative Risk	Absolute effect	Quality
Change in patient reported migraine frequency	15	12	-	MD 2.16 lower (5.78 lower to 1.46 higher	LOW
Change in patient reported migraine intensity	15	12	-	MD 0.06 lower (1.06 lower to 0.94 higher)	VERY LOW

19.3.3.1 Economic evidence

No relevant economic evaluations comparing cognitive coping with attention control in people with migraine were identified.

19.3.3.2 Evidence statements

Clinical:

One study with 27 people with migraine suggested that cognitive coping may be more clinically effective than attention control in reducing migraine frequency but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

In one study with 27 people with migraine there is too much uncertainty to determine whether there is a difference between cognitive coping and active control in reducing migraine intensity. [Very low quality].

No studies reported outcome data for responder rate, migraine days, functional health status or quality of life, resource use, use of acute medication or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing cognitive coping with attention control in people with migraine were identified.

19.3.4 Psychological therapy vs topiramate

Table 170: Relaxation vs topiramate – Quality assessment

Outcome	No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision
Responder rate (50% reduction in migraine frequency)[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change patient reported in migraine days[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient reported migraine frequency (attacks per month)[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Change in patient reported migraine intensity (VAS 0-100)[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Headache specific quality of life MSQoL (0-100) [260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Use of acute pharmacological treatment[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Functional health status and health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Single blind (assessor blind only).
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 171: Relaxation vs topiramate – Clinical summary of findings

Outcome	Relaxation	Topiramate	Relative risk (95% CI)	Absolute effect	Quality
Responder rate (50% reduction in migraine frequency)	7/30 (23.3%)	8/31 (25.8%)	RR 0.9 (0.37 to 2.18)	26 fewer per 1000 (from 163 fewer to 305 more)	LOW
Change patient reported in	30	31	-	MD 0.61 higher (0.9 lower to	LOW

Outcome	Relaxation	Topiramate	Relative risk (95% CI)	Absolute effect	Quality
migraine days				2.12 higher)	
Change in patient reported migraine frequency (attacks per month)	30	31	-	MD 0.26 lower (1.04 lower to 0.52 higher)	LOW
Change in patient reported migraine intensity (VAS 0-100)	30	31	-	MD 8.6 higher (0.96 lower to 18.16 higher)	LOW
Headache specific quality of life MSQoL (0-100)	30	31	-	MD 0.7 higher (5.82 lower to 7.22 higher)	LOW
Use of acute pharmacological treatment	30	30	-	MD 0.13 lower (1.64 lower to 1.38 higher)	LOW

19.3.4.1 Economic evidence

No relevant economic evaluations comparing psychological therapies with topiramate in people with migraine were identified.

The cost of a six-month course of topiramate for the prophylaxis of migraine was calculated for the original economic model described in 14.4 and Appendix M. This cost is around £126 per person over six months and includes the drug cost and two GP visits.

19.3.4.2 Evidence statements

Clinical:

One study with 61 people with migraine with or without aura suggested that there is no clinically important difference between relaxation and topiramate in improving responder rate at 3 months but there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that there is no clinically important difference between relaxation and topiramate in reducing the number of migraine days at 3 months, but there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that there is no clinically important difference between relaxation and topiramate in reducing migraine frequency at 3 months, but there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that there is no clinically important difference between relaxation and topiramate in reducing migraine intensity at 3 months, but there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that there is no clinically important difference between relaxation and topiramate in improving migraine specific quality of life at 3 months, but there is some uncertainty. [Low quality].

One study with 61 people with migraine without aura suggested that there is no clinically important difference between relaxation and topiramate in reducing the use of acute pharmacological medication at 3 months, but there is some uncertainty. [Low quality].

No studies reported outcome data for functional health status (not headache specific), resource use or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing psychological therapies with topiramate in people with migraine were identified. The cost of a six-month course of topiramate for the prophylaxis of migraine was calculated for the original economic model on prophylactic treatment of migraine and it is around £126 per person and includes the drug cost and two GP visits. No data on the cost of psychological therapies was found and it is unclear whether psychological therapies would be more or less costly than topiramate.

19.4 Recommendations and link to evidence

The GDG agreed not to make a recommendation on the use of psychological therapies for the prophylactic treatment of primary headaches as there was not enough evidence to form a recommendation for or against its use.

Recommendation	
Relative values of different outcomes	The GDG agreed that change in patient reported migraine frequency was the most important outcome, in the absence of any data for migraine days and responder rate.
Trade off between clinical benefits and harms	There was no available data reviewed on adverse events associated with psychological therapies. It was not thought that any serious harms were associated with these therapies.
Economic considerations	Psychological therapies are associated with some costs. In the absence of good evidence on the effectiveness of psychological therapies it is difficult to judge whether their costs would be offset by their effectiveness at reducing headache frequency.
Quality of evidence	All evidence reviewed was low or very low quality. The difficulty in finding a good active control was acknowledged which was reflected by the low number of studies included. No economic evidence was identified.
Other considerations	The GDG acknowledged the difficulty of having a good active control for psychological therapies. It was noted that in practice psychological therapies focus on treating the affective component separately to the headache and would assess both outcomes separately, however this review focuses only on treatment of the headache rather than any psychological components. **Research recommendations:** The GDG agreed to make a research recommendation for the use of psychological therapies for people with chronic headache disorders to strengthen the evidence base. See appendix M.

20 Prophylactic non-pharmacological management of primary headache with dietary supplements and herbal remedies

20.1 Introduction

The GDG were interested in both herbal remedies and dietary supplements for the prophylaxis of primary headaches. These two are presented together here, but were reviewed as two separate review questions.

20.2 Dietary supplements

Magnesium, vitamin B12, coenzyme Q10 and riboflavin (vitamin B2) have been used for the prophylaxis of migraine with and without aura. A well-balanced diet provides all of these. However, they can also be taken as dietary supplements.

Magnesium is a mineral which stabilises and relaxes smooth muscle, such as those found in blood vessel walls. Magnesium is available on prescription in the UK, but the oral doses sometimes used for migraine prophylaxis are unlicensed. Magnesium preparations can be bought from pharmacies or health-food stores. Vitamin B12 and riboflavin (B2) regulate metabolism whereas coenzyme Q10 has a specific role in mitochondrial energy metabolism and is produced naturally in our bodies. Oral high dose riboflavin is not available as a medicine in the UK. However, it may be available to purchase from some health-food stores as a food supplement.

20.2.1 Clinical question

For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin (B2))?

A literature search was conducted for RCTs comparing the clinical effectiveness of different dietary supplements for the prophylactic treatment of primary headache. The interventions we included in our search were dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin (B2)), with or without prophylactic pharmacological treatment. We looked for any studies that compared the effectiveness of any or all of these treatments with placebo, prophylactic pharmacological treatment, pharmacological therapy, acupuncture, psychological therapy, herbal remedies and manual therapy (see protocol C.2.12).

Imprecision for the effect size relating to the outcome headache or migraine days was assessed using a value agreed by the GDG for the MID of 0.5 days.

20.2.2 Magnesium vs placebo

20.2.2.1 Clinical evidence

See evidence tables in appendix section E.3.4, forest plots in Figures 180-185, appendix G.2.11.

One study was identified comparing trimagnesium dicitrate with placebo in people with migraine with or without aura[194]. No studies were identified for other primary headaches. The dose of magnesium used in the study was 600mg (24 millimoles) per day. Available case analysis (ACA) data were available for responder rate, however for all other outcomes ACA numbers could not be determined so ITT analysis with last observation carried forward has been used, as reported in the paper.

Table 172: Trimagnesium dicitrate vs placebo– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Responder rate (50% reduction)[194]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in patient reported migraine days[194]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in patient reported migraine intensity[194]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (c)
Change in patient reported migraine frequency[194]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Use of acute pharmacological treatment[194]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (c)
Functional health status	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events[194]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (d)

(a) *Allocation concealment and method of randomisation not reported.*
(b) The upper or lower limit of the confidence interval crosses the minimal important difference making the effect size uncertain.
(c) The confidence intervals cross the minimal important difference in both directions making the effect size very uncertain.
(d) The upper limit of the confidence interval crosses the minimal important difference, and the line of no effect making the effect size uncertain.

Table 173: Trimagnesium dicitrate vs placebo– Clinical summary of findings

Outcome	Trimagnesium dicitrate	Placebo	Relative Risk	Absolute effect	Quality
Responder rate (50% reduction)	19/36 (52.8%)	11/32 (34.4%)	RR 1.54 (0.87 to 2.71)	186 more per 1000 (from 45 fewer to 588 more)	VERY LOW
Change in patient reported migraine days (SD)	-2.49 (0.05) n=43	-1.16 (3.89) n=38	-	MD 1.33 lower (2.57 to 0.09 lower)	LOW
Change in patient reported migraine intensity (SD)	-2.06 (2.77) n=43	-1.25 (2.29) n=38	-	MD 0.81 lower (1.91 lower to 0.29 higher)	VERY LOW
Change in patient reported migraine frequency (SD)	-1.51 (2.07) n=43	-0.58 (2.3) n=38	-	MD 0.93 lower (1.89 lower to 0.03 higher)	LOW
Use of acute pharmacological treatment (SD)	-5.07 (6.58) n=43	-2.4 (6.59) n=38	-	MD 2.67 lower (5.54 lower to 0.2 higher)	VERY LOW
Incidence of serious adverse events	3/43 (7%)	0%	-	-	VERY LOW

20.2.2.2 Economic evidence

No relevant economic evaluations comparing magnesium with placebo were identified.

20.2.2.3 Evidence statements

Clinical:

One study with 81 people suggested that trimagnesium dicitrate may be more clinically effective than placebo in increasing responder rate in the prophylactic treatment of migraine, but there is some uncertainty. [Very low quality].

One study with 81 people suggested that trimagnesium dicitrate may be more clinically effective than placebo in reducing the number of patient reported migraine days in the prophylactic treatment of migraine, but there is some uncertainty. [Low quality].

One study with 81 people suggested that trimagnesium dicitrate may be more clinically effective than placebo in reducing patient reported migraine intensity in the prophylactic treatment of migraine, but there is considerable uncertainty. [Very low quality].

One study with 81 people suggested that trimagnesium dicitrate may be more clinically effective than placebo in reducing patient reported migraine frequency in the prophylactic treatment of migraine, but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

One study with 81 people suggested that trimagnesium dicitrate may be more clinically effective than placebo in reducing the use of acute pharmacological treatment the prophylactic treatment of migraine, but the effect size is too small to be clinically effective and there is considerable uncertainty. [Very low quality].

One study with 81 people suggested that trimagnesium dicitrate may be less clinically effective than placebo in preventing occurrence of adverse events, but there is considerable uncertainty.

[Very low quality].

Economic:

No economic evidence on magnesium was identified.

20.2.3 Riboflavin vs placebo

20.2.3.1 Clinical evidence

See evidence tables in appendix section E.3.4, forest plots in Figure 186, appendix G.2.11.

One study was identified comparing riboflavin with placebo in people with migraine with or without aura[221]. No studies were identified for other primary headaches. The dose of riboflavin used in the study was 400mg per day. Data analysed as ITT with last observation carried forward for missing data has been presented, as it was not possible to interpret numbers for available case analysis.

Table 174: Riboflavin vs placebo– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Responder rate (50% reduction)[221]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine days	0	-	-	-	-	-
Change in patient reported migraine intensity	0	-	-	-	-	-
Change in patient reported migraine frequency	0	-	-	-	-	-
Functional health status	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Small study size.

Table 175: Riboflavin vs placebo – Clinical summary of findings

Outcome	Riboflavin	Placebo	Relative Risk	Absolute effect	Quality
Responder rate (50% reduction)	17/28 (60.7%)	4/26 (15.4%)	RR 3.95 (1.53 to 10.2)	454 more per 1000 (from 82 more to 1415 more)	MODERATE

20.2.3.2 Economic evidence

No relevant economic evaluations comparing riboflavin with placebo were identified.

20.2.3.3 Evidence statements

Clinical:

One study with 54 people showed that riboflavin is more clinically effective that placebo at increasing responder rate in the prophylactic treatment of migraine. [Moderate quality].

Economic:

No economic evidence on riboflavin was identified.

20.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 20.4.

20.3 Herbal remedies

Feverfew (Tanacetum parthenium) is a medicinal herb which contains parthenolide. This might prevent migraine by relieving spasms in smooth muscle tissue and acting as an anti-inflammatory. Butterbur (Petasites hybridus root) is a perennial shrub, which also contains chemicals with potential antispasmodic and anti-inflammatory activity. These are available from some pharmacies and health-food stores. Given that they may interact with other prescribed medicines, it is advisable to check with a pharmacist before purchasing.

Butterbur was identified for consideration in the guideline at the scoping stage. In January 2012 prior to consultation of the draft guideline the MHRA issued a safety warning about the use of butterbur. This section therefore reports on the evidence review of butterbur completed for the guideline but the safety warning from the MHRA precluded making a recommendation for this product.

20.3.1 Clinical question

For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with herbal remedies?

A literature search was conducted for RCTs comparing the clinical effectiveness of different herbal remedies for the prophylactic treatment of primary headache. The interventions we included in our search were herbal remedies (e.g. feverfew, butterbur), with or without prophylactic pharmacological treatment. We looked for any studies that compared the effectiveness of any or all of these treatments with placebo, prophylactic pharmacological treatment, pharmacological therapy, acupuncture, psychological therapy, dietary supplements and manual therapy (see protocol C.2.13).

One Cochrane review was identified on the use of feverfew in the prevention of migraine but was excluded as it included crossover trials and had no minimum sample size (some included studies had less than twenty five participants per arm)[202]. Any studies that were relevant to our review protocol were included.

Imprecision for the effect size relating to the outcome headache or migraine days was assessed using a value agreed by the GDG for the MID of 0.5 days.

20.3.2 Butterbur vs placebo

20.3.2.1 Clinical evidence

See Evidence tables in appendix section E.3.4, Forest Plots in Figures 187-191, appendix G.2.12.

Two studies were identified that compared butterbur with placebo[54,96,156]. One of the included studies was originally published in 2000[96], and updated in 2004[60].

The population of both of the included studies was adults with migraine with or without aura.

Different doses of butterbur were taken by the people in the studies. One study had two intervention groups that received different doses (50mg or 75 mg per day) of butterbur[156]. In the other study, the dose of butterbur given was unclear; the original study states that the intervention group received 150 mg of butterbur per day[96], and the reanalysis states that the intervention group took 100mg per day[54].

Table 176: Butterbur vs placebo– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Responder rate (50% reduction)[54,96,156]	2	Randomised trials	Serious [(a), (d)]	Serious [(e)]	No serious indirectness	Very serious [(c)]
Change in patient reported migraine intensity[54,96]	1	Randomised trials	Serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(c)]
Change in patient reported migraine frequency[54,96]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Use of acute pharmacological treatment [54,96]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious [(c)]
Serious adverse events[156]	1	Randomised trials	Serious [(d)]	No serious inconsistency	No serious indirectness	Very serious [(c)]
Change in patient reported headache days	0	-	-	-	-	-

Functional health status	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-

(a) Allocation concealment was unclear.
(b) The confidence interval crosses one of the minimal important differences making the effect size uncertain.
(c) The confidence intervals cross the minimal important difference in both directions making the effect size very uncertain.
(d) Large numbers of dropouts (more than 10%).
(e) Unexplained heterogeneity.

Table 177: Butterbur vs placebo– Clinical summary of findings

Outcome	Intervention	Control	Relative Risk	Absolute effect	Quality
Responder rate (50% reduction)	116/187 (62%)	43/102 (42.2%)	RR 1.41 (1.1 to 1.79)	173 more per 1000 (from 42 more to 333 more)	VERY LOW
Change in patient reported headache days	-	-	-	-	-
Change in patient reported migraine intensity (mean, SD)	3.1 (1.73) n=33	3.4 (1.08) n=27	-	MD 0.3 lower (1.02 lower to 0.42 higher)	VERY LOW
Change in patient reported migraine frequency (mean, SD)	1.8 (0.95) n=33	2.6 (1.15) n=27	-	MD 0.8 lower (1.34 to 0.26 lower)	LOW
Use of acute pharmacological treatment	6/33 (18.2%)	7/27 (25.9%)	RR 0.70 (0.27 to 1.84)	78 fewer per 1000 (from 189 fewer to 218 more)	VERY LOW
Serious adverse events	3/154 (1.9%)	3/75 (4%)	RR 0.49 (0.10 to 2.36)	20 fewer per 1000 (from 36 fewer to 54 more)	VERY LOW

20.3.2.2 Economic evidence

No relevant economic evaluations comparing butterbur with placebo were identified.

20.3.2.3 Evidence statements

Clinical:

Two studies with 289 people with migraine suggested that butterbur may be more clinically effective than placebo in increasing responder rate, but there is considerable uncertainty. [Very low quality].

In one study with 60 people with migraine there is too much uncertainty to determine whether there is a difference between butterbur and placebo in reducing migraine intensity. [Very low quality].

One study with 60 people with migraine suggested that butterbur may be more clinically effective than placebo in reducing migraine frequency, but there is considerable uncertainty. [Low quality].

One study with 60 people with migraine suggested that butterbur may be more clinically effective than placebo in the use of acute pharmacological medication, but there is considerable uncertainty. [Very low quality].

One study with 229 people with migraine suggested that butterbur may be more clinically effective than placebo in the number of people that reported serious adverse events, but there is considerable uncertainty. [Very low quality].

Economic:

No economic evidence on butterbur was identified.

20.3.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 20.4.

20.3.3 Feverfew vs placebo

20.3.3.1 Clinical evidence

See evidence tables in appendix section E.3.4, forest plots in Figures 192-195, appendix G.2.12.

Two studies were identified that compared feverfew with placebo in adults with migraine with or without aura[59,198]. The range of doses administered was 2.08mg-18.75mg per day.

One study presented data analysed as ITT and per protocol [198]; available case analysis numbers could not be determined using the information provided. Due to the high rate of dropouts from the study, per protocol analysis has been used where available in the absence of available case data.

One study had three intervention arms that received different doses of feverfew; one received 2.08mg per day, one received 6.25mg per day and the other received 18.75mg per day[198]. The results for these three arms were pooled for the analysis.

Table 178: Feverfew vs placebo– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Responder rate (50% reduction)[59,198]	2	Randomised trials	Serious (a), (c)	Serious (d)	No serious indirectness	Very serious (b)
Change in patient reported migraine days[59]	1	Randomised trials	Serious (c)	No serious inconsistency	No serious indirectness	Very serious (b)
Change in patient reported migraine frequency[198]	1	Randomised trials	Serious (a), (c)	No serious inconsistency	No serious indirectness	Very serious (b)
Serious adverse events[59]	1	Randomised trials	Serious (c)	No serious inconsistency	No serious indirectness	Very serious (b)
Change in patient reported migraine intensity	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Functional health status	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-

(a) Allocation concealment was unclear.
(b) The confidence intervals cross the minimal important difference in both directions making the effect size very uncertain.
(c) Large numbers of dropouts (more than 10%).
(d) Unexplained heterogeneity.

Table 179: Feverfew vs placebo – Clinical summary of findings

Outcome	Intervention	Control	Relative Risk	Absolute effect	Quality
Responder rate (50% reduction)	52/201 (25.9%)	25/116 (21.6%)	RR 1.12 (0.46 to 2.74)	26 more per 1000 (from 116 fewer to 375 more)	VERY LOW
Change in patient reported migraine days (mean, SD)	4.74 (2.83) n=89	5.33 (2.79) n=81	-	MD 0.59 lower (1.44 lower to 0.26 higher)	VERY LOW
Change in patient	-0.46 (1.64) n=85	-0.7 (1.9) n=25	-	MD 0.24 higher (0.58 lower to	VERY LOW

reported migraine frequency (mean, SD)				1.06 higher)	
Incidence of serious adverse events	3/108 (2.8%)	2/110 (1.8%)	RR 1.53 (0.26 to 8.96)	10 more per 1000 (from 13 fewer to 129 more)	VERY LOW

20.3.3.2 Economic evidence

No relevant economic evaluations comparing feverfew with placebo were identified.

20.3.3.3 Evidence statements

Clinical:

In two studies with 317 people with migraine, there is too much uncertainty to determine whether there was a difference between feverfew and placebo in improving responder rate. [Very low quality].

One study with 170 people with migraine suggested that feverfew may be more clinically effective than placebo in reducing the number of patient reported migraine days, but there is considerable uncertainty. [Very low quality].

In one study with 110 people with migraine there is too much uncertainty to determine whether there was a difference between feverfew and placebo in the reduction of patient reported migraine frequency. [Very low quality].

One study with 218 people with migraine suggested that people taking placebo experienced fewer serious adverse events than people taking feverfew, but there is considerable uncertainty. [Very low quality].

Economic:

No economic evidence on feverfew was identified.

20.4 Recommendations and link to evidence

Recommendations	**Advise people with migraine that riboflavin (400 mg[nn] once a day) may be effective in reducing migraine frequency and intensity for some people.**
Relative values of different outcomes	The GDG agreed that responder rate should be considered the most important outcome.
Trade off between clinical benefits and harms	Decrease in migraine frequency and intensity and increase in responder rate needs to be balanced against the adverse events that may be attributed to riboflavin.
Economic considerations	No relevant economic evaluations comparing riboflavin with placebo were identified. It is very uncertain whether riboflavin would represent a good value

[nn] At the time of publication (September 2012), riboflavin did not have a UK marketing authorisation for this indication but is available as a food supplement. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

	for money for the NHS. However if people are willing to pay for it, they should be informed that riboflavin may reduce migraine frequency and intensity in some people.
Quality of evidence	This recommendation is based on moderate quality evidence from one outcome (responder rate). No economic evidence was found on this question.
Other considerations	All studies had a population of people with migraine with or without aura, there was no evidence for use of dietary or herbal supplements in people with other types of primary headache. In all of the included studies people took acute pharmacological medication throughout the study. The review also demonstrated evidence for trimagnesium dicitrate (low quality) for change in patient reported headache days and reduction in headache frequency and very low quality evidence for improving headache intensity, responder rate and reducing the use of acute pharmacological treatment. However, trimagnesium dicitrate does not ahave a marketing authorisation in the UK for medical use at the time of publication and is not available as a food supplement, although other magnesium salt preparations are available. Although the evidence review did not identify issues with the safety of butterbur, the MHRA issued a warning in January 2012 about an association between use of butterbur and liver toxicity. The doses of riboflavin shown to be effective in the review was 400mg per day. Riboflavin 400 mg/day did not have marketing authorisation for migraine at the time of publication, but is available as a food supplement. This recommendation does not justify NHS prescription and refers to self-purchase.

21 Prophylactic non-pharmacological management of primary headaches with exercise

21.1 Introduction

Although there is little published scientific rationale for exercise as a treatment for primary headaches, and during a headache attack exercise may make symptoms worse, it is a commonly recommended treatment for headaches[27]. Aerobic exercise may have a direct effect on primary headache by changing the levels of centrally acting neurotransmitters. Alternatively it may be mediated through its effect on mood. For example, depression and migraine are co-morbid and exercise can help to improve depression[109,168]. Other forms of exercise, such as yoga, are more focussed on physical, mental and spiritual disciplines. Positive effects may occur through psychological mechanisms. It might be conceptualised as a mind-body therapy which has any positive effects through psychological mechanisms rather than the exercise itself.

Regular exercise has many health benefits in general and if it was effective in reducing the impact of migraine, tension type headache and medication overuse headache, it could be a useful addition, or alternative to, conventional pharmacological treatments.

21.1.1 Clinical question

For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with exercise programmes?

A literature search was conducted for RCTs comparing the clinical effectiveness of different exercise programmes for the non- pharmacological management of primary headache. We looked for any studies that compared the effectiveness of any exercise programme with usual care. The GDG took the view that it would not be feasible to have a placebo or sham control group for studies of exercise and therefore studies comparing exercise to usual, or self-care were considered (see protocol C.2.14).

The search identified two relevant studies that were included in the review. One study compared yoga to self-care[110] and one study compared an exercise programme to pharmacological management with topiramate[260]. Due to the heterogeneous nature of the comparison groups, the data has been analysed separately.

Imprecision for the effect size relating to the outcome headache or migraine days was assessed using a value agreed by the GDG for the MID of 0.5 days.

21.1.2 Yoga vs self-care

21.1.2.1 Clinical evidence

See evidence tables in appendix section E.3.5, forest plots in Figures 196-198, appendix G.2.13.

One study was identified comparing yoga with self-care in people with primary headaches[110].

The study included in this review had a population of people with migraine without aura; no studies assessed the use of exercise in the management of other primary headaches. The population of the study were all female aged 20 to 25 years.

The intervention group practiced yoga for 60 minutes, 5 times a week. The specific type of yoga that was practised and the content of a 60 minute session was not reported.

Table 180: Yoga vs self care– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Change in patient reported migraine intensity [110]	1	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Change in patient reported migraine frequency [110]	1	Randomised trials	Very serious [(a), (b)]	No serious inconsistency	No serious indirectness	No serious imprecision
Use of acute pharmacological treatment [110]	1	Randomised trials	Very serious [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Responder rate (50% reduction)	0	-	-	-	-	-
Change in patient reported migraine days	0	-	-	-	-	-
Functional health status	0	-	-	-	-	-
Migraine specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Allocation concealment was not reported, open label study and population of study was not a representative sample as all participants were aged 20-25 years.
(b) Unclear reporting of baseline migraine frequency.

Table 181: Yoga vs self care – Clinical summary of findings

Outcome	Exercise (yoga) N=32	Self care N=33	Relative Risk	Absolute effect	Quality
Change in patient reported migraine frequency	32	33	-	MD 5.62 lower (6.58 to 4.66 lower)	LOW
Change in patient reported migraine intensity	32	33	-	MD 2.28 lower (2.54 to 2.02 lower)	LOW
Use of acute pharmacological treatment	32	33	-	MD 2.57 lower (3.04 to 2.1 lower)	LOW

21.1.2.2 Economic evidence

No relevant economic evaluations comparing yoga with self-care were identified.

21.1.2.3 Evidence statements

Clinical:

One study with 72 people with migraine without aura showed that yoga is more clinically effective than self-care at reducing migraine frequency at 12 weeks follow up. [Low quality].

One study with 72 people with migraine without aura showed that yoga is more clinically effective than self-care at reducing migraine intensity at 12 weeks follow up. [Low quality].

One study with 72 people with migraine without aura showed that yoga is more clinically effective than self-care at reducing use of acute pharmacological medication at 12 weeks follow up. [Low quality].

No studies reported outcome data for responder rate, change in patient reported migraine days, functional health status, migraine specific quality of life, resource use or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing yoga with self-care were identified.

21.1.3 Exercise vs topiramate

21.1.3.1 Clinical evidence

See evidence tables in appendix section E.3.5, forest plots in Figures 199-204, appendix G.2.13.

One study was identified comparing exercise with topiramate in people with migraine with or without aura[260]. No studies assessed the use of exercise compared to topiramate in the management of other primary headaches.

Data analysed by available case analysis could not be interpreted from this paper, therefore data reported are analysed by ITT with last observation carried forward as reported in the paper.

Table 182: Exercise vs topiramate– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Responder rate (50% reduction in migraine frequency)[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision [(b)]
Change in patient reported migraine days[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(c)]
Change in patient reported migraine frequency[260] (attacks per month)	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(c)]
Change in patient reported migraine intensity [260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(c)]
Use of acute pharmacological treatment[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(c)]
Migraine specific quality of life[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(c)]
Functional health status and health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Single blind study (evaluator blind only). Unclear how long exercise group were supervised or if they exercised alone. Self-selected participant group.
(b) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.
(c) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 183: Exercise vs topiramate – Clinical summary of findings

Outcome	Exercise N=30	Topiramate N=31	Relative Risk	Absolute effect	Quality
Responder rate (50% reduction in frequency)	9/30 (30%)	8/31 (25.8%)	RR 1.16 (0.52 to 2.61)	41 more per 1000 (from 124 fewer to 415 more)	VERY LOW
Change in patient reported migraine days	30	31	-	MD 0.15 lower (1.66 lower to 1.36 higher)	LOW
Change in patient reported migraine frequency (attacks per month)	30	31	-	MD 6.6 higher (2.96 lower to 16.16 higher)	LOW
Change in patient reported migraine intensity	30	31	-	MD 0.3 lower (1.08 lower to 0.48 higher)	LOW
Migraine specific quality of life	30	31	-	MD 0.01 lower (1.52 lower to 1.5 higher)	LOW
Use of acute pharmacological treatment	30	31	-	MD 2.6 higher (3.78 lower to 8.98 higher)	LOW

21.1.3.2 Economic evidence

No relevant economic evaluations comparing exercise with topiramate were identified.

The cost of a six-month course of topiramate for the prophylaxis of headache was calculated for the original economic model described in 14.4 and Appendix L. This cost is around £126 per person over six months and includes the drug cost and two GP visits. No data on the cost of exercise was found and it is unclear whether exercise would be more or less costly than topiramate.

21.1.3.3 Evidence statements

Clinical:

One study with 61 people with migraine with or without aura suggested that exercise is more clinically effective than topiramate at increasing responder rate at 3 months follow up but there is considerable uncertainty. [Very low quality].

In one study with 61 people with migraine with or without aura, suggested that exercise is more effective than topiramate in reducing the number of patient reported migraine days at 3 month follow- up, but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that exercise is more effective than topiramate at reducing migraine frequency at 3 month follow up, but the effect size is too small to be clinically effective, and there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that topiramate is more clinically effective than exercise in reducing migraine intensity at 3 month follow up, but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that exercise may be more effective than topiramate at improving migraine specific quality of life at 3 month follow up, but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

In one study with 61 people with migraine with or without aura there is too much uncertainty to determine whether there was a difference between exercise and topiramate in the use of acute pharmacological treatment. [Low quality].

No studies reported outcome data for functional health status and health related quality of life, resource use or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing exercise with topiramate in people with migraine were identified. The cost of a six-month course of topiramate for the prophylaxis of migraine was calculated for the original economic model on prophylactic treatment of migraine and it is around £126 per person and includes the drug cost and two GP visits. No data on the cost of exercise was found and it is unclear whether exercise would be more or less costly than topiramate.

21.1.4 Exercise vs relaxation

21.1.4.1 Clinical evidence

See evidence tables in appendix section E.3.5, forest plots in Figures 205-210, appendix G.2.13.

One study was identified comparing exercise with relaxation in people with migraine[260].

The included study had a population of people with migraine; no studies assessed the use of exercise compared to relaxation in the management of other primary headaches.

Data analysed by available case analysis could not be interpreted from this paper, therefore data reported are analysed by ITT with last observation carried forward as reported in the paper.

Table 184: Exercise vs relaxation – Quality assessment

Outcome	No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Responder rate (50% reduction in migraine frequency)[260]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)
Change patient reported in migraine days[260]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)
Change in patient reported migraine frequency (attacks per month)[260]	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)
Change in patient	1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)

Outcome	No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
reported migraine intensity (VAS 0-100)[260]						
Migraine specific quality of life (0-100) [260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(c)]
Use of acute pharmacological treatment[260]	1	Randomised trials	Serious [(a)]	No serious inconsistency	No serious indirectness	Serious [(c)]
Functional health status and health related quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-
Incidence of serious adverse events	0	-	-	-	-	-

(a) Single blind study (evaluator blind only). Unclear how long exercise group were supervised or if they exercised alone. Self-selected participant group.
(b) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.
(c) The confidence interval crosses one minimal important difference making the effect size uncertain.

Table 185: Exercise vs relaxation – Clinical summary of findings

Outcome	Exercise	Relaxation	Relative risk (95% CI)	Absolute effect	Quality
Responder rate (50% reduction in migraine frequency)	9/30 (30%)	7/30 (23.3%)	RR 1.29 (0.55 to 3)	68 more per 1000 (from 105 fewer to 467 more)	VERY LOW
Change patient reported in migraine days	30	30	-	MD 0.76 lower (2.28 lower to 0.76 higher)	LOW
Change in patient reported migraine frequency (attacks per month)	30	30	-	MD 0.04 lower (0.81 lower to 0.73 higher)	LOW
Change in patient reported migraine intensity (VAS 0-100)	30	30	-	MD 2 lower (11.7 lower to 7.7 higher)	LOW
Migraine specific quality	30	30	-	MD 1.9 higher (4.62 lower to	LOW

Outcome	Exercise	Relaxation	Relative risk (95% CI)	Absolute effect	Quality
of life (0-100)				8.42 higher)	
Use of acute pharmacological treatment	30	30	-	MD 0.12 higher (1.39 lower to 1.63 higher)	LOW

21.1.4.2 Economic evidence

No relevant economic evaluations comparing exercise with relaxation were identified.

21.1.4.3 Evidence statements

Clinical:

One study with 61 people with migraine with or without aura suggested that exercise may be more clinically effective than relaxation in improving responder rate in the prophylactic treatment of migraine at 3 months but there is considerable uncertainty. [Very low quality].

One study with 61 people with migraine with or without aura suggested that exercise is more clinically effective than relaxation in reducing the number of migraine days at 3 months, but there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura showed that there is no clinically important difference between exercise and relaxation in reducing migraine frequency at 3 months, but there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that exercise is more clinically effective than relaxation in reducing migraine intensity at 3 months, but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that relaxation is more effective than exercise in improving migraine specific quality of life at 3 months but the effect size is too small to be clinically important and there is some uncertainty. [Low quality].

One study with 61 people with migraine with or without aura suggested that there is no clinically important difference between exercise and relaxation in reducing the use of acute pharmacological medication in the prophylactic treatment of migraine at 3 months but there is some uncertainty. [Low quality].

No studies reported outcome data for functional health status, resource use or incidence of serious adverse events.

Economic:

No relevant economic evaluations comparing exercise with relaxation were identified.

21.2 Recommendations and link to evidence

The GDG decided that there was not enough evidence to form a recommendation for or against the use of exercise for migraine.

Recommendation	
Relative values of different outcomes	The GDG agreed that change in migraine days and responder rate were the most important outcomes, however change in patient reported migraine frequency and intensity were also important to consider.
Trade off between clinical benefits and harms	There was no data on serious adverse events reported in the studies included in this review. The GDG agreed that there were not any serious harms to consider.
Economic considerations	Exercise programmes, if provided by the NHS, would be associated with some costs. In the absence of good evidence on the effectiveness of exercise programmes, it is difficult to judge whether their costs would be offset by their effectiveness at reducing headache frequency and intensity.
Quality of evidence	There was low quality evidence from one small trial (n=72) comparing yoga and self-care, and one small trial (n=61) comparing exercise and topiramate. In the yoga trial, the population was very specific and therefore the results are not directly applicable to the general migraine population in the UK. Both studies reported some evidence that exercise may be beneficial compared to usual care or relaxation or equally effective to topiramate. However this was from open label studies with low or very low quality evidence. The effect of exercise programmes on the management of primary headaches other than migraine was not assessed. No economic evaluations were identified.
Other considerations	The GDG agreed that there was not enough evidence to form a recommendation for or against aerobic exercise or yoga for the prophylactic treatment of migraine. The available data for yoga was specific to a particular approach, the full details of which were not available. The programme was quite intensive, 5 days a week for one hour a day, in a very specific population, likely to be highly motivated (20-25 years old females who were paid to take part). The GDG agreed that this was not necessarily directly applicable to the UK health care system and would be difficult to replicate. **Research recommendation:** The GDG agreed to make a research recommendation for exercise in people with chronic headache to strengthen the evidence base. See appendix M3.

22 Prophylactic non-pharmacological management of primary headaches with education and self management

22.1 Introduction

Self management and education programmes are used for a wide range of chronic disorders. Self management programmes combine elements of psychological treatments such as cognitive behavioural therapy, mind-body therapies such as relaxation along with exercise and activity. Such programmes are widely available through initiatives such as the expert patient programme. These are usually lay-led group activities lasting for a period of weeks. In the context of headache management these might also include educational components addressing drug and other specific treatments for headaches. People living with chronic headache might also join generic pain self management courses. The shared experience of others within the group may also support any therapeutic effect. Stand-alone educational programmes for headaches would aim to impart knowledge around headache management using a variety of media. The GDG were interested in the evidence for both of these management strategies in primary headache.

22.1.1 Clinical question

For people with primary headaches, what is the clinical evidence and cost-effectiveness of non-pharmacological management with education and self-management programmes?

A literature search was conducted for RCTs comparing the clinical effectiveness of different education and self-management programmes for the non-pharmacological management of primary headache. We looked for any studies that compared the effectiveness of any education and/or self-management programme with usual care (see protocol C.2.15).

Four studies were identified comparing education and self-management to usual care. Three were in populations with mixed primary headaches[3,136,268]. The fourth was in people with migraine[128]. A further study that was initially included in this review focused on the delivery of a multidisciplinary care package[142]. After discussion with the GDG it was agreed that the multidisciplinary intervention did not meet the protocol, and therefore this study was excluded. The study is summarised in an evidence table in Appendix E.3.6 for information.

The GDG were also interested in the management of tension type headache and cluster headache, but no evidence was found on the treatment of these headaches in the isolation of migraine.

22.1.2 Education and self-management vs usual care (migraine with or without aura)

22.1.2.1 Clinical evidence

See evidence tables in appendix section E.3.6, forest plots in Figures 211-215, appendix G.2.14.

One study was identified for this comparison[128]. Education and self-management can refer to a variety of interventions. In the study included in this review, the people in the intervention group received a book that included information on biofeedback, relaxation and cognitive restructuring. The control group also received a book but this provided information about headache only. Blinding was unclear in this study, although it is assumed to be single blind (participants informed that two different books were being tested).

Due to the way that the data were reported in the included study[128] the outcomes could not be meta- analysed.

Table 186: Education and self-management vs usual care (migraine) – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported migraine frequency [128]	1	Randomised trial	Very serious [(a)]	N/A[(c)]	No serious indirectness	N/A [(c)]
Use of acute pharmacological treatment[128] (mean number of doses per week)	1	Randomised trial	Very serious [(a)]	N/A[(c)]	No serious indirectness	N/A[(c)]
Patient's perception of the usefulness of the programmes[128] (0–5, higher score= better)	1	Randomised trial	Very serious [(a),(b)]	N/A[(c)]	No serious indirectness	N/A[(c)]
Responder rate (50% reduction)	0	-	-	-	-	-
Change in patient reported migraine days	0	-	-	-	-	-
Change in patient reported migraine intensity	0	-	-	-	-	-
Functional health status and quality of life	0	-	-	-	-	-
Migraine specific quality of life	0	-	-	-	-	-
Resource use	0	-	-	-	-	-

(a) Unclear blinding and allocation concealment (assumed single blind from study text), all outcomes reported were patient perceived and therefore highly subjective, more than 50% of study population did not complete the study and the characteristics of the intervention and control groups was not comparable at baseline.
(b) Unclear whether method of analysis is validated.
(c) Inconsistency and imprecision could not be assessed as data couldn't be meta-analysed.
N/A=not applicable.

Table 187: Education and self-management vs usual care (migraine) – Clinical summary of findings

Outcome	Education and self-management	Control	Relative risk[a]	Absolute effect[a]	Quality
Migraine frequency (% decrease)	62%	14%	-	-	VERY LOW
Use of acute pharmacological treatment (mean number of doses per week)	**Baseline**: 6.6 **3 months:** 4.1	**Baseline:** 2.8 **3 months:** 2.2	-	-	VERY LOW
Patient's perception of the usefulness of the programme (0–5, higher score = better)	**Baseline:** 2.8 **3 months:** 2.6	**Baseline:** 3.8 **3 months:** 3.5	-	-	VERY LOW

(a*) Relative risk and absolute effect not calculated as data could not be meta-analysed*

22.1.2.2 Economic evidence

No relevant economic evaluations comparing education and self-management of people with migraine vs usual care were identified.

22.1.2.3 Evidence statements

Clinical:

One study with 117 people with migraine suggested that education and self-management group is more effective than usual care in reducing migraine frequency than, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

One study with 117 people with migraine suggested that education and self-management may be more effective than usual care in reducing the mean number of doses of acute pharmacological treatment per week, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

One study with 117 people with migraine suggested that there is no difference between education and self-management and usual care with respect to the patient's perception of the usefulness of the programme, but the difference is uncertain as no comparative analysis could be carried out. [Very low quality].

Economic: No relevant economic evaluations comparing education and self-management of people with migraine vs usual care were identified.

22.1.2.4 Recommendations and link to evidence

See recommendations and link to evidence in section 22.2.

22.1.3 Education and self-management vs usual care (mixed headache)

22.1.3.1 Clinical evidence

See evidence tables in appendix section E.3.5, forest plots in Figures 180-185, appendix G.2.13.

The primary headache types in the population of the three studies included in this review were migraine, tension type headache, mixed migraine and tension type headache and non-migrainous headache[3,136,268]. One study had a population of children and adolescents aged 10 – 18 years[3], one study had a population aged 16- 18 years[136] and the third did not state the age range of the included population[268]. Blinding was not stated in any study, assumed to be open label.

The interventions in the included studies varied considerably;

- One study had a clinical model as the intervention, which included self-management and relaxation components[3].
- Two studies were three armed trials [136,268]. Both of these had a self-help relaxation group and a usual care group. The third arm was either group relaxation[268] or therapist-assisted relaxation[136].
- There was variation in the way the education and self-management interventions were delivered; either via contact with a healthcare professional[3,136,268], and/ or written instructions[268] or audiotape recordings[136].
- The intensity and duration of the interventions varied within and between studies, this ranged from a single one hour education session[3] to one and a half hours contact with a therapist, twice a week for four weeks[268].

There care received by the comparison groups also varied. One study had a standard neurologist consultation as control[3], one study had a waiting list control group[268]and in the other study the control group monitored their headaches [136]. Both of these have been called usual care.

Outcome data from one study[3] could not be meta-analysed due to the way that it was reported. The data is summarised in Table 188.

Table 188: Summary of findings: resource use outcomes (Abram 2007[3])

Outcome	Headache clinical model (intervention)	Traditional clinical model (comparison)
Resource use - psychological treatment (% use)	14.6% [(a)]	7.5% [(a)]
Resource use - calls to neurology clinic (% use)	19.1% [(a)]	11.5% [(a)]
Resource use - emergency department visits (% use)	7.7% [(a)]	7.6% [(a)]

(a) The study reported change scores only, no baseline data was available.

Table 189: Education and self-management vs usual care (mixed headache) – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
Responder rate (50% reduction)- *self help vs therapist assisted relaxation* [136]	1	Randomised trial	Very serious [(a), (b)]	No serious inconsistency	No serious indirectness	Very serious [(c)]
Responder rate (50% reduction)- *self help vs usual care*[136,268]	2	Randomised trial	Very serious [(a), (b) (d),]	No serious inconsistency	No serious indirectness	Serious [(e)]
Responder rate (50%	1	Randomised trial	Very serious [(b), (d)]	No serious inconsistency	No serious indirectness	Very serious [(c)]

reduction)- *self help relaxation vs group relaxation*[268]						
Responder rate (50% reduction)- *group relaxation vs usual care*[268]	1	Randomised trial	Very serious (b), (d)	No serious inconsistency	No serious indirectness	Very serious (c)
Resource use[3]	1	Randomised trials	Very serious (d)	N/A (f)	No serious indirectness	N/A (f)
Patient's perception of the usefulness of the programmes[136]	1	Randomised trial	Very serious (a), (b)	No serious inconsistency	No serious indirectness	Very serious (c)
Change in patient reported headache days	0	-	-	-	-	-
Change in patient reported headache intensity	0	-	-	-	-	-
Change in patient reported headache frequency	0	-	-	-	-	-
Use of acute pharmacological treatment	0	-	-	-	-	-
Functional health status	0	-	-	-	-	-
Headache specific quality of life	0	-	-	-	-	-

(a) One study had restrictions applied to randomisation and selection bias.
(b) Outcomes reported earlier than originally stated in study.
(c) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.
(d) Method of randomisation was unclear and blinding and allocation concealment were not reported.
(e) The confidence interval crosses one of the minimal important differences making the effect size uncertain.
(f) Could not be assessed as data could not be analysed.

Table 190: Education and self-management vs usual care (mixed headache) – Clinical summary of findings

Outcome	Intervention	Control	Relative Risk	Absolute effect	Quality
Responder rate (50% reduction)- self help vs therapist assisted relaxation	6/16 (37.5%)	1/14 (7.1%)	RR 0.88 (0.06 to 12.73)	9 fewer per 1000 (from 67 fewer to 833 more)	VERY LOW
Responder rate (50% reduction) self help vs usual care	6/30 (20%)	1/25 (3.6%)	RR 3.93 (0.75 to 20.75)	117 more per 1000 (from 10 fewer to 790 more)	VERY LOW
Responder rate (50% reduction) self help relaxation vs group relaxation	5/14 (35.7%)	4/13 (30.8%)	RR 1.16 (0.4 to 3.41)	49 more per 1000 (from 185 fewer to 742 more)	VERY LOW
Responder rate (50% reduction) group relaxation vs usual care	4/13 (30.8%)	1/14 (7.1%)	RR 4.31 (0.55 to 33.7)	235 more per 1000 (from 32 fewer to 1000 more)	VERY LOW
Confidence rating Mean [SD] (n)	3.9 [0.5] (n=16)	4.1 [0.6] (n=14)	-	MD -0.20 (-0.60 to 0.20)	VERY LOW
Resource use (psychological treatment, neurology clinic calls, Emergency department visits) Range	7.7- 19.1%	7.5-11.5%	N/A*	N/A*	LOW

** Could not be assessed as data could not be analysed*

22.1.3.2 Economic evidence

No relevant economic evaluations comparing education and self-management of people with mixed headache vs usual care were identified.

22.1.3.3 Evidence statements

Clinical:

In one study with 46 people aged 16-18 years with mixed primary headache there is too much uncertainty to determine whether there is a difference between self-help relaxation and therapist assisted relaxation in increasing responder rate. [Very low quality].

One study with 46 people aged 16-18 years with mixed primary headache, and one study with 48 adults with mixed primary headache suggested that self-help relaxation may be more effective than the self-monitoring or waiting list control in increasing responder rate, but there is some uncertainty. [Very low quality].

In one study with 48 adults with mixed primary headache there is too much uncertainty to determine whether there is a difference between self-help relaxation and group relaxation in increasing responder rate. [Very low quality].

One study with 48 adults with mixed primary headache suggested that group relaxation may be more effective than waiting list control in increasing responder rate, but there is considerable uncertainty. [Very low quality].

In one study with 46 people aged 16-18 years there is too much uncertainty to determine whether there was a difference in participants' perception of usefulness between self help relaxation and therapist assisted relaxation. [Very low quality].

In one study with 81 children aged 10-18 years with mixed primary headache there is too much uncertainty to determine whether there was a difference between the headache clinical model and traditional clinical model in resource use. [Low quality].

Economic:

No relevant economic evaluations comparing education and self-management of people with mixed headache vs usual care were identified.

22.2 Recommendations and link to evidence

The GDG decided that there was not enough evidence to form a recommendation for or against the use of education and self management programmes.

Recommendation	
Relative values of different outcomes	The GDG agreed that responder rate was the most important outcome.
Trade off between clinical benefits and harms	The GDG that there was no significant risk associated with the interventions included in the review.
Economic considerations	Strategies including education and self-management of people with headache or migraine are associated with some costs, mainly the cost of clinical staff time. In the absence of good evidence on the effectiveness of these strategies, it is difficult to judge whether their costs would be offset by their effectiveness.
Quality of evidence	The majority of evidence reviewed was very low quality, mainly from studies assumed to be open label, although information was not reported on blinding status. The types of intervention included varied considerably. The evidence reviewed was not consistently in favour of education or self-management programmes. No economic evidence was identified.
Other considerations	The GDG agreed that there was not enough evidence to form a recommendation for or against education and self-management programmes based on the available evidence. The GDG agreed there is evidence (not relevant to this review protocol) that self-management programmes can be helpful and are important to consider[81], but could not be supported by the evidence reviewed here. **Research recommendation:** The GDG agreed to make a research recommendation for education and self-management in people with chronic headache disorders, to strengthen the evidence base. See appendix M.

23 Management of medication overuse headache

23.1 Introduction

Medication overuse headache are frequent or daily headaches which occur as result of taking excessive acute relief medication for migraine or tension type headache in a susceptible person. All acute relief medication drugs have been implicated including simple analgesics, opiates, NSAIDs and triptans. The aetiology is unknown but may be related to the sensitisation of central pain processing pathways.

Not only can sustained medication overuse cause headache but it can result in tolerance and addiction to drugs. Management may be hindered by the fact that participants may have an artificially low view of (or consciously under-report) the scale of their medication use. Unfortunately, many people will relapse after an initially successful withdrawal. Given the complexities of management of this headache, the GDG were interested in looking for the evidence for the different management strategies currently used.

23.1.1 Clinical question

What is the clinical evidence and cost-effectiveness of withdrawal strategies (of abortive treatments), psychological therapies, corticosteroids and NSAIDs for the treatment of probable medication overuse headache?

A literature search was conducted for RCTs and observational studies comparing the clinical effectiveness of different strategies for the management of medication overuse headache. The management strategies we included in our search were withdrawal strategies, psychological therapies, corticosteroids and NSAIDs. We looked for any studies that compared the effectiveness of withdrawal strategies with each other, psychological therapies with attention control, corticosteroids or NSAIDS with placebo and all of these interventions with one another (See protocol C.2.16). Each of the studies included in the evidence reviews define medication overuse headache slightly define differently. (See Evidence tables, Appendix E4).

The GDG were interested in the use of psychological therapies, corticosteroids and NSAIDs to treat medication overuse headache, but no evidence was found in the review and therefore there is no section in this chapter.

Imprecision for the effect size relating to the outcome headache or migraine days was assessed using a value agreed by the GDG for the MID of 0.5 days.

23.1.2 Withdrawal strategies vs prophylactic treatment

23.1.2.1 Clinical evidence

See evidence tables in appendix section E.4, forest plots in Figures 216-222, appendix G.3.

One study was identified comparing withdrawal treatment to prophylactic treatment[97]. This is an open label randomised clinical trial.

Table 191: Withdrawal treatment vs prophylactic treatment-Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in patient reported headache days (at 3 months)[97]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in patient reported headache days (at 12 months)[97]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Responder rate (at 12 months)[97]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in functional health status (MCS-12)(at 12 months)[97]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Very serious (c)
Change in functional health status [PCS-12](at 12 months)[97]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in acute medication use –(at 3 months)[97]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Change in acute medication use-(at 12 months)[97]	1	Randomised trials	Very serious (a)	No serious inconsistency	No serious indirectness	Serious (b)
Relapse back to MOH	0	-	-	-	-	-
Headache specific QoL	0	-	-	-	-	-
Resource use	0	-	-	-	-	-

(a) Method of allocation concealment was unclear; open label (no blinding of participants, care administrators or study investigators).
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.

Table 192: Withdrawal treatment vs prophylactic treatment – Clinical summary of findings

Outcome	Withdrawal treatment	Prophylactic treatment	Relative risk	Absolute effect	Quality
Change in patient reported headache days (at 3 months)	20	17	-	MD 3 higher (1.62 lower to 7.62 higher)	VERY LOW
Change in patient reported headache days (at 12 months)	20	17	-	MD 5.2 higher (1.13 lower to 11.53 higher)	VERY LOW
Responder rate (at 12 months)	4/14 (28.6%)	9/16 (56.3%)	RR 0.51 (0.2 to 1.29)	276 fewer per 1000 (from 450 fewer to 163 more)	VERY LOW
Change in functional health status (MCS-12) (at 12 months)	20	17	-	MD 0.7 higher (12.91 lower to 14.31 higher)	VERY LOW
Change in functional health status (PCS-12)(at 12 months)	20	17	-	MD 13.7 lower (29.19 lower to 1.79 higher)	VERY LOW
Change in acute medication use (at 3 months)	20	17	-	MD 5.9 lower (12.4 lower to 0.6 higher)	VERY LOW
Change in acute medication use (at 12 months)	20	17	-	MD 1.9 lower (7.1 lower to 3.3 higher)	VERY LOW

23.1.2.2 Economic evidence

No economic evaluations comparing withdrawal strategies to prophylactic treatment were identified. The GDG discussed the economic implications of withdrawal strategies compared to prophylactic treatment. There are higher medication costs in the prophylactic treatment strategy due to the prophylactic treatment itself but also to the more frequent acute medication use; however in the studies included in the clinical review (23.1.2) inpatient and outpatient detoxification programmes were components of the withdrawal strategies and their costs make withdrawal strategies more costly.

23.1.2.3 Evidence statements

Clinical:

One study with 64 people with suspected medication overuse headache suggested that prophylactic treatment may be more clinically effective than withdrawal treatment in reducing the number of headache days at 3 months follow-up, but there is some uncertainty. [Very low quality].

One study with 64 people with suspected medication overuse headache suggested that prophylactic treatment may be more clinically effective than withdrawal treatment in reducing the number of headache days at 12 months follow-up, but there is some uncertainty. [Very low quality].

One study with 64 people with suspected medication overuse headache suggested that prophylactic treatment may be more clinically effective than withdrawal treatment in improving the responder rate at 12 months follow-up, but there is some uncertainty. [Very low quality].

In one study with 64 people with suspected medication overuse headache, there is too much uncertainty to determine whether there is a difference between withdrawal treatment and prophylactic treatment in improving quality of life, assessed with the mental health component score of SF-12 at 12 months follow-up. [Very low quality].

One study with 64 people with suspected medication overuse headache suggested that prophylactic treatment may be more clinically effective than withdrawal treatment in improving the physical health component score of SF-12 from baseline at 12 months follow-up, but there is some uncertainty. [Very low quality].

One study with 64 people with suspected medication overuse headache suggested that withdrawal treatment may be more clinically effective than prophylactic treatment in reducing the use of acute medication at 3 months follow-up, but there is some uncertainty. [Very low quality].

One study with 64 people with suspected medication overuse headache suggested that withdrawal treatment may be more clinically effective than prophylactic treatment in reducing the use of acute medication at 12 months follow-up, but there is some uncertainty. [Very low quality].

No studies reported outcome data for relapse back to medication overuse headache, headache specific quality of life or resource use.

Economic:

Withdrawal strategies have lower cost of medications compared to prophylactic treatment; however they might have higher costs associated with outpatient and inpatient detoxification programmes.

23.1.3 Outpatient withdrawal treatment vs inpatient withdrawal treatment

23.1.3.1 Clinical evidence

See evidence tables in appendix section E.4, forest plots in Figures 223-227, appendix G.3.

Four studies were identified comparing inpatient withdrawal treatment to outpatient withdrawal treatment[43,213,214,246]. All studies were open label randomised clinical trials.

Table 193: Outpatient withdrawal vs inpatient withdrawal– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Responder rate[213,214, 43]	2	Randomised trials	Very serious[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Change in patient reported headache days[246]	1	Randomised trials	Very serious[(c)]	No serious inconsistency	No serious indirectness	Serious[(b)]

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Relapse back to MOH at 1 year[213,214]	1	Randomised trials	Very serious[(a)]	No serious inconsistency	No serious indirectness	Very serious[(d)]
Relapse back to MOH at 5 years[246]	1	Randomised trials	Very serious[(c)]	No serious inconsistency	No serious indirectness	Very serious[(d)]
Change in patient reported headache intensity[246]	1	Randomised trials	Very serious[(c)]	No serious inconsistency	No serious indirectness	No serious imprecision
Functional health status	0	-	-	-	-	-
Headache specific QoL	0	-	-	-	-	-
Change in acute medication use	0	-	-	-	-	-
Resource use	0	-	-	-	-	-

(a) Method of allocation concealment was unclear; open label (no blinding of participants, care administrators or study investigators).
(b) The confidence interval crosses one minimal important difference making the effect size uncertain.
(c) Method of randomisation was unclear; open label (no blinding of participants, care administrators or study investigators).
(d) The confidence interval crosses the minimal important difference in both directions making the effect size very uncertain.

Table 194: Outpatient withdrawal vs inpatient withdrawal – Clinical summary of findings

Outcome	Outpatient withdrawal	Inpatient withdrawal	Relative risk	Absolute effect	Quality
Responder rate	44/73 (60.3%)	44/71 (62%)	RR 0.98 (0.76 to 1.26)	12 fewer per 1000 (from 149 fewer to 161 more)	VERY LOW
Change in patient reported headache days	41	60	-	MD 3 lower (7.21 lower to 1.21 higher)	VERY LOW
Relapse back to MOH at 1 year	6/26 (23.1%)	7/28 (25%)	RR 0.92 (0.36 to 2.39)	20 fewer per 1000 (from 160 fewer to 348 more)	VERY LOW
Relapse back to MOH at 5 years	6/41 (14.6%)	15/60 (25%)	RR 0.59 (0.25 to 1.38)	103 fewer per 1000 (from 188 fewer to 95 more)	VERY LOW
Change in patient reported headache intensity	41	60	-	MD 0.1 lower (1.07 lower to 0.87 higher)	LOW

23.1.3.2 Economic evidence

No economic evaluations comparing outpatient withdrawal treatment with inpatient withdrawal treatment were identified.

Based on the studies[213,214] included in our clinical review (23.1.3.1), both outpatient and inpatient withdrawal treatments are associated with drug costs. However, inpatient withdrawal treatment is expected to have higher costs due to the hospital admission.

23.1.3.3 Evidence statements

Clinical:

Two studies with 200 people with suspected medication overuse headache suggested that there is no difference between outpatient and inpatient withdrawal at improving responder rate at 12 months follow-up, but there is some uncertainty. [Very low quality].

One study with 257 people with suspected medication overuse headache suggested that outpatient withdrawal may be more clinically effective than inpatient withdrawal in reducing the number of headache days at 5 years follow-up, but there is some uncertainty. [Very low quality].

In one study with 120 people with suspected medication overuse headache, there is too much uncertainty to determine whether there is a difference between outpatient withdrawal and inpatient withdrawal in reducing relapse at 12 months follow-up. [Very low quality].

One study with 257 people with suspected medication overuse headache suggested that outpatient withdrawal may be more clinically effective than inpatient withdrawal at reducing relapse at 5 years follow-up, but there is considerable uncertainty. [Very low quality].

One study with 257 people with suspected medication overuse headache showed that there is no difference between outpatient and inpatient withdrawal at reducing headache intensity at 5 years follow-up. [Low quality].

No studies reported outcome data for functional health status and quality of life, change in acute medication use or resource use.

Economic:

No economic evidence was found. Both outpatient and inpatient withdrawal treatments are expected to have considerable costs; inpatient withdrawal treatment is expected to have higher costs compared to outpatient withdrawal treatment.

23.2 Recommendations and link to evidence

	Explain to people with medication overuse headache that it is treated by withdrawing overused medication. **Advise people to stop taking all overused acute headache medications for at least 1 month and to stop abruptly rather than gradually.** **Advise people that headache symptoms are likely to get worse in the short term before they improve and that there may be associated withdrawal symptoms, and provide them with close follow-up and support according to their needs.** **Consider prophylactic treatment for the underlying primary headache disorder in addition to withdrawal of overused medication for people with medication overuse headache.**
Relative values of different outcomes	The GDG agreed that reduction in the number of headache days was considered to be the most important outcome when considering the patient's perspective.
Trade off between clinical benefits and harms	Headache symptoms typically get worse for up to two weeks before improvement. Other withdrawal symptoms depend on drug being used Relapse rate is very high.
Economic considerations	The GDG discussed the economic implications of withdrawal strategies compared to prophylactic treatment. There are higher medication costs in the prophylactic treatment strategy due to the prophylactic treatment itself but also to the more frequent acute medication use; however inpatient and outpatient detoxification programmes are also associated with costs. The GDG considered advising people to withdraw the overused medication as the most cost-effective option. However, when this proves unsuccessful, given the evidence on its clinical benefit, the adjunct of prophylactic treatment was considered cost-effective.
Quality of evidence	The recommendations were based on very low quality evidence from one study[97] and the consensus opinion of the GDG. No economic evidence was found on medication overuse headache.
Other considerations	The GDG recommended a minimum period of withdrawal of one month, and acknowledged that although this was different from the IHS criteria, which state a minimum of 8 weeks as the period of withdrawal, it is a more practical approach. The GDG experience was that the majority of people could manage withdrawal without the addition of adjunctive treatments such as steroids, anxiolytics and antiemetics. These have been used to assist withdrawal and manage associated symptoms. There is evidence that the majority of people can withdraw from overused treatment without further medication[213]. However, the GDG acknowledged that some people will benefit from introduction of prophylactic treatment for their primary headache disorder. This can be instituted at the time of withdrawal of acute medication but the GDG did not consider this was always necessary. Withdrawal of medication may result in significant reduction of headache so prophylaxis might not be required. The GDG also discussed the issues with abrupt and gradual withdrawal and acknowledged that in the first week or two after stopping medications, most people experience a worsening of symptoms, before improvement. Patient experience suggested that gradual withdrawal is preferred. The GDG

	Explain to people with medication overuse headache that it is treated by withdrawing overused medication. **Advise people to stop taking all overused acute headache medications for at least 1 month and to stop abruptly rather than gradually.** **Advise people that headache symptoms are likely to get worse in the short term before they improve and that there may be associated withdrawal symptoms, and provide them with close follow-up and support according to their needs.** **Consider prophylactic treatment for the underlying primary headache disorder in addition to withdrawal of overused medication for people with medication overuse headache.**
	concluded that this may differ was according to the individual concerned and was best decided on a case by case basis and following discussion between practitioner and patient. The GDG also felt that gradual withdrawal could be managed in the community by those experienced in managing withdrawal. **Research recommendation:** The GDG agreed to form a research recommendation to investigate whether pharmacological treatments used for prophylaxis or steroids can help withdrawal from overused medication for people with medication overuse headache as there was an absence of evidence for this, but the GDG considered it may be of benefit to some people. See appendix M.

Recommendations	**Do not routinely offer inpatient withdrawal for medication overuse headache.** **Consider specialist referral and/or inpatient withdrawal of overused medication for people who are using strong opioids, or have relevant comorbidities, or in whom previous repeated attempts at withdrawal of overused medication have been unsuccessful.**
Relative values of different outcomes	The GDG agreed that responder rate and reduction in headache days were the most relevant outcomes for this recommendation. The recommendation was also based on GDG informal consensus.
Trade off between clinical benefits and harms	The aim of withdrawal management is to help the person stop using the medications causing their headache. Maximising the likelihood of success would be beneficial to the individual and less costly to health service overall. There is a high relapse rate associated with management of medication overuse headache which may occur within the period of withdrawal. There is often a worsening of symptoms before any improvement is seen. However, the benefits of subsequent successful withdrawal greatly outweigh this.
Economic considerations	No economic evidence was found on medication overuse headache. The GDG considered the resources associated with different strategies and concluded that inpatient withdrawal management has high costs due to hospital admission. In the absence of good quality evidence on its effectiveness the GDG decided offering inpatient withdrawal management to all people with medication overuse headache does not represent a good use of NHS

Recommendations	**Do not routinely offer inpatient withdrawal for medication overuse headache.** **Consider specialist referral and/or inpatient withdrawal of overused medication for people who are using strong opioids, or have relevant comorbidities, or in whom previous repeated attempts at withdrawal of overused medication have been unsuccessful.**
	resources. However, targeting inpatient management to those people who would benefit from it the most was considered a good use of NHS resources. Referring people to specialists is associated with costs. However, referring only selected people was considered a good use of NHS resources.
Quality of evidence	The recommendation is based on the consensus opinion of the GDG as the evidence reviewed was of very low quality. This evidence suggested that community or outpatient treatment was better than inpatient treatment with respect to reducing the number of headache days and relapse back to medication overuse headache, but the GDG informal consensus decision was that in some specific cases, inpatient withdrawal may be appropriate. No economic evidence was found on medication overuse headache.
Other considerations	The GDG also discussed the practical aspects of implementation of this recommendation. The majority of cases can be managed in a primary care setting. It was discussed that inpatient withdrawal should take place in centres with specialist expertise in this area and that those services may differ by areas e.g. they may be within a drug dependency service or a specialist headache service. The GDG discussed the practical aspects of referral and agreed that specialist referral could be to a community drugs team if available and deemed appropriate.

Recommendations	**Review the diagnosis of medication overuse headache and further management 4–8 weeks after the start of withdrawal of overused medication.**
Relative values of different outcomes	GDG informal consensus was used to form this recommendation.
Trade off between clinical benefits and harms	There is a high relapse rate associated with management of medication overuse headache which may occur within the period of withdrawal. There is often a worsening of symptoms before any improvement is seen. However, the benefits of subsequent successful withdrawal greatly outweigh this.
Economic considerations	No economic evidence was reviewed to inform this recommendation. Reviewing diagnosis and further management at 4-8 weeks is also associated with costs and no economic evidence was reviewed to inform this recommendation.
Quality of evidence	These recommendations were based on the consensus opinion of the GDG. No economic evidence was found on medication overuse headache.
Other considerations	Due consideration should also be given to informing people about medication overuse headache and its prevention.

Management during pregnancy and contraceptive use

24 Management of primary headaches during pregnancy

24.1 Introduction

Healthcare professionals are well placed to advise women and girls planning pregnancy who suffer with primary headache disorders.

Migraine without aura often improves in the second and third trimesters of pregnancy and during lactation[164,230]. Migraine with aura however is more likely to continue throughout pregnancy as can cluster headache. If the woman presents for the first time with aura in pregnancy it is important to exclude serious conditions which can mimic migraine, including thrombocytopenia, cerebral venous sinus thrombosis or imminent eclampsia. A woman or girl who presents with migraine for the first time in pregnancy often has migraine with aura.

If migraine or cluster headache does occur, drug treatment may be necessary, and women will want to know what they can safely take. The GDG were interested in looking for the evidence for the use of treatments where advice isn't already well known. The treatments were: oxygen, triptans and verapamil. There is already advice available for women on use of common treatments for primary headache disorder such as aspirin, NSAIDs and paracetamol during pregnancy. Oxygen, triptans and verapamil have specific uses in cluster headache and migraine and women who do not respond to simpler treatments may be using these before they conceive and may have need to consider continued use during pregnancy. Evidence in this group is limited and thus it is advisable to use as few drugs as possible.

24.1.1 Clinical question

What is the evidence for adverse fetal events in females with primary headaches during pregnancy using triptans, oxygen, or verapamil?

A literature search was conducted for cohort studies and case control studies comparing the incidence of serious adverse events in:

- Pregnant women and girls aged 12 or over who were treated with therapeutic oxygen compared to pregnant women not treated with oxygen
- Pregnant women and girls aged 12 or over with primary headache who were exposed to triptans compared to pregnant women with or without primary headache not taking a triptan
- Pregnant women and girls aged 12 or over who were exposed to verapamil compared to pregnant women not taking verapamil.

The reviews for therapeutic oxygen and verapamil were not limited to studies in cluster headache due to the limited amount of data that were known to be available prior to beginning the search.

(See protocols in appendix C.3.1)

24.1.2 100% oxygen

Three studies were identified as potentially relevant for this review, but were not included because two focussed on carbon monoxide poisoning and the third reported use of 100% oxygen in newborn infants[70,129,226].

24.1.3 Triptans

24.1.3.1 Clinical evidence

See evidence tables in appendix section E.5.1, forest plots in Figures 228-238, appendix G.4.1.

Three studies were identified as relevant to this review question[184,187,227]. They were all prospective cohort studies. Two studies obtained data from national birth registries and prescription databases[184,187] and the third obtained data from women calling a teratogen advice service[227].

All studies had three arms; pregnant women with migraine who had been treated with triptans, pregnant women with migraine who had not been treated with triptans, and pregnant women who did not have migraine and had not been treated with triptans.

With regards to the group of pregnant women with migraine who had been treated with triptans, two studies focussed on pregnant women who had been treated with sumatriptan[187,227] and one study assessed pregnant women who had been treated with any triptan[184].

There was heterogeneity between the studies in the control groups in each of the three studies (women who had not been treated with triptans 'absence of risk factor'). The three control groups were as follows:

- Pregnant women who contacted the teratogen service and used other drugs such as acetaminophen, NSAIDs and narcotic analgesics[227]
- Women with migraine who had not reported any triptan use during pregnancy[184]
- Women with migraine who redeemed at least one prescription for sumatriptan or ergotamine 52-12 weeks prior to conception, but not during pregnancy[187].

The outcome defined in the protocol was fetal adverse events. No study reported this as a single outcome, specific fetal adverse events were reported individually. Quality has been assessed by study rather than by outcome as the same criteria applied to each outcome (see Table 195 for more detail).

The minimum set of confounding factors that were pre-specified consisted of: age, cigarette and alcohol consumption and other drug use. No studies included in this review included all of these confounding factors.

Table 195: Pregnant women with migraine exposed to triptans vs pregnant women with migraine not exposed to triptans - Study quality checklist

Reference	Representative population sample	Loss to follow up	Prognostic factor measured appropriately	Outcomes adequately measured	Confounders accounted for	Appropriate statistical analysis
Shuhaiber et al, 1998[227]	Yes	Unclear (a)	Unclear (b)	Unclear (e)	No (f)	No (i)
Nezvalova-Henriksen et al, 2010[184]	Yes	Unclear (a)	Unclear (c)	Yes	Unclear (g)	Yes
OLESEN 2000[187]	Yes	Unclear (a)	Unclear (d)	Yes	Unclear(h)	Yes

(a) Dropouts not reported.
(b) Triptan use was self reported.
(c) Triptan use was self reported and migraine diagnosis was not validated.
(d) The migraine control group was women who redeemed prescriptions before conception; it is possible that prescriptions redeemed before pregnancy were used during pregnancy, therefore triptan exposure could be underestimated.
(e) Outcomes measured with Self report questionnaire and heterogeneity of outcome assessment within the study.
(f) Univariate analysis of confounding factors undertaken- those that were significant were adjusted for (still birth outcome only).
(g) Concomitant medication use not identified as a potential confounding factor, other essential confounding factors identified.
(h) Does not report Odds Ratio s (OR). ANOVA used to analyse continuous outcomes. Chi squared used to analyse categorical data and, Fishers exact test used to compare rate of major birth defects between groups.

Table 196: Pregnant women with migraine exposed to triptans vs pregnant women with migraine not exposed to triptans – Clinical summary of findings

Outcome	Number of studies	Triptan exposed	Migraine control	Effect size
Spontaneous abortion[227]	1	11/96 (11.5%)	6/96 (6.3%)	OR (95% CI)*: 1.94 (0.69, 5.448)
Therapeutic abortion[227]	1	4/96 (4.2%)	2/96 (2.1%)	OR (95% CI)*: 2.04 (0.37, 11.43)
Gestational age <37 weeks	3	8/96 (8.4%) [227]	16/96 (16.8%)	OR (95% CI)*: 0.45 (0.18, 1.12)
		86/1535 (5.6%)[184]	30/373 (8.0%)	OR (95% CI)*: 0.68 (0.44, 1.05)
		5/34 (14.7%)[187]	3/89 (3.4%)	OR (95% CI)**: 3.3 (1.3, 8.5). OR (95% CI)*: 4.94 (1.11, 21.97)
Major birth defects	2	1/82 (1.2%)[227]	1/90 (1%)	RR: 1.05† OR (95% CI)*: 1.10 (0.07, 17.86)
		46/1535 (3%)[184]	11/373 (2.9%)	OR (95% CI)*: 1.02 (0.52, 1.98)
Any malformations[184]	1	75/1535 (4.9%)	22/373 (5.9%)	OR (95% CI)*: 0.82 (0.50, 1.34)
Stillbirth[184]	*1*	*0/1535*	*2/373 (0.5%)*	OR (95% CI)*: 0.05 (0.00, 1.01)
Perinatal death[184]	1	6/1535 (0.4%)	3/373 (0.8%)	OR (95% CI)*: 0.48 (0.12, 1.94)
Death during 1st 12 months of life[184]	1	5/1535 (0.3%)	0/373	OR (95% CI)*: 2.68 (0.15, 48.65)
Low birth weight (<2500g)	2	65/1535 (4.2%)[184]	19/373 (5.1%)	OR (95% CI)*: 0.82 (0.49, 1.39)
		1/34 (2.4%)[187]	5/89 (5.6%)	OR (95% CI)**: 2.3 (0.3, 17.6)

Outcome	Number of studies	Triptan exposed	Migraine control	Effect size
				OR (95% CI)*: 0.51 (0.06, 4.52)
APGAR[(a)] score <7 at 1 minute[184]	1	88/1535 (5.7%)	18/373 (4.8%)	OR (95% CI)*: 1.20 (0.71, 2.02)
APGAR[(a)] score <7 at 5 minutes[184]	1	22/1535 (1.4%)	4/373 (1.1%)	OR (95% CI)*: 1.34 (0.46, 3.92)

(a) APGAR= a method to assess the health of a newborn child immediately after birth
*** Crude odds ratio (95% confidence interval) calculated by NCGC*
*** Adjusted odds ratio (95% confidence interval) calculated by study*
† Relative risk, calculated by study

24.1.3.2 Economic evidence

No economic evidence comparing pregnant women with migraine exposed to triptans vs pregnant women with migraine not exposed to triptans were identified.

24.1.3.3 Evidence statements

Although imprecision was not assessed for prognostic reviews the statement of uncertainty reflects the GDG's confidence of the evidence.

Clinical:

One study with 192 people suggested that pregnant women with migraine who took triptans during pregnancy have a higher incidence of spontaneous abortion than those who did not take triptans during pregnancy, but there is considerable uncertainty. [Very low quality].

One study with 192 people suggested that pregnant women with migraine who took triptans during pregnancy have a higher incidence of therapeutic abortion than those who did not take triptans, but there is considerable uncertainty. [Very low quality].

In three studies with 2193 people, there is too much uncertainty to determine whether there is a difference between pregnant women with migraine who took triptans during pregnancy and those who did not take triptans during pregnancy or those who were assumed not to have taken triptans during pregnancy in the number of infants born at less than 37 weeks gestation. [Very low quality].

In two studies with 2080 people, there is too much uncertainty to determine whether there is a difference between pregnant women with migraine who took triptans during pregnancy and those who did not take triptans during pregnancy in the number of infants with major birth defects. [Very low quality].

One study with 1708 people suggested that pregnant women with migraine who took triptans during pregnancy have a lower incidence of infants with any congenital malformation than those who did not take triptans during pregnancy, but there is considerable uncertainty. [Very low quality].

One study with 1708 people suggested that pregnant women with migraine who took triptans during pregnancy have lower incidence of stillbirth than those who did not use triptans during pregnancy, but there is considerable uncertainty. [Very low quality].

One study with 1708 people suggested that in pregnant women with migraine who took triptans during pregnancy there is a lower incidence of perinatal death than those who did not use triptans during pregnancy, but there is considerable uncertainty. [Very low quality].

One study with 1708 people suggested that in pregnant women with migraine who took triptans during pregnancy there is a higher incidence of infant death during the first 12 months of life than those who did not use triptans during pregnancy, but there is considerable uncertainty. [Very low quality].

Two studies with 2031 people suggested that in pregnant women with migraine who took triptans during pregnancy there is a lower incidence of low birth weight infants (<2500g) than in those who did not use triptans during pregnancy or in those who were assumed to not to have taken triptans during pregnancy, but there is considerable uncertainty. [Very low quality].

One study with 1708 people suggested that in pregnant women with migraine who took triptans during pregnancy there is a higher incidence of APGAR score <7 at 1 minute than those who did not take triptans during pregnancy, but there is considerable uncertainty. [Very low quality].

One study with 1708 people suggested that in women who took triptans during pregnancy there is a higher incidence of APGAR score <7 at 5 minutes than in women who used triptans in the 6 months prior to pregnancy, but there is considerable uncertainty. [Very low quality].

Economic:

No economic evidence comparing pregnant women with migraine exposed to triptans vs pregnant women with migraine not exposed to triptans were identified.

24.1.3.4 Recommendations and link to evidence

See recommendations and link to evidence in section 24.2.

24.1.4 Verapamil

24.1.4.1 Clinical evidence

See evidence tables in appendix section E.5.1, forest plots in Figures 239-244, appendix G.4.1.

One study was included in this review[265]. This study included pregnant women who had taken any calcium channel blocker. The outcomes for women taking the calcium channel blocker verapamil were reported separately, so this data was included in the review.

The population of the study who had the presence of risk factor was pregnant women who had been exposed to verapamil, though it is not stated whether the women were taking verapamil for migraine or for other indications.

The group with the absence of risk factor were pregnant women who had been counselled during pregnancy about exposures known to be non-teratogenic.

The study reported results that were adjusted for the following confounding variables: maternal age, concomitant medication, alcohol and cigarette consumption, previous miscarriage and birth defects in previous offspring.

Table 197: Pregnant women exposed to verapamil vs pregnant women not exposed to calcium channel blockers – Quality assessment

Reference	Representative population sample	Loss to follow up	Prognostic factor measured appropriately	Outcomes adequately measured	Confounders accounted for	Appropriate statistical analysis
Weber-Schoendorfer et al, 2008[265]	Yes [(a)]	Unclear [(b)]	Unclear [(c)]	Unclear [(d)]	Yes	Yes

(a) Study included pregnant women taking any calcium channel blocker, but separates the results for verapamil.
(b) Dropouts not reported.
(c) Prognostic factor measured by self report questionnaire.
(d) Outcomes measured by questionnaire; variation in person competing questionnaire-could be women, physician or paediatrician.

Table 198: Pregnant women exposed to verapamil vs pregnant women not exposed to calcium channel blockers – Clinical summary of findings

Serious adverse event	WEBER 2008[265]
Miscarriage	*Verapamil exposed:* 4/62 *Control:* 59/806 *OR (95% CI)**:* 0.87 (0.31, 2.49)
Stillbirth (excluding elective termination of pregnancy)	*Verapamil exposed:* 1/62 *Control:* 6/806 *OR (95% CI)**:* 2.19 (0.26, 18.45)
Elective termination of pregnancy (ETOP)	*Verapamil exposed:* 4/62 *Control:* 30/806 *OR (95% CI)**:* 1.78 (0.61, 5.24)
Pre-term children (<37 weeks)	*Verapamil exposed:* 12/62 *Control:* 47/806 *OR (95% CI)**:* 3.88 (1.93, 7.77)
All birth defects	*Verapamil exposed:* 6/62 *Control:* 33/806 *OR (95% CI)**:* 2.51 (1.01, 6.24)
Major birth defects	*Verapamil exposed:* 2/62 *Control:* 14/806 *OR (95% CI)**:* 1.89 (0.42, 8.49)

*OR (95% CI)**= crude Odds Ratio (95% confidence interval) calculated by NCGC*

24.1.4.2 Economic evidence

No economic evidence comparing pregnant women exposed to verapamil with pregnant women not exposed to verapamil were identified.

24.1.4.3 Evidence statements

Although imprecision was not assessed for prognostic reviews the statement of uncertainty reflects the GDG's confidence of the evidence.

Clinical:

One study with 868 pregnant women suggested that there is a lower incidence of miscarriage in pregnant women who take verapamil compared to pregnant women who do not take a calcium channel blocker, but there is considerable uncertainty. [Very low quality].

One study with 868 pregnant women suggested that there is a higher incidence of still births in pregnant women who take verapamil compared to pregnant women who do not take a calcium channel blocker, but there is considerable uncertainty. [Very low quality].

One study with 868 pregnant women suggested that there is a lower incidence of elective termination of pregnancy in pregnant women who take verapamil compared to pregnant women who do not take a calcium channel blocker, but there is considerable uncertainty. [Very low quality].

One study with 868 pregnant women suggested that there is a higher incidence of preterm children (<37 weeks gestation) in pregnant women who take verapamil compared to pregnant women who do not take a calcium channel blocker, but there is considerable uncertainty. [Very low quality].

One study with 868 pregnant women suggested that there is a higher incidence of all birth defects in pregnant women who take verapamil compared to pregnant women who do not take a calcium channel blocker, but there is some uncertainty. [Very low quality].

One study with 868 pregnant women suggested that there is a higher incidence of major birth defects in pregnant women who take verapamil compared to pregnant women who do not take a calcium channel blocker, but there is considerable uncertainty. [Very low quality].

Economic:

No economic evidence comparing pregnant women exposed to verapamil with pregnant women not exposed to verapamil were identified.

24.2 Recommendations and link to evidence

Recommendations	**Offer pregnant women paracetamol for the acute treatment of migraine. Consider the use of a triptan[oo] or an NSAID after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy.**
Relative values of different outcomes	The GDG considered all serious adverse events reported for decision making. This recommendation was also made partially on GDG informal consensus.
Trade off between clinical benefits and harms	The GDG noted that many people continue to suffer migraine during pregnancy as they avoid medication due to not being certain of the risks. It was agreed that the evidence reviewed did not indicate an increased risk of the use of triptans during pregnancy and therefore people should be made aware of this to avoid suffering unnecessarily. There is not conclusive evidence of safety, but the evidence is reassuring. High doses of aspirin recommended for migraine are considered potentially harmful in pregnancy so should be avoided in pregnancy. The GDG agreed that possible risks NSAID during pregnancy are known and their use should be

[oo] At the time of publication (September 2012), triptans (with the exception of nasal sumatriptan) did not have a UK marketing authorisation for this indication in people aged under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

	avoided during the third trimester.
Economic considerations	No economic evidence was identified specifically on the treatment of migraine during pregnancy. The GDG believed the conclusions and economic considerations described in chapter 11 are also applicable to this specific population.
Quality of evidence	The evidence reviewed was very low quality evidence. The use of NSAID was not reviewed as the GDG agreed this was already established. No economic evidence was identified specifically on the treatment of migraine during pregnancy.
Other considerations	The reviewed evidence was in people with mild to moderate migraine only. The relative contraindications depending on the stage of pregnancy should be considered when prescribing acute treatments. There is some evidence that migraine often resolves during pregnancy (in 70% of people)[164,230] which may reduce the need for acute treatment in many people.

Recommendations	**Seek specialist advice if prophylactic treatment for migraine is needed during pregnancy.**
Relative values of different outcomes	This recommendation was based on GDG informal consensus.
Trade off between clinical benefits and harms	The GDG agreed that some people may require prophylaxis during pregnancy, in the absence of evidence for safety of recommended prophylactic treatment during pregnancy, a specialist should be consulted.
Economic considerations	No economic evidence was identified on this topic. Seeking specialist advice is associated with some costs (i.e. the cost of the specialist's time). This could be simply a phone call which would not represent an intensive use of NHS resources. The GDG considered this extra cost to be justified given the potential risks associated with migraine prophylaxis during pregnancy.
Quality of evidence	This recommendation was based on GDG consensus.
Other considerations	The GDG considered that if prophylaxis was required, specialist advice should be obtained so that women could receive treatment during their pregnancy. This could be advice over the telephone, to avoid any delay in prescribing treatment that would be associated with referral.

Recommendations	**Seek specialist advice if treatment for cluster headache is needed during pregnancy.**
Relative values of different outcomes	The GDG considered all serious adverse events reported. This recommendation was based on GDG consensus.
Trade off between clinical benefits and harms	The GDG agreed that there was not conclusive evidence for the safety of verapamil during pregnancy, and no evidence was available on the risks of oxygen during pregnancy. Decision whether or not to use verapamil may be patient choice weighing up risks and benefits. No evidence was available on the use of oxygen however the GDG were aware that the amount of exposure is of concern, and there are risks to premature babies.
Economic considerations	Referring women with cluster headache during pregnancy to a specialist is

	associated with the cost of an extra visit. The GDG considered this extra cost to be justified given the potential risks associated with headache treatment during pregnancy.
Quality of evidence	The only available evidence in this review was very low and low quality evidence from people using calcium channel blockers for a range of reasons (not necessarily cluster headache). No evidence was available for the safety of oxygen treatment during pregnancy. No economic evidence was available on women with cluster headache during pregnancy.
Other considerations	The GDG noted that there is anecdotal evidence of a two-thirds chance that an individual won't get a bout of cluster headache during pregnancy. Clinical experience suggests most women use oxygen and stop taking verapamil. Steroids and occipital nerve block are also a possibility rather than verapamil. The GDG considered that if prophylaxis was required, specialist advice should be obtained so that women could receive treatment during their pregnancy. This could be advice over the telephone, to avoid any delay in prescribing treatment that would be associated with referral.

25 Combined hormonal contraception use in girls and women with migraine with or without aura

25.1 Introduction

Migraine is common condition in women during their reproductive years. Many women who have migraine require contraception. Combined hormonal contraception, in particular the oral contraceptive pill, can be used to manipulate the timing and onset of menstruation and could theoretically be helpful to women who particularly suffer from pure menstrual or menstrual related migraine. Epidemiological evidence has suggested increased risk of ischaemic stroke in women with migraine with aura[75]. The GDG were interested in the balance of risks in relation to hormonal contraception for women with migraine.

25.1.1 Clinical question

What risks are associated with use of hormonal contraception in females aged 12 or over with migraine?

A literature search was conducted for cohort studies and case control studies comparing the incidence of serious adverse events in women with migraine who were using combined hormonal contraception to women with migraine who were not using any combined hormonal contraception. Studies were included if they were in a broader population but data in women with and without migraine was able to be separated (See protocol C.3.2).

The evidence available for this question was limited and an expert was co-opted to provide the GDG with advice. They attended the meeting where the evidence was presented and informed discussion, but were not present for, or involved in, any discussions about recommendations.

25.1.2 Migraine and hormonal contraception

25.1.2.1 Clinical evidence

See evidence tables in appendix section E.5.2, forest plots in Figures 245-249, appendix G.4.2.

Two studies were included in this review. The populations did not match the criteria in the review protocol correctly, however the GDG agreed they did provide some useful relevant information and therefore they were included in the analysis.

One study assessed the risk of stroke in women with migraine and combined hormonal contraception use was adjusted for as a confounding factor[148,149]. In the other study, odds ratios were presented in comparison to a baseline group of women who did not have migraine or use combined hormonal contraception[34].

Oral contraceptives were used as the mode of combined hormonal contraception in both studies. No information was provided on the types of oral contraceptives that were used specific ally by women with migraine.

No evidence was found on worsening of migraine with the use of combined hormonal contraception.

Studies were excluded when the data were not interpretable. This was also the case if data were from older studies and presented relative risks and odds ratios interchangeably and raw data were not provided for analysis.

Table 199: Migraine and hormonal contraception - Summary of study quality

Reference	Representative population sample	Attrition bias	Prognostic factors measured appropriately	Outcomes adequately measured	Key confounders accounted for and appropriate analysis used	Overall quality
Chang 1999*[34]	Unclear[(a)]	No	Unclear [(b)]	Yes	Yes	LOW
Lidegaard 2002[148,149]	Unclear[(a)]	No	Unclear [(b)]	Yes	No [(C)]	VERY LOW

** Outcomes measured were ischaemic and haemorrhagic stroke.*
(a) Both were case control studies in people who already had the outcome; unclear if representative of all people with migraine.
(b) Potential recall bias as cases and controls may provide information differently.
(c) Reports crude odds ratios of stroke in people with migraine and odds ratios adjusted for oral contraceptive use only in the same group; other confounders were not adjusted for in this analysis.

Table 200: Migraine and hormonal contraception - Clinical summary of findings

Reference	Outcome	Adjusted odds ratios	95% confidence interval
Chang 1999(a)[34]	**Migraine with hormonal contraception vs No migraine with no hormonal contraception**		
	Ischaemic stroke	16.9	2.72-105
	Haemorrhagic stroke	1.10	0.40- 3.02
	Migraine without hormonal contraception vs No migraine with no hormonal contraception		
	Ischaemic stroke	2.27	0.69-7.47
	Haemorrhagic stroke	1.13	0.60-2.13
Lidegaard 2002(b)[148,149]	**Migraine vs no migraine (adjusted for oral contraceptive use)**		
	Stroke	3.20	2.5-4.10

(a) Adjusted for high blood pressure, education, smoking categories, family history of migraine, alcohol consumption and social class.
(b) Not adjusted for any other confounding factors except oral contraceptive use; crude odds ratio: 3.2.

25.1.2.2 Economic evidence

No relevant economic evaluations were identified which compared women with migraine who used hormonal contraception vs women without migraine who did not use hormonal contraception, or women with migraine vs women without migraine.

25.1.2.3 Evidence statements

Although imprecision was not assessed for prognostic reviews the statement of uncertainty reflects the GDG's confidence of the evidence.

Clinical:

One study with 1027 participants that adjusted for all major confounders showed that women with migraine who use combined hormonal contraception have higher odds of ischaemic stroke compared to women who do not have migraine and do not use hormonal contraception. [Low quality].

One study with 1027 participants that adjusted for all major confounders suggested that women with migraine who use combined hormonal contraception have higher odds of haemorrhagic stroke as compared to women who do not have migraine and do not use hormonal contraception, but the effect size is too small to be clinically effective and there is considerable uncertainty. [Low quality].

One study with 1027 participants that adjusted for all major confounders suggested that women with migraine who do not use combined hormonal contraception have higher odds of ischaemic stroke compared to women who do not have migraine and do not use combined hormonal contraception, but there is considerable uncertainty. [Low quality].

One study with 1027 participants that adjusted for all major confounders suggested that women with migraine who do not use combined hormonal contraception have higher odds of haemorrhagic stroke compared to women who do not have migraine and do not use combined hormonal contraception, but the effect size is too small to be clinically effective and there is considerable uncertainty. [Low quality].

One study with 365 women with migraine which did not adjust for other confounding factors showed that the odds of stroke in women with migraine remains unchanged when adjusted for oral contraceptive use. [Very low quality].

Economic:

No relevant economic evaluations were identified which compared women with migraine who used combined hormonal contraception vs women without migraine who did not use combined hormonal contraception, or women with migraine vs women without migraine.

25.2 Recommendations and link to evidence

Recommendations	**Do not routinely offer combined hormonal contraceptives for contraception to women and girls who have migraine with aura.**
Relative values of different outcomes	The GDG considered the incidence of cardiovascular events (thromboembolic stroke) to be the most important outcome. GDG informal consensus was also used to form this recommendation.
Trade off between clinical benefits and harms	There is an increased risk of ischaemic stroke in people with migraine with aura. This is multiplied in people using combined hormonal contraception.
Economic considerations	There are no direct substantial costs associated with this recommendation. On the other hand, this recommendation could save costs as it aims at avoiding serious adverse events such as ischaemic stroke which would require costly treatment.
Quality of evidence	This recommendation was based on the consensus opinion of the GDG. There was limited evidence from this review regarding the use of hormonal contraception in women with migraine. The population in one study [34] consisted of over 70% of people with migraine with aura which is a greater proportion of people with aura than in the migraine population. No economic evidence was found on this question.
Other considerations	The GDG used expert advice and informal consensus to inform the development of this recommendation. The GDG agreed that although the evidence available was of low quality, and the absolute numbers of people affected is low, the potentially devastating effect of a stroke in a young woman should be avoided if possible. Given that there are many other forms of contraception now available the GDG considered the use of combined hormonal contraception is not justified in this group. The combined oral contraceptive pill can used for other medical reasons, for example, to manage conditions such as polycystic ovarian syndrome. The balance of risks and benefits are likely to be different than for a woman using the combined hormonal contraception for contraception alone and this balance would need consideration between healthcare professional and patient. This recommendation is therefore specific to contraception. The current advice from the WHO in Medical Eligibility criteria for

	contraceptive use[49] recommends that oral contraceptive pill should not be used in women with aura at any age. The UK eligibility criteria for contraceptive (UKMEC) use recommends that the use of combined hormonal contraceptive methods represents an unacceptable risk for women with aura; and that if a person has not had any migraine with aura for more than 5 years the risk generally outweigh the benefits. The UK Faculty of Sexual and Reproductive Health (www.fsrh.org/) in recent guidance on use of combined hormonal contraception re-iterates the UKMEC advice that the use of combined hormonal contraception presents an unacceptable risk in women with migraine with aura[78]. The GDG were aware that the recommendation could be viewed as potentially restrictive in that the ICHD criteria indicate that two attacks of migraine with aura are required for an ICHD diagnosis of migraine with aura disorder and this guideline is recommending a less strict definition for the generalist. The GDG considered that the wording of the recommendation allowed the healthcare professional to use clinical judgement or call on expert advice if needed.

26 Abbreviations

Acronym	Abbreviation
ACA	Available case analysis
ACE (inhibitor)	Angiotensin-converting-enzyme (inhibitor)
AE	Adverse events
AIDS	Acquired immune deficiency syndrome
ANOVA	Analysis of variance
ARB	Angiotensin II receptor blockers
ASA	Acetylsalicylic acid (aspirin)
AZT	Azidothymidine
bid	Twice daily
BNF	British National Formulary
Ca^{++}	Calcium
CCA	Cost-consequences analysis
CCB	Calcium channel blocker
CCT	Controlled clinical trial
CDH	Chronic daily headache
CEA	Cost-effectiveness analysis
CI	Confidence interval
CNS	Central nervous system
COCP	Combined oral contraceptive pill
CSMT	Chiropractic spinal manipulative therapy
CT	Computerised tomography (scan)
CUA	Cost-utility analysis
df	Degrees of freedom
DH	Department of Health
DHE	Dihydroergotamine
ECG	Electrocardiogram
FDI	Functional disability inventory
GDG	Guideline development group
GP	General practitioner
GPRD	General practice research database
GPwSI	General practitioner with a special interest (in headache)
GRADE	Guidelines Recommendations Assessment Development Evaluation
GRP	Guideline review panel
HADS	Hospital anxiety and depression scale
HES	Hospital episode statistics
HIV	Human immunodeficiency virus
HIT6	Headache impact test-6
HRQL	Health related quality of life
HRT	Hormone replacement therapy
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

Acronym	Abbreviation
ICHD	International classification of headache disorders
ICU	Intensive care unit
IHS	International Headache Society
im	Intramuscular
INB	Incremental net benefit
IQR	Inter quartile range
ITT	Intention to treat (analysis)
iv	Intravenous
LS	Least square
MAO	Monoamine oxidase
MHRA	Medicines and healthcare products regulatory agency
MIDAS	Migraine disability assessment
mITT	Modified intention to treat (analysis)
MOH	Medication overuse headache
MRI	Magnetic resonance imaging
MSQoL	Migraine specific quality of life
N/A	Not applicable
NHS	National health service
NICE	National institute for health and clinical excellence
NMA	Network meta-analysis
NNT	Number needed to treat
NPR	National patient register
NPV	Negative predictive value
NR	Not reported
NS	Not significant
NSAID	Non-steroidal anti-inflammatory drug
OCP	Oral contraceptive pill
OR	Odds ratio
PASA	NHS purchasing and supply agency
pedMIDAS	Paediatric migraine disability assessment
PICO	Framework incorporating patients, interventions, comparisons, outcomes
PP	Per protocol
PPIP	Patient and public involvement programme
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised clinical trial
RR	Relative risk or risk ratio
sc	Subcutaneous
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean

Acronym	Abbreviation
SF-36	Short form-36
SR	Systematic review
SNRI	Serotonin-norepinephrine re-uptake inhibitor
SSRI	Selective serotonin re-uptake inhibitor
TAR	Therapist assisted relaxation
TCM	Traditional Chinese medicine
TENS	Transcutaneous electrical nerve stimulation
TIA	Transient ischaemic attack
tid	Three times a day
TTH	Tension type headache
VAS	Visual analogue scale
VRS	Verbal rating scale
vs	Versus
WHO	World Health Organisation

27 Glossary

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acute glaucoma	Also known as acute narrow angle glaucoma. Glaucoma is an uncommon eye condition that results from blockage of the drainage of fluid from the eye. Symptoms of acute glaucoma may include headache with a painful red eye and misty vision or haloes, and in some cases nausea. Acute glaucoma may be differentiated from cluster headache by the presence of a semi-dilated pupil as compared to the presence of a constricted pupil in cluster headache.
Acute medical admission	A medical admission concerned with the immediate and early specialist management of adults suffering from a wide range of medical conditions who present to, or from within, hospitals, requiring urgent or emergency care.
Adherence	The extent to which the person's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the person is free to decide whether or not to adhere to the doctor's recommendation.
Adjustment	A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.
Appraisal of Guidelines, Research and Evaluation (AGREE)	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Ataxia	Lack of balance and/or coordination
Available case analysis	A strategy for analysing data from a randomised controlled trial which assumes that participants missing are missing at random. Analysis of participants for whom there is outcome data reported.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Bout (cluster headache bout)	The duration over which recurrent cluster attacks are occurring, usually lasts some weeks or months.

Term	Definition
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group.
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cochrane Library	A regularly updated electronic collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Combined hormonal contraception	A form of birth control which suppresses ovulation by the combined actions of the hormones oestrogen and progesterone.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the

Term	Definition
	true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may used when there is a lack of strong evidence on a particular topic. Unless specifically stated, this refers to informal consensus methods. (See GDG informal consensus).
Control group	A group of people recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Diplopia	Double vision
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.

Term	Definition
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Ergot	Refers to all ergot and ergotamine derivatives.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Expert opinion	Opinion derived from seminal works and appraised national and international guidelines. This also includes invited clinical experts.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health related variables.
GDG informal consensus	GDG informal consensus may be used when there is a lack of strong evidence on a particular topic to reach an agreement for a recommendation. Informal consensus methods involved discussion based on shared clinical experience and voting for agreement. (See consensus methods).
General practitioner with a special interest (GPwSI)	GPs that supplement their generalist role by delivering a clinical service beyond the normal scope of general practice. The GPwSIs referred to in this guideline are those with a special interest in headache.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Giant cell arteritis	Giant cell arteritis, also commonly known as temporal arteritis, is characterised by the inflammation of the wall of medium and large arteries. Branches of the carotid artery and the ophthalmic artery are preferentially involved giving rise to symptoms of headache, visual disturbances and jaw claudication.
Gold standard	See 'Reference standard'.
GRADE / GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.

Term	Definition
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Imprecision	Results are imprecise when studies include relatively few participants and few events and thus have wide confidence intervals around the estimate of effect relative to the clinically important threshold.
Immunosuppressive	An agent capable of suppressing the immune response of an individual.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per person associated with an intervention minus the mean cost per person associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question or recommendation made.
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Intervention	Healthcare action intended to benefit the person being treated, for example, drug treatment, surgical procedure, psychological therapy.
Intracranial	Intracranial refers to anything that is within the cranium, the bony structure that houses and protects the brain.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention

Term	Definition
	compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a person would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Limitations (literature review)	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of effect.
Loss to follow-up	Also known as attrition. The loss of participants during the course of a study. Participants that are lost during the study are often call dropouts.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meningitis	Meningitis is the inflammation of the meninges, the thin membranous covering of the brain and the spinal cord. This is most often caused by a bacterial or viral infection and characterized by fever, vomiting, intense headache, and stiff neck.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
MID (minimal important difference)	The minimum difference in benefit or harm in the outcome of interest that patients and health care professionals perceive as clinically important.
Monocular visual symptoms	Visual symptoms that occur in one eye only
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Network meta-analysis	A network meta-analysis is a method for simultaneously comparing multiple treatments in a single meta-analysis.
Non-oral	This guideline refers to buccal, intravenous, intramuscular or rectal preparations as non-oral.
Number needed to treat (NNT)	The number of people that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Orthostatic headache	Headache that is related to or caused by sitting or standing upright.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See ‘Intermediate outcome’.
Peri-menstrual	Relating to, being in, or occurring around the menstrual period
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the

Term	Definition
	risk that a possible association could be missed.
Positive diagnosis	A positive diagnosis is one based on the typical clinical picture that does not require any further investigations to exclude alternative explanation for a patient's symptoms.
Primary care	Healthcare delivered to people outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prophylaxis	A measure taken for the prevention of a disease or condition.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	A systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the person's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Reference standard	The reference standard is the test which defines whether the person has a disease condition or not. Ideally, it should be a diagnostic test that is 100% sensitive and 100% specific for the disease in question and should be applied to all the participants in the study. Also known as 'gold standard'.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and

Term	Definition
	care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of participants protects against this bias.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Specialist	Within this guideline, the term specialist refers to either a neurologist, GPwSI (in headache), paediatric neurologist or paediatrician with a special interest in headache.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Temporal arteritis	Also called giant cell arteritis / cranial arteritis. Temporal arteritis is characterized by inflammation of the walls of the temporal arteries in the head (see Giant cell arteritis).
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Valsava	A forceful attempt at expiration while holding the nostrils closed and keeping the mouth shut, for example, in strenuous coughing, straining during a bowel movement, or lifting a heavy weight.

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