NCGC National Clinical Guideline Centre

Headaches

Diagnosis and management of headaches in young people and adults

Clinical Guideline 150

Appendices

September 2012

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Appendices

Appendix A: Scope

A.1 Guideline title

Headaches: diagnosis and management of headaches in young people and adults

A.1.1 Short title

Headaches

A.2 The remit

The Department of Health has asked NICE: 'To produce a clinical guideline on the diagnosis and management of headaches in adolescents and adults.'

A.3 Clinical need for the guideline

A.3.1 Epidemiology

a) Headache is the most common neurological problem presented to general practitioners and to neurologists. Headache accounts for 4% of primary care consultations and up to 30% of neurology appointments. The International Classification of Headache Disorders (ICHD-11) lists more than 200 headache types.

b) Headache disorders are classified as primary or secondary. The most common primary headache disorders are tension-type headache, migraine and cluster headache. Secondary headaches are attributed to underlying disorders and include headache associated with giant cell arteritis, raised intracranial pressure and medication overuse.

c) Headache disorders are a cause of pain and disability to individuals and also a significant 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.

A.3.2 Current practice

a) Healthcare professionals can find the diagnosis of headache difficult, and both people with headache and their healthcare professionals can be concerned about possible underlying causes.

b) People with headache alone are unlikely to have 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.

c) Many people with headache do not have an accurate diagnosis of headache type. GPs lack confidence in their ability to diagnose common headache disorders and can feel under pressure to refer patients for specialist opinion and investigation. Most common headache types are diagnosed on clinical history, and most common primary headaches can be managed in primary care.

d) Improved recognition of primary headaches would help the generalist clinician to manage headaches more effectively, allow better targeting of treatment and potentially improve patient quality of life and reduce unnecessary investigations.

A.4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

A.4.1 Population

A.4.1.1 Groups that will be covered

a) Young people (12 years and older) and adults.

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

A.4.1.2 Groups that will not be covered

a) Children younger than 12 years.

A.4.2 Healthcare setting

a) All settings in which NHS care is received.

A.4.3 Clinical management

A.4.3.1 Key clinical issues that will be covered

a) Diagnosis of the following primary headaches:

- migraine with or without aura
- menstrual related migraine
- chronic migraine
- tension-type headache
- cluster headache.

Consideration will also be given to people whose headaches have characteristics of more than one primary headache syndrome.

b) Diagnosis of medication overuse headache.

c) Characteristics of headaches that may be related to serious underlying disease and need specific investigations and management.

d) Acute pharmacological management of the headache types specified in 4.3.1 a, with:

- antiemetics
- aspirin
- non-steroidal anti-inflamatory drugs (NSAIDs)
- opioids
- oxygen
- paracetamol

- triptans.

e) Prophylactic pharmacological treatment for the headache types specified in 4.3.1 a, with:

- ACE inhibitors and angiotensin II receptor antagonists
- antidepressants (serotonin–norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors and tricyclics)
- beta blockers (for example, propranolol)
- calcium channel antagonists
- corticosteroids
- lithium
- melatonin
- neuromodulators or anticonvulsants
- serotonergic modulators (for example, pizotifen).

f) Non-pharmacological treatment for the headache types specified in 4.3.1 a, with:

- acupuncture
- dietary supplements, (for example, magnesium, vitamin B12, coenzyme Q10 and riboflavin)
- education and self-management programmes
- imaging
- lifestyle factors (dietary manipulation and exercise)
- manual therapies
- psychological therapies (for example, cognitive behaviour therapy [CBT]).

g) Information and support for patients and carers.

h) Prevention and treatment of medication overuse headache.

i) Management during pregnancy.

j) Choice of contraception in women with migraine.

k) Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

A.4.3.2 Clinical issues that will not be covered

a) Management of primary headaches other than those specified in 4.3.1 a.

b) Investigation and management of secondary headache other than medication overuse headache.

c) Diagnosis and management of cranial neuralgias and facial pain.

d) Management of comorbidities.

A.4.4 Main outcomes

a) Time to freedom from pain, and remaining pain free during the 24 hours following acute treatment.

b) Changes in patient-reported headache frequency and intensity; for example, headache days in the past month, days lost from usual activity, measures of headache frequency, intensity and effect on life. This last point will be measured using headache specific questionnaires, for example the headache impact test or migraine disability assessment test.

c) Functional health status and health-related quality of life (for example using the SF-36 health survey or EuroQoL).

d) Over-the-counter drug usage.

e) Medication overuse headache.

f) Resources use, including GP consultation, A&E attendance, investigations and referral to secondary care.

A.4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

Significant issues for potential health economic analysis are the cost effectiveness of imaging as a management strategy, and sequencing of drugs for treatment.

A.4.6 Status

A.4.6.1 Scope

This is the final scope.

A.4.6.2 Timing

The development of the guideline recommendations will begin in December 2010.

A.5 Related NICE guidance

A.5.1 Published guidance

- Depression. NICE clinical guideline 90 (2009). Available from www.nice.org.uk/guidance/CG90
- Glaucoma. NICE clinical guideline 85 (2009). Available from www.nice.org.uk/guidance/CG85
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Head injury. NICE clinical guideline 56 (2007). Available from www.nice.org.uk/guidance/CG56
- Hypertension. NICE clinical guideline 34 (2006). Available from www.nice.org.uk/guidance/CG34
- Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005). Available from www.nice.org.uk/guidance/CG27
- Anxiety. NICE clinical guideline 22 (2004). Available from www.nice.org.uk/guidance/CG22

A.5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Percutaneous closure of patent foramen ovale for recurrent migraine. NICE Interventional procedure guidance. Publication expected Winter 2010.

A.6 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix B: Declarations of interest

B.1 Ria Bhola

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Declared Personal Pecuniary interest: Participated in an advisory group meeting on the use of botulinum toxin-A in chronic migraine for Allergan (May 2010).	None
Second GDG Meeting [7/01/11]	Declared Personal Pecuniary interest: Consulting for Neuralieve on the single use Transcranial Magnetic Stimulation device (STMS) declared on 21.1.11.	None
Third GDG Meeting [18.02.11]	Nothing to declare	None
Fourth GDG Meeting [25.03.11]	Nothing to declare	None
Fifth GDG Meeting [4.05.11]	Did not attend	None
Sixth GDG Meeting [3.06.11]	Did not attend	None
Seventh GDG Meeting [1.07.11]	Did not attend	None
Eighth GDG Meeting [19.08.11]	Declared Personal Pecuniary interest: Paid for work with the Migraine Trust to write an online course for nurses on Headache (work expected to continue for a number of months). Declared 24/09/11.	None
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Did not attend	None
Twelfth GDG Meeting [29.06.12]	Nothing to declare	None

B.2 Sam Chong

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Nothing to declare	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Did not attend	None
Fourth GDG Meeting [25.03.11]	Did not attend	None
Fifth GDG Meeting [4.05.11]	Nothing to declare	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Nothing to declare	None
Eighth GDG Meeting [19.08.11]	Nothing to declare	None
Ninth GDG Meeting [7.10.11]	Did not attend	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Declared Personal Pecuniary interest: Lecture and Advisory Board Meeting paid for by Astellas, maker of the 8% Capsaicin patch Declared Personal non-pecuniary interest: Helping Prof Chambers in his study on the use of clopidogrel for migraine. Have shown an interest in taking part in the Migraine and Botulinum Toxin study run by Kantar Health but have not started this study. Personal non-personal pecuniary interest: Attended European Federation of Neurological science meetings sponsored by Lundbeck.	None
Twelfth GDG Meeting [29.06.12]	Nothing to declare	None

B.4 Brendan Davies

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Declared Personal Pecuniary interest: Fee paid Medical Consultancy work for Allergan UK (declared 8/9/2010) Declared Non-Personal Pecuniary Interest: Unrestricted educational grant from Allergan to fund a specialist headache nurse and administrator for 1 year (funding received August 2011, application declared 8/9/2010, confirmed 02/12/11). Declared Personal Non-Pecuniary Interest: Trustee for UK Headache charity the Migraine Trust (declared 8/9/2010) Recent 21K unrestricted educational grant Aug 2011 for headache clinic nurse from Allegan 02/12/11. Declared Personal Non-Pecuniary Interest: Medical Advisor, UK Headache charity, Migraine Action Association (declared 8/9/2010). Council member, British Association for Study of Headache (declared 8/9/2010). Chairman of headache and pain section of ABN (Association of British neurologists) (declared 02/12/11).	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Nothing to declare	None
Fourth GDG Meeting [25.03.11]	Did not attend	None
Fifth GDG Meeting [4.05.11]	Did not attend	None
Sixth GDG Meeting [3.06.11]	Declared Personal Pecuniary interest: Commissioned to deliver talk on treatment of chronic migraine at midlands regional launch of Botox by Allergan Pharma-£1K (declared 18/06/2011)	None
Seventh GDG Meeting [1.07.11]	Nothing to declare	None
Eighth GDG Meeting [19.08.11]	Nothing to declare	None
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None

GDG meeting	Declaration of Interests	Action taken
Eleventh GDG Meeting [27.1.12]	Did not attend	None
Twelfth GDG Meeting [29.06.12]	Decared Personal pecuniary interest: Received remuneration from Allergan for teaching at a workshop on the clinical technique of Botox injection for Chronic migraine to pharmaceutical sales representatives. Declared Non-personal pecuniary interest: Received an unrestricted educational grant funding for support costs for the Keele Headache teaching courses for doctors, specialist nurses and paramedical staff interested in headache disorders to be held in September 2012. Prospective funds verbally agreed from St Jude Medical, Gammacore, Menarini and eNeura device and pharmaceutical companies.	None

B.5 Mark Dunne-Willows

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Nothing to declare	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Did not attend	None
Fourth GDG Meeting [25.03.11]	Nothing to declare	None
Fifth GDG Meeting [4.05.11]	Did not attend	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Nothing to declare	None
Eighth GDG Meeting [19.08.11]	Nothing to declare	None
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG	Nothing to declare	None

GDG meeting	Declaration of Interests	Action taken
Meeting [27.1.12]		
Twelfth GDG Meeting [29.06.12]	Nothing to declare	None

B.6 Carole Gavin

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Nothing to declare	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Did not attend	None
Fourth GDG Meeting [25.03.11]	Nothing to declare	None
Fifth GDG Meeting [4.05.11]	Nothing to declare	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Did not attend	None
Eighth GDG Meeting [19.08.11]	Nothing to declare	None
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Nothing to declare	None
Twelfth GDG Meeting [29.06.12]	Nothing to declare	None

B.7 Devina Halsall

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Nothing to declare	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Nothing to declare	None
Fourth GDG Meeting [25.03.11]	Nothing to declare	None
Fifth GDG Meeting [4.05.11]	Nothing to declare	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Nothing to declare	None
Eighth GDG Meeting [19.08.11]	Nothing to declare	None
Ninth GDG Meeting [7.10.11]	Did not attend	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Nothing to declare	None
Twelfth GDG Meeting [29.06.12]	Did not attend	None

B.9 Kay Kennis

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Nothing to declare	None
Second GDG Meeting [7/01/11]	Declared Personal Pecuniary interest: Travel grant attending BASH meetings (various drug companies) declared on 21.1.11	None
Third GDG Meeting [18.02.11]	Nothing to declare	None
Fourth GDG Meeting [25.03.11]	Nothing to declare	None
Fifth GDG Meeting [4.05.11]	Nothing to declare	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Nothing to declare	None
Eighth GDG Meeting [19.08.11]	Nothing to declare	None
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Nothing to declare	None
Twelfth GDG Meeting [29.06.12]	Nothing to declare	None

B.11 David Kernick

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Personal Pecuniary interest: Lecture and advise Allergan Advisory Board on Botox - July 2010. Guest of European Headache Society meeting Oct 2010 (Travel, accommodation & registration only) declared 1st October 2010. MSD educational video (2010). Haymarket, Sterling and Mark Allen (publishers and conference organisers). Educational articles and lectures. (Last article Oct 2010).	None
Second GDG Meeting [7/01/11]	Did not attend	None
Third GDG Meeting [18.02.11]	Nothing to declare	None
Fourth GDG Meeting [25.03.11]	Nothing to declare	None
Fifth GDG Meeting [4.05.11]	Nothing to declare	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Nothing to declare	None
Eighth GDG Meeting [19.08.11]	Nothing to declare	None
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Nothing to declare	None
Twelfth GDG Meeting [29.06.12]	Nothing to declare	None

B.13 Manjit Matharu

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Declared Personal Non Pecuniary Interest: Director of Headache Masterclass Ltd which organises educational courses on headaches for doctors (Decelared 10/10/10)	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Nothing to declare	None
Fourth GDG Meeting [25.03.11]	Nothing to declare	None
Fifth GDG Meeting [4.05.11]	Nothing to declare	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Nothing to declare	None
Eighth GDG Meeting [19.08.11]	Declared Personal Pecuniary Interest: Advisory board and honoraria for teaching courses for Allergan (Declared 15/07/11) Declared non Personal Interest The Headache Group at the National Hospital for Neurology and Neurosurgery has received unrestricted educational grants from Allergan. (Declared 15/07/11) In addition, Merck Sharpe and Dohme, and Medtronic Ltd have provided funds for organising teaching courses for doctors. (declared 8/9/2010)	None
Ninth GDG Meeting [7.10.11]	Advisory board for St Jude's medical (9/9/2011)	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Member of headache and pain section of ABN (Association of British neurologist) Declared 02/12/11	None
Twelfth GDG Meeting [29.06.12]	Nothing to declare	None

B.14 Peter May

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Nothing to declare	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Nothing to declare	None
Fourth GDG Meeting [25.03.11]	Nothing to declare	None
Fifth GDG Meeting [4.05.11]	Nothing to declare	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Nothing to declare	None
Eighth GDG Meeting [19.08.11]	Nothing to declare	None
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Nothing to declare	None
Twelfth GDG Meeting [29.06.12]	Nothing to declare	None

B.16 Wendy Thomas

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Declared Non Personal Pecuniary interest: MSD: fund website and education project for the Migraine Trust. Supported Headache UK's work with the All Party Parliamentary Group on Primary Headache Disorders. Chair of Headache UK and the donation is made through the Migraine Trust. (Declared 4/10/10). Menarini: donated £500 to the Migraine Trust and £500 to Headache UK via the Migraine Trust (declared 4/10/10). Declared Personal Non-Pecuniary interest: Chief Executive of the Migraine Trust which has an interest in the matter under consideration.	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Nothing to declare	None
Fourth GDG Meeting [25.03.11]	Did not attend	None
Fifth GDG Meeting [4.05.11]	Declared Non Personal Pecuniary: Allergan Support grant £20K (5K for all Parliamentary Group)to Migraine Trust received feb 2011 (declared 8/4/11)	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Declared Non Personal Pecuniary: 20K from Allergan and 2K from Neurolieve (TMS) for advocacy/comms work - declared on 17/06/2011	None
Eighth GDG Meeting [19.08.11]	Nothing to declare	None
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Nothing to declare	None
Twelfth GDG Meeting [29.06.12]	Declared Non-personal pecuniary interest: Grant received from Allergan, May 2012 (£25,000) to support the Migraine Trust Advocacy Service.	None

B.18 Martin Underwood

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Nothing to declare	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Declared Non Personal Pecuniary: Research grant awarded to a member of department by the General Chiropractic Council. (Declared 24/02/11). Co-aplicant on a project (observational study of adverse events from osteopathy) funded by National Council of Osteopathic Research (Declared 24/02/11). 1) A member of department, I will be leading has been awarded a research grant by general chiropractic council. 2) I am co applicant in a project funded by national council osteopathic research (Declared 24/02/11). Declared Personal Non-Pecuniary Interest: Gave president's lecture for college of chiropractors in 2011 (no fee).	None
Fourth GDG Meeting [25.03.11]	Nothing to declare	None
Fifth GDG Meeting [4.05.11]	Nothing to declare	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Declared Non-Pecuniary Interest: Commented on behalf of General Chiropractic Council on Brontfort report on manual therapy commissioned by the general chiropractic council (included manual therapy for headache) and had further input into a discussion with Advertising Standards Authority about criteria for advertising by chiropractors (no fee) (15/7/11). Co-investigator in an HTA funded trial of a cognitive behavioural approach for low back pain - with a positive result (15/7/11). Co-investigator on an research for patient benefit (NIHR) grant comparing group and individual acupuncture for OA knee 15/7/11). Declared Non Personal Pecuniary Interest: Co-investigator on two studies funded by national Council for Osteopathic research into adverse events after manual therapy defining these and doing a systematic review (15/7/11).	Did not chair afternoon session of GDG when recommendations for non-pharmacological treatments were made.
Eighth GDG Meeting [19.08.11]	Nothing to declare	None

GDG meeting	Declaration of Interests	Action taken
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Nothing to declare	None
Twelfth GDG Meeting [29.06.12]	Nothing to declare Non-personal pecuniary interest declared: After completion of the guideline and before its publication a member of Martin Underwood's division obtained substantial funding from Bayer for an investigator led study in an unrelated clinical area.	None

B.19 William Whitehouse

GDG meeting	Declaration of Interests	Action taken
First GDG meeting [3.12.10]	Nothing to declare	None
Second GDG Meeting [7/01/11]	Nothing to declare	None
Third GDG Meeting [18.02.11]	Did not attend	None
Fourth GDG Meeting [25.03.11]	Did not attend	None
Fifth GDG Meeting [4.05.11]	Did not attend	None
Sixth GDG Meeting [3.06.11]	Nothing to declare	None
Seventh GDG Meeting [1.07.11]	Nothing to declare	None
Eighth GDG Meeting [19.08.11]	Did not attend	None
Ninth GDG Meeting [7.10.11]	Nothing to declare	None
Tenth GDG Meeting [18.11.11]	Nothing to declare	None
Eleventh GDG Meeting [27.1.12]	Did not attend	None
Twelfth GDG Meeting [29.06.12]	Nothing to declare	None

B.21 Dons Coleston-Shields – co-opted expert

GDG meeting	Declaration of Interests	Action taken
Seventh GDG Meeting [1.07.11]	None	None – did not attend for recommendation discussion

B.22 George Rix – co-opted expert

GDG meeting	Declaration of Interests	Action taken
Seventh GDG Meeting [1.07.11]	None	None – did not attend for recommendation discussion

B.23 Persis Tamboly – co-opted expert

GDG meeting	Declaration of Interests	Action taken
Seventh GDG Meeting [1.07.11]	None	None – did not attend for recommendation discussion

B.24 Anne MacGregor – co-opted expert

GDG meeting	Declaration of Interests	Action taken
Tenth GDG Meeting [18.11.11]	Declared Personal pecuniary interest: In the last 12 months: • Berlin-Chemie A Menarini Suomi OY (Finland) – Lecture fee received. • Menarini (UK) – Articles fees received and ongoing. • Merck Sharpe and Dohme – Consultancy fees received and ongoing. • Allergan – Consultancy fees received. Declared non-personal pecuniary interest: In the last 12 months my organisation has received the following research funds: • Merck Sharpe and Dohme: part funding for an Investigator Initiated Study. Protocol in the Molecular Genetics of Menstrual Migraine (ongoing). • Merck Sharpe and Dohme: payment for a phase 3 clinical trial (ongoing). • Addex Pharmaceuticals: payment for a phase 2 clinical trial (completed). The organisation has also received educational grants from Merck Sharpe and Dohme and Menarini. Declared Personal non-pecuniary interest: British Association for the Study of Headache Guidelines for Healthcare. Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache (3rd edition revision 1 in press).	None – did not attend for recommendation discussion

GDG meeting	Declaration of Interests	Action taken
	• Map of Medicine Headache Pathway Review. • Until June 2010; member of the medical advisory board of Migraine Action, a trustee of the Migraine Trust and honorary Treasurer of the International Headache Society. • Reviewer for the SIGN Headache guidelines. • Responsible for the treatment recommendations at the City of London Migraine Clinic.	

Appendix C: Review protocols

C.1 Assessment and diagnosis

C.1.1 Indications for consideration of additional investigation

Component	Description
Review question	For young people and adults with HIV presenting with new onset headache, how common are serious intracranial abnormalities?
Objectives	To determine the occurrence of serious intracranial abnormalities in people with HIV and new onset headache, compared to people with HIV without headache.
Population	People aged 12 or over with HIV and new onset headache in isolation of other symptoms
Comparisons	People aged 12 or over with HIV without headache
Presence / absence of risk factor	Occurrence of serious intracranial abnormalities
Study design	Cohort studies Case control
Exclusions	Non-English studies Abstracts
How the information will be searched	Databases: Medline, Embase Language: restrict to English only
The review strategy	Minimum n=any Report any serious intracranial abnormalities as reported in the studies Record CD4 count if reported

Component	Description
Review question	For young people and adults with a history of malignancy presenting with new onset headache, how common are serious intracranial abnormalities?
Objectives	To determine the occurrence of serious intracranial abnormalities in people with cancer and new onset headache, compared to the occurrence in the general population.
Population	People aged 12 or over with cancer and new onset headache in isolation of other symptoms
Comparisons	People aged 12 or over with cancer, without headache
Presence / absence of risk factor	Occurrence of serious intracranial abnormalities
Study design	Cohort studies Case control
Exclusions	Non-English studies Abstracts
How the information will be searched	Databases: Medline, Embase Language: restrict to English only
The review strategy	Minimum n=any Report any serious intracranial abnormalities as reported in the studies

Component	Description
Review 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?
Objectives	To determine the occurrence of serious intracranial abnormalities in people with early morning headache or new onset frequent headache that lasts for more than one month and is otherwise unexplained, compared to people without early morning headaches / new onset daily headache.
Population	People aged 12 or over with early morning headache or new onset frequent headache that lasts for more than 1 month, in isolation of other symptoms (unexplained)
Comparisons	People aged 12 or over without early morning headache or new onset daily headache that lasts for more than one month
Presence / absence of risk factor	Occurrence of serious intracranial abnormalities
Study design	Cohort studies Case control
Exclusions	Non-English studies Abstracts
How the information will be searched	Databases: Medline, Embase Language: restrict to English only
The review strategy	Minimum n=any Report any serious intracranial abnormalities as reported in the studies NB. Also look in search on headaches with cancer & imaging questions. Report incidence figures and headache type

C.1.2 Identifying people with primary headache

Component	Description
Review question	What is the accuracy of case finding questionnaires for diagnosing primary headache disorders and medication overuse headache?
Objectives	To examine the effectiveness of tools to aid in diagnosis of primary headaches and medication overuse headache.
Population	Females aged 12 or over with migraine Subgroups: • 12-18 years old
Intervention	Case finding questionnaires
Comparison	Gold standard - full assessment following ICHD-II criteria (diagnosis)
Outcomes	• Positive predictive value: True positive & false positive: TP/(TP+FP) • Negative predictive value: True negative & false negative: TN/(FN+TN) • Sensitivity : TP/(FN+TP) • Specificity : TN/(FP+TN)
Study design	Diagnostic studies / validation studies
Exclusions	Abstracts only Non English papers
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only

Component	Description
The review strategy	• Minimum n=100 • Meta-analysis will be undertaken if >5 comparable studies are identified

C.1.3 Headache diaries for the diagnosis of primary headaches and medication overuse headache

Component	Description
Review question	What is the clinical and cost effectiveness of using diaries for the diagnosis of people with suspected primary headaches and medication overuse headache?
Objectives	To examine the effectiveness of patient diaries as diagnostic tools in patients with suspected primary headaches and medication overuse headache.
Population	People aged 12 or over with suspected primary headache Possible subgroups: • 12-18 years old
Interventions	Patient diaries: paper or electronic
Comparisons	Gold standard - full assessment by headache specialist following ICHD-II criteria (diagnosis)
Outcomes	• Number of people correctly diagnosed • Positive predictive value (True positive & false positive: TP/(TP+FP)) • Negative predictive value (True negative & false negative: TN/(FN+TN)) • Sensitivity : TP/(FN+TP) • Specificity : TN/(FP+TN)
Study design	• Diagnostic studies
Exclusions	Abstracts only Non-English
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only
The review strategy	Minimum n: any Review diagnosis and management separately.

C.1.4 Headache diaries for the management of primary headaches and medication overuse headache

Component	Description
Review question	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?
Objectives	To examine the effectiveness of patient diaries as management tools in patients with primary headaches and medication overuse headache.
Population	People aged 12 or over with primary headache Possible subgroups: • 12-18 years old
Interventions	Patient diaries: paper or electronic
Comparisons	No diary
Outcomes	• Clinical headache outcomes (for RCTs) • Patients' and practitioners' experience of using diaries
Study design	• RCTs (only look at other study designs if no RCTs)

	• Qualitative studies / Systematic review
Exclusions	Abstracts only Non-English
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only
The review strategy	Minimum n: any Review diagnosis and management separately.

C.1.5 Diagnosis of primary headaches and medication overuse headache

Component	Description
Review 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 • medication overuse headache
Objectives	To determine the key characteristics that signify diagnosis of primary headache
Population	People aged 12 or over with primary headache Subgroups: • 12-18 years of age
Interventions	N/A
Comparisons	N/A
Outcomes	N/A
Study design	N/A
Exclusions	N/A
How the information will be searched	ICHD-II criteria will be used so no literature search will be conducted
The review strategy	By consensus based on existing ICHD-II criteria

C.1.6 The role of imaging in diagnosis and management of primary headaches

C.1.6.1 Imaging for diagnosis in people with suspected primary headache

Component	Description
Review question	Should young people and adults with suspected primary headaches be imaged to rule out serious pathology?
Objectives	To determine the utility of imaging to detect serious underlying pathology in people with headaches.
Population	People aged 12 or over with suspected primary headache. Possible subgroups: • 12-18 years old • Pregnant women
Interventions	Imaging with CT, MRI or MRI variants
Comparisons	N/A

Component	Description
Outcomes	Percent with serious intracranial abnormalities, e.g.: • Tumour/neoplasm (subdivide into types) • Abscess • Subdural haematoma • Hydrocephalus • Arterio-venous malformations
Study design	Cohort studies Case control
Exclusions	Non-English studies Abstracts
How the information will be searched	Databases: Medline, Embase Language: restrict to English only
The review strategy	Minimum n=any

C.1.6.2 Imaging as a management strategy for people with suspected primary headaches

Component	Description
Review 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?
Objectives	To examine the benefits and disadvantages of imaging in reducing the impact on people with primary headaches
Population	People aged 12 or over with primary headache Subgroups: • Headache type (migraine, cluster headache, tension type headache) • 12-18 years old
Interventions	• MRI scan • MRI variants: MRI + contrast, MR angiography • CT scan
Comparisons	No imaging
Outcomes	• 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 of 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
Study design	RCTs only
Exclusions	Less than 3 months study duration Non-English studies
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only

Component	Description
The review strategy	Minimum n:20 in each arm for RCTs Observational studies n=500 Outcomes to be recorded at 3 months and 1 year if reported Differences between primary and secondary care to be recorded if reported If RCTs are identified the results will, where appropriate, contribute to a meta-analysis.

C.2 Management

C.2.1 Information and support for people with headache disorders

Component	Description
Review question	What information and support do people with primary headaches say they want?
Objectives	To assess what information and support patients with primary headaches say they want
Population	People aged 12 or over with primary headache Subgroups: • 12-18 years old • Pregnant people • Learning disabilities / Any vulnerable group • All age bands
Interventions	Patient information and support
Comparisons	No comparison
Outcomes	• Patients' preferences
Study design	Qualitative data (e.g. interviews, focus groups)
Exclusions	Abstracts only Non English studies
How the information will be searched	Databases: Medline, Embase, Cinahl Language: restrict to English only
The review strategy	• Minimum n=any

C.2.2 Acute pharmacological treatment of tension type headache

Component	Description
Review question	In people with tension type headache, what is the clinical evidence and cost-effectiveness for acute pharmacological treatment with: • Aspirin • NSAIDs • Opioids • Paracetamol
Objectives	To assess the clinical and cost effectiveness of aspirin, NSAIDs, opioids and paracetamol as acute pharmacological treatment of tension type headache.
Population	People aged 12 or over with primary headache Possible subgroups: • 12-18 years old • Pregnant people • Route of administration
Interventions	• Aspirin

Component	Description
	• NSAIDs • Opioids (weak and strong) • Paracetamol
Comparisons	All compared to each other: Placebo, aspirin, paracetamol, NSAIDs, strong and week opioids
Outcomes	• Time to freedom from pain • Headache response at up to 2 hours • Pain free at 2 hours • 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
Study design	RCTs
Exclusions	Abstracts only Non English studies.
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only
The review strategy	• Minimum n=25 per arm • Studies not included in analysis if more than one headache attack treated per drug (unless data for one attack only available) • Include crossover trials if: all patients received both treatments, and only treated one attack or, if data for first treatment period available • Consider dose if reported • Consider route of administration if reported – see subgroups • Data will be meta-analysed if possible • Treatment comparisons will be both direct and mixed

C.2.3 Acute pharmacological treatment of migraine

Component	Description
Review question	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 • Corticosteroids
Objectives	To assess the clinical and cost effectiveness of antiemetics, aspirin, NSAIDs, opioids, oxygen, paracetamol, triptans, ergots and corticosteroids as acute pharmacological treatment of migraine with or without aura.
Population	People aged 12 or over with primary headache Possible subgroups: • 12-18 years old • Pregnant people

Component	Description
	• Route of administration
Interventions	• Antiemetics • Aspirin • NSAIDs • Opioids (weak and strong) • Paracetamol • Triptans • Ergots (ergotamine / dihydroergotamine) • Corticosteroids
Comparisons	All compared to each other: • Aspirin, paracetamol, NSAIDS, triptans, NSAIDs, weak opioids, strong opioids, triptans, ergots, corticosteroids • all +/- antiemetics and antiemetics alone
Outcomes	• 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 Functional health status and health related quality of life (e.g. SF-36 or EuroQoL) • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies.
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only
The review strategy	• Minimum n=25 per arm (Cluster headache n=any) • Studies not included in analysis if more than one headache attack treated per drug (unless data for one attack only available) • Include crossover trials if: all patients received both treatments, and only treated one attack or, if data for first treatment period available • Consider dose if reported • Consider route of administration if reported – see subgroups (buccal and oral together for triptans) • Data will be meta-analysed if possible • Treatment comparisons will be both direct and mixed

C.2.4 Acute pharmacological treatment of cluster headache

Component	Description
Review 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

Component	Description
	• Opioids
Objectives	To assess the clinical and cost effectiveness of oxygen, triptans and ergots as acute pharmacological treatment of cluster headache
Population	People aged 12 or over with primary headache Possible subgroups: • 12-18 years old • Pregnant people • Route of administration
Interventions	• Aspirin • Paracetamol • Oxygen (high and low flow) • Triptans • Ergots (ergotamine / dihydroergotamine) • NSAIDs • Opioids (weak and strong)
Comparisons	All compared to each other (except oxygen) or placebo: • High and low flow oxygen +/- triptans or ergots vs no treatment or air
Outcomes	• Time to freedom from pain • Headache response at up to 2 hours • Reduction in pain at 30 minutes • Functional health status and health related quality of life (e.g. SF-36 or EuroQoL) • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies.
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only
The review strategy	• Minimum n=any • Studies not included in analysis if more than one headache attack treated per drug (unless data for one attack only available) • Include crossover trials if: all patients received both treatments, and only treated one attack or, if data for first treatment period available • Consider dose if reported • Consider route of administration if reported – see subgroups (buccal and oral together for triptans) • Data will be meta-analysed if possible • Treatment comparisons will be both direct and mixed

C.2.5 Prophylactic pharmacological treatment of tension type headache

Component	Description
Review 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 antagonists (ARBs) • Antidepressants (SNRIs, SSRIs, tricyclics) • Beta blockers • Antiepileptics

Component	Description
Objectives	To assess the clinical and cost effectiveness of ACE inhibitors and angiotensin II receptor antagonists, antidepressants, beta blockers and antiepileptics as prophylactic pharmacological treatment of tension type headache.
Population	People aged 12 or over with primary headache Possible subgroups: • 12- 18 years old • Pregnant people • Dose
Interventions	• ACE inhibitors and angiotensin II receptor antagonists • Antidepressants (SNRIs, SSRIs, tricyclics) • Beta blockers • Antiepileptics
Comparisons	All compared to each other or placebo: ACE inhibitors or ARBs, SNRIs, SSRIs, tricyclics, betablockers, antiepileptics.
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only
The review strategy	• Minimum n=25 per arm • Minimum trial duration: 3 months • Outcomes to be recorded at 3 months and 1 year if reported • Consider dose if reported (mg/kg in children) • Consider route of administration if reported • Data will be meta-analysed if possible • Treatment comparisons will be both direct and mixed • Antiepileptics analysed by drug *post hoc GDG agreement due to differing mechanisms of action per drug.

C.2.6 Prophylactic pharmacological treatment of migraine

Component	Description
Review question	In people with migraine with or without aura and chronic 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

Component	Description
	• Antiepileptics • Other serotonergic modulators
Objectives	To assess the clinical and cost effectiveness of ACE inhibitors and angiotensin II receptor antagonists, antidepressants, beta blockers, calcium channel blockers, antiepileptics and other serotonergic modulators as prophylactic pharmacological treatment of migraine with or without aura and chronic migraine.
Population	People aged 12 or over with primary headache Possible subgroups: • 12-18 years old • Pregnant people • Previous treatment exposure: None, 1, 2 or 3, 4 or more • Dose
Interventions	• ACE inhibitors and angiotensin II receptor antagonists • Antidepressants (SNRIs, SSRIs, tricyclics) • Beta blockers • Calcium channel blockers • Antiepileptics • Other serotonergic modulators (e.g. pizotifen, methysergide, cyproheptadine, dihydroergotamine)
Comparisons	All compared to each other or placebo: ACE inhibitors or ARBs, SNRIs, SSRIs, tricyclics, betablockers, antiepileptics, other serotonergic modulators.
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only
The review strategy	• Minimum n=25 per arm • Minimum trial duration: 3 months • Outcomes to be recorded at 3 months and 1 year if reported • Previous treatment exposure: None, 1,2or3, 4 or more • Consider dose if reported (mg/kg in children) • Consider route of administration if reported • Data will be meta-analysed if possible • Treatment comparisons will be both direct and mixed • Antiepileptics analysed by drug *post hoc GDG agreement due to differing mechanisms of action per drug.

C.2.7 Prophylactic pharmacological treatment of menstrual migraine

Component	Description
Review 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 • Antidepressants (SNRIs, SSRIs, tricyclics) • Beta blockers • Calcium channel blockers • Antiepileptics • Triptans • Other serotonergic modulators • NSAIDs • Hormonal therapy (Contraceptives)
Objectives	To assess the clinical and cost effectiveness of ACE inhibitors and angiotensin II receptor antagonists, antidepressants, beta blockers, calcium channel blockers, antiepileptics, triptans, other serotonergic modulators, NSAIDs, and hormonal therapy as prophylactic pharmacological treatment of menstrual migraine or menstrual related migraine.
Population	People aged 12 or over with primary headache Possible subgroups: • 12-8 years old • Pregnant people
Interventions	• ACE inhibitors and angiotensin II receptor antagonists • Antidepressants (SNRIs, SSRIs, tricyclics) • Beta blockers • Calcium channel blockers • Antiepileptics • Triptans • Other serotonergic modulators (e.g. pizotifen, methysergide, cyproheptadine, dihydroergotamine) • NSAIDs • Hormonal therapy (Contraceptives)
Comparisons	All compared to each other: Placebo, ACE inhibitors or ARBs, SNRIs, SSRIs, tricyclics, betablockers, antiepileptics, triptans, other serotonergic modulators, NSAIDs, hormonal therapy.
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only

Component	Description
The review strategy	• Minimum n=25 per arm • Minimum trial duration: 3 months • Outcomes to be recorded at 3 months and 1 year if reported • Previous treatment exposure: None, 1,2or3, 4 or more • Consider dose if reported (mg/kg in children) • Consider route of administration if reported • Data will be meta-analysed if possible • Treatment comparisons will be both direct and mixed • Antiepileptics analysed by drug *post hoc GDG agreement due to differing mechanisms of action per drug.

C.2.8 Prophylactic pharmacological treatment of cluster headache

Component	Description
Review question	In people with cluster headache, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: • Calcium channel blockers • Corticosteroids (oral only) • Lithium • Melatonin • Antiepileptics • Triptans • Other serotonergic modulators
Objectives	To assess the clinical and cost effectiveness of calcium channel blockers, corticosteroids, lithium, melatonin, antiepileptics, triptans and other serotonergic modulators as prophylactic pharmacological treatment of cluster headache.
Population	People aged 12 or over with primary headache Possible subgroups: • 12-18 years old • Pregnant people
Interventions	• Calcium channel blockers • Corticosteroids (oral only) • Lithium • Melatonin • Antiepileptics • Triptans • Other serotonergic modulators
Comparisons	All compared to each other or placebo: Calcium channel blockers, oral corticosteroids, lithium, melatonin, antiepileptics, triptans, other serotonergic modulators (including ergots)
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events

Component	Description
Study design	RCTs
Exclusions	Abstracts only Non English studies
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only
The review strategy	• Minimum n=any • Outcomes to be recorded at any time point • Consider dose if reported (mg/kg in children) • Consider route of administration if reported • Data will be meta-analysed if possible • Treatment comparisons will be both direct and mixed

C.2.9 Prophylactic non-pharmacological management of primary headaches with acupuncture

Component	Description
Review question	For people with 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 non-pharmacological management with acupuncture
Objectives	To assess the clinical and cost effectiveness of acupuncture, as non-pharmacological management of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache).
Population	People aged 12 or over with primary headache Subgroups: • 12-18 years old • Pregnant people
Interventions	Acupuncture +/- prophylactic pharmacological treatment
Comparisons	Sham acupuncture +/- prophylactic pharmacological treatment / pharmacological therapy / psychological therapy / herbal remedies / dietary supplements / manual therapy
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed Language: restrict to English only
The review strategy	• Minimum n=25 (per arm) • Outcomes to be recorded at 3 months and 1 year if reported • Randomised crossover trials excluded

Component	Description
	• Data will be meta-analysed if possible

C.2.10 Prophylactic non-pharmacological management of primary headaches with manual therapies

Component	Description
Review question	For people with 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 non-pharmacological management with manual therapies?
Objectives	To assess the clinical and cost effectiveness of manual therapies as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache).
Population	People aged 12 or over with primary headache Subgroups: • 12-18 years old • Pregnant people
Interventions	Manual therapies
Comparisons	Usual care
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed Language: restrict to English only
The review strategy	• Minimum n=25 (per arm) • Outcomes to be recorded at 3 months and 1 year if reported • Randomised crossover trials excluded • Data will be meta-analysed if possible

C.2.11 Prophylactic non-pharmacological management of primary headaches with psychological therapies

Component	Description
Review question	For people with primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with psychological therapies?
Objectives	To assess the clinical and cost effectiveness of psychological therapies as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache).

Component	Description
Population	People aged 12 or over with primary headache Subgroups: • 12-18 years old • Pregnant people
Interventions	Psychological therapies (Cognitive behavioural therapy (CBT), biofeedback, controlled breathing, progressive muscle relaxation (PMR), relaxation, guided visualisation, mindfulness, attention control training (ACT), finger/hand warming)
Comparisons	Attention control
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed Language: restrict to English only
The review strategy	• Minimum n=25 (total) • Outcomes to be recorded at 3 months and 1 year if reported • Randomised crossover trials excluded • Data will be meta-analysed if possible

C.2.12 Prophylactic non-pharmacological management of primary headaches with dietary supplements

Component	Description
Review question	For people with 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 non-pharmacological management with dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin (B2))
Objectives	To assess the clinical and cost effectiveness of dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin(B2)) as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache).
Population	People aged 12 or over with primary headache Subgroups: • 12-18 years old • Pregnant people
Interventions	Dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin(B2) +/- prophylactic pharmacological treatment
Comparisons	Placebo vs +/- prophylactic pharmacological treatment / pharmacological therapy / acupuncture / psychological therapy / herbal remedies / manual therapy
Outcomes	• Change in patient-reported headache days, frequency and intensity

Component	Description
	• Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed Language: restrict to English only
The review strategy	• Minimum n=25 (per arm) • Outcomes to be recorded at 3 months and 1 year if reported • Randomised crossover trials excluded • Data will be meta-analysed if possible

C.2.13 Prophylactic non-pharmacological management of primary headaches with herbal remedies

Component	Description
Review question	For people with primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine) what is the clinical evidence and cost-effectiveness of non-pharmacological management with herbal remedies?
Objectives	To assess the clinical and cost effectiveness of herbal remedies (e.g. feverfew and butterbur) as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache).
Population	People aged 12 or over with primary headache Subgroups: • 12-18 years old • Pregnant people
Interventions	Dietary supplements (e.g. feverfew, butterbur) +/- prophylactic pharmacological treatment
Comparisons	Placebo vs +/- prophylactic pharmacological treatment / pharmacological therapy / acupuncture / psychological therapy / herbal remedies / manual therapy
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies

Component	Description
	Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed Language: restrict to English only
The review strategy	• Minimum n=25 (per arm) • Outcomes to be recorded at 3 months and 1 year if reported • Randomised crossover trials excluded • Data will be meta-analysed if possible

C.2.14 Prophylactic non-pharmacological management of primary headaches with exercise

Component	Description
Review question	For people with primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with exercise programmes?
Objectives	To assess the clinical and cost effectiveness of exercise programmes as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache).
Population	People aged 12 or over with primary headache Subgroups: • 12-18 years old • Pregnant people
Interventions	Exercise programmes
Comparisons	Usual care
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events
Study design	RCTs
Exclusions	Abstracts only Non English studies Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed Language: restrict to English only
The review strategy	• Minimum n=25 (per arm) • Outcomes to be recorded at 3 months and 1 year if reported • Randomised crossover trials excluded • Data will be meta-analysed if possible

C.2.15 Prophylactic non-pharmacological management of primary headaches with education and self management

Component	Description
Review question	For people with 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 non-pharmacological management with education and self-management programmes?
Objectives	To assess the clinical and cost effectiveness of education and self management programmes as non-pharmacological treatment of primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache, cluster headache).
Population	People aged 12 or over with primary headache Subgroups: • 12-18 years old • Pregnant people
Interventions	Education and self-management programmes
Comparisons	Usual care
Outcomes	• Change in patient-reported headache days, frequency and intensity • Responder rate (50% reduction) • Functional health status and health-related quality of life (e.g. SF-36, or Euro-QoL) • Headache specific QOL (e.g. MIDAS, HIT 6) • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Patient's perception of the usefulness of programmes
Study design	RCTs
Exclusions	Abstracts only Non English studies Randomised crossover trials
How the information will be searched	Databases: Medline, Embase, the Cochrane Library, Cinahl, Amed Language: restrict to English only
The review strategy	• Minimum n=25 (total) • Outcomes to be recorded at 3 months and 1 year if reported • Randomised crossover trials excluded • Data will be meta-analysed if possible

C.2.16 Management of medication overuse headache

Component	Description
Review 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?
Objectives	To identify the clinical evidence and assess the cost effectiveness of withdrawal strategies, psychological therapies, corticosteroids or NSAIDs for the treatment of probable medication overuse headache.
Population	People aged 12 or over with suspected medication overuse headache Subgroups: • 12-18 years old
Interventions	• Withdrawal strategies for abortive treatments (stop suddenly, withdraw gradually,

	inpatient, outpatient supportive packages) • Psychological therapies • Corticosteroids • NSAIDS
Comparisons	• Withdrawal strategies vs each other • Psychological therapies vs attention control • Corticosteroids / NSAIDS vs placebo
Outcomes	• 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 QoL (e.g. MIDAS, HIT 6) • Resource use including GP consultation, A&E attendance, investigations and referral to secondary care • Functional health status and health related quality of life (e.g. SF-36 or EuroQoL)
Study design	RCTs If no RCTs found, lower quality evidence will be considered
Exclusions	Abstracts only Non English papers
How the information will be searched	Databases: Medline, Embase, the Cochrane Library Language: restrict to English only
The review strategy	• Minimum n=25 per arm • Outcomes to be recorded at 3 months and 1 year if reported • Data will be meta-analysed if possible

C.3 Management during pregnancy and contraceptive use

C.3.1 Management of primary headaches during pregnancy

Component	Description
Review question	What is the evidence for adverse fetal events in females with primary headaches during pregnancy using triptans?
Objectives	To determine the safety of triptans for use during pregnancy
Population	Pregnant women and girls aged 12 or over with primary headache
Presence of risk factor	Pregnant women with headache taking a triptan
Absence of risk factor	Pregnant women with or without headache, not taking a triptan
Outcomes	Fetal adverse events
Study design	Cohort studies Triptan registries (published only)
Exclusions	Abstracts only Non English papers
How the information will be searched	Databases: Medline, Embase, Triptan or teratology registers Language: restrict to English only
The review strategy	• Minimum n=50 • Consider dose if reported

Component	Description
	• Consider route of administration if reported • Ideally adjusted for: Age, smoking, alcohol, other drug use

Component	Description
Review question	What is the evidence for adverse fetal events in females using oxygen or verapamil during pregnancy?
Objectives	To determine the safety of oxygen or verapamil for use during pregnancy
Population	Pregnant women and girls aged 12 or over
Presence of risk factor	Pregnant women taking oxygen or verapamil
Absence of risk factor	Pregnant women not taking oxygen or verapamil
Outcomes	Fetal adverse events
Study design	Cohort studies
Exclusions	Abstracts only Non English papers
How the information will be searched	Databases: Medline, Embase Language: restrict to English only
The review strategy	• Minimum n=50 • Consider dose if reported • Consider route of administration if reported • Ideally adjusted for: Age, smoking, alcohol, other drug use

C.3.2 Combined hormonal contraceptive use in girls and women with migraine

Component	Description
Review question	What risks are associated with use of hormonal contraception in females aged 12 or over with migraine?
Objectives	To assess what adverse events are associated with the use of hormonal contraception in females ages 12 or over with migraine
Population	Females aged 12 or over with migraine Subgroups: • Migraine type (with and without aura)
Presence of risk factor	• Combined oral contraceptive pill • Progesterone only contraceptive pill / contraceptive pill without oestrogen • Progesterone implanted coil • Progesterone implant • Depot injection
Absence of risk factor	• Non-hormonal / other
Outcomes	• Incidence of serious adverse events • Worsening effect on headache syndrome
Study design	• Prospective cohort studies • Case control
Exclusions	Abstracts only Non English papers

Component	Description
How the information will be searched	Databases: Medline, Embase Language: restrict to English only
The review strategy	Minimum n=500 for cohort Ideally adjusted for: Age, smoking, familial risk

C.4 Health economics

Component	Description
Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to the review questions set out above.
Criteria for considering studies for the review	Populations, interventions and comparators, and date cut-offs as specified in the question-specific review protocols. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Outcomes	Costs; QALYs; incremental costs and QALYs; any other measure of effectiveness reported together with costs.
Search strategy	See D.1.17
Review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual[582], Appendix H. **Inclusion/exclusion criteria** If a study is rated as both 'Directly applicable' and 'Minor limitations' (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. • If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. • If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of the call for evidence • abstract-only studies • letters • editorials • reviews of economic evaluations[(a)] • foreign language articles **Where there is discretion** The health economist should be guided by the following hierarchies. Setting: 1. UK NHS 2. OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden)

Component	Description
	3. OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) 4. Non-OECD settings (always 'Not applicable') Economic study type: 1. Cost-utility analysis 2. Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis) 3. Comparative cost analysis 4. Non-comparative cost analyses including cost of illness studies (always 'Not applicable') Year of analysis: • The more recent the study, the more applicable it is Quality and relevance of effectiveness data used in the economic analysis: • The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered

Appendix D: Literature search strategies

Contents

Introduction

Search strategies used for the **headache guideline** were run in accordance with the NICE Guidelines Manual 2009[582]**.** All searches were run up to **13 March 2012** unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text.

Scoping searches

Scoping searches were conducted in September 2010 using the following websites and databases (listed below in alphabetical order). Browsing or simple search strategies were employed. The search results were used to provide information for scope development and project planning.

Guidelines	Website address
British Association for the Studies of Headache (BASH)	www.bash.org.uk/
CMA Infobase (Canadian guidelines)	www.cma.ca/cpgs
European Federation of Neurological Societies	www.efns.org/
Guidelines International Network	www.g-i-n.net/
Health Technology Assessments	www.crd.york.ac.uk/
International Headache Society	www.ihs-headache.org/
National Guidelines Clearinghouse	www.guideline.gov/
New Zealand Guidelines Group	www.nzgg.org.nz/
NHMRC (Australian Guidelines)	http://www.nhmrc.gov.au/guidelines/
NICE Guidelines	http://guidance.nice.org.uk/
Scottish Intercollegiate Guidelines Network	www.sign.ac.uk/
Specialist Organisations (not listed above)	Various
Reviews, clinical evidence sources, economic evaluations	**Website address**
BMJ Clinical Evidence	clinicalevidence.bmj.com/
Cochrane Library (Systematic Reviews)	www.thecochranelibrary.com/
NHS Evidence	www.nelh.nhs.uk/
Other sources as agreed by reviewers	**Website address**
British National Formulary (BNF)	bnf.org/
electronic Medicines Compendium (eMC)	www.medicines.org.uk/

Clinical searches

All searches for **clinical reviews** were run in Medline (OVID) and Embase (OVID). Some searches were also run in The Cochrane Library (Wiley) (for intervention reviews), PsycINFO (for psychological therapies and education questions), Cinahl (for patient information and alternative therapies) and Amed (for complementary and alternative therapies). Typically, searches were constructed in the following way:

- A PICO format was used for intervention searches. **Population** (P) terms were combined with **intervention** (I) and sometimes **comparison** (C) terms. An intervention can be a drug, a procedure or a diagnostic test. **Outcomes** (O) are rarely used in search strategies for interventions. Study design filters were a13ed where appropriate.
- A PEO format was used for **prognosis** searches where **population (P)** terms were combined with **exposure (E)** terms and sometimes **outcomes (O)**.
- An exclusion filter was applied using the 'NOT' boolean operator to most searches in order to eliminate studies about animals, letters, editorials, comments and non-english articles.
- The structure for each search is reported in section D.1.

Economic searches

Searches for **economic** and **quality of life evidence** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). NHS EED and HTA were searched via the Centre for Reviews and Dissemination (CRD) interface. The structure for each search is reported in section D.1.

D.1 Structure of search strategies – listed by search

D.1.1 Assessment and diagnosis - indications for consideration of additional investigation

The following three questions were searched using a single strategy:

Q1. For young people and adults with HIV presenting with new onset headache, how common are serious intracranial abnormalities?

Q2. For young people and adults with a history of malignancy presenting with new onset headache, how common are serious intracranial abnormalities?

Q3. 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?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Primary headaches (section D.2.2) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	HIV, cancer, early morning headaches & frequent new onset headaches (section D.4.1)	Not applicable	Observational studies (section D.5.3) [for all searched databases]	All years - 13/03/2012 Medline & Embase

D.1.2 Assessment and diagnosis – identifying people with primary headaches

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Headaches – all (section D.2.1) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Screening questionnaires (section D.4.2)	Not part of search	Diagnostic accuracy (section D.5.4) [for all searched databases]	All years - 13/03/2012 Medline & Embase

D.1.3 Assessment and diagnosis – headache diaries

The following two questions were searched using a single strategy:

Q1. What is the clinical and cost effectiveness of using diaries for the diagnosis of people with suspected primary headaches and medication overuse headaches?

Q2. What is the clinical effectiveness, and patients' and practitioners' experience, of using diaries for the management of people with primary headaches and medication overuse headaches?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Headaches – all (section D.2.1) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Diary terms (section D.4.3)	Not part of search	No study filter used	All years - 13/03/2012 Medline, Embase, Cochrane & Cinahl

D.1.4 Assessment and diagnosis – imaging for diagnosis

Q1. Should young people and adults with suspected primary headaches be imaged to rule out serious pathology?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Primary headaches (section D.2.2) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Imaging terms (section D.4.4)	Not part of search	Observational studies (section D.5.3) [for all searched databases]	All years - 13/03/2012 Medline & Embase

D.1.5 Assessment and diagnosis – imaging for managment

Q1. 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?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Headaches – all (section D.2.1) 'NOT'ed with exclusion filter in Medline & Embase	Imaging terms (section D.4.4)	Not part of search	RCTs and SRs (sections D.5.1 & D.5.2) [Medline and Embase only]	All years - 13/03/2012 Medline, Embase & Cochrane

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
(section D.3)				

D.1.6 Patient information searches

Q1. What information and support do people with primary headaches say they want?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Primary headaches focused search (section D.6) Search 'NOT'ed with exclusion filter (section D.3)	Patient information terms (section D.6)	Not applicable	Qualitative literature terms (section D.6) [Medline, Embase & Cinahl]	All years - 13/03/2012 [Medline, Embase & Cinahl]

D.1.7 Treatment of cluster headaches

One search was conducted to identify all RCTs and systematic reviews in cluster headaches. This would have identified studies relevant to cluster headaches covering several questions. This search also overlaps with the searches for non-pharmacological treatment of cluster headaches. The questions and structure of searches for these are listed in section D.1.12. Two questions not covered by any other search are:

Q1. In people with cluster headache, what is the clinical evidence and cost-effectiveness for acute pharmacological treatment with aspirin, paracetamol, oxygen, triptans, ergots, NSAIDs or opioids?

Q2. 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 or serotonergic modulators?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Cluster headache (section D.2.5) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Not applicable	Not part of search	RCTs or SRs (sections D.5.1 & D.5.2) [Medline, Embase, PsycINFO & Cinahl only]	All years - 13/03/2012 Medline, Embase, Cochrane, AMED PsycINFO, Cinahl

D.1.8 Treatment of acute migraine

Q1. 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?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Migraine (section D.2.3) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Pharmacological terms for: antiemetics aspirin, NSAIDs, opioids, paracetamol, triptans, ergots & corticosteroids combined using the 'OR' boolean operator (section D.4.5)	Not part of search	RCTs or SRs (sections D.5.1 & D.5.2) [Medline, Embase & Cinahl only]	All years - 13/03/2012 Medline, Embase, Cochrane & Cinahl

D.1.9 Treatment of acute tension type headache

Q1. In people with tension type headache, what is the clinical evidence and cost-effectiveness for acute pharmacological treatment with: aspirin, NSAIDs, opioids and paracetamol?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Tension type headache (section D.2.4) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Pharmacological terms for: aspirin, NSAIDs, opioids & paracetamol combined using the 'OR' boolean operator (sections D.4.5.2 & D.4.5.6)	Not part of search	RCTs or SRs (sections D.5.1 & D.5.2) [Medline, Embase & Cinahl only]	All years - 13/03/2012 Medline, Embase, Cochrane & Cinahl

D.1.10 Treatment of migraine and tension type headache with pharmacological prophylaxis

The following two questions were searched using a single strategy:

Q1. In people with migraine, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: ACE inhibitors, angiotensin II receptor antagonists, antidepressants (SNRIs, SSRIs, tricyclics), beta blockers, calcium channel blockers, antiepileptics and other serotonergic modulators?

Q2. In people with tension type headache, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: ACE inhibitors, angiotensin II receptor antagonists, antidepressants (SNRIs, SSRIs, tricyclics), beta blockers and antiepileptics?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population(s)	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Migraine or tension type headache (sections D.2.3 & D.2.4) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Pharmacological terms for: ACE inhibitors, angiotensin II receptor antagonists, antidepressants (SNRIs, SSRIs, tricyclics), beta blockers, calcium channel blockers, antiepileptics and serotonergic modulators combined using the 'OR' boolean operator (section D.4.6)	Not part of search	RCTs or SRs (sections D.5.1 & D.5.2) [Medline, Embase & Cinahl only]	All years - 13/03/2012 Medline, Embase, Cochrane & Cinahl

D.1.11 Treatment of pure menstrual and menstrual related migraine with pharmacological prophylaxis

The following question was searched using two search strategies. Several of the drugs used in the acute treatment of menstrual related migraine were covered by the search relating to pharmacological prophylaxis for migraine. This search identified studies related to drugs not covered in the previous search.

Q1. In people with pure menstrual and menstrual related migraine, what is the clinical evidence and cost-effectiveness for prophylactic pharmacological treatment with: ACE inhibitors, angiotensin II receptor antagonists, antidepressants (SNRIs, SSRIs, tricyclics), beta blockers, calcium channel blockers, antiepileptics, triptans, other serotonergic modulators, NSAIDs and hormonal therapy (contraceptives)?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Menstrual migraine (section D.2.6) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Pharmacological terms for: NSAIDs, triptans & hormonal contraceptives combined using the 'OR' boolean operator (sections D.4.5.5, D.4.5.6, D.4.5.7)	Not part of search	RCTs or SRs (sections D.5.1 & D.5.2) [Medline, Embase & Cinahl only]	All years - 13/03/2012 Medline, Embase, Cochrane & Cinahl

D.1.12 Non-pharmacological treatment of primary headaches

The following five questions were searched using a single strategy:

Q1. 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 non-pharmacological management with acupuncture?

Q2. 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 non-pharmacological management with dietary supplements (e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin (B2))?

Q3. For people with the following primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine) what is the clinical evidence and cost-effectiveness of non-pharmacological management with herbal remedies?

Q4. For people with the following primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with exercise programmes?

Q5. 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 non-pharmacological management with manual therapies?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Headaches – all (section D.2.1) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Non-pharmacological terms for: acupuncture, dietary supplements, herbal remedies, exercise programmes and manual therapies combined using the 'OR' boolean operator (section D.4.7.1, D.4.7.2, D.4.7.3, D.4.7.4 & D.4.7.5)	Not part of search	RCTs or SRs (sections D.5.1 & D.5.2) [Medline, Embase, & Cinahl only]	All years - 13/03/2012 Medline, Embase, Cochrane, Cinahl & AMED

The following two questions were searched using a single strategy:

Q1. 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 non-pharmacological management with education and self-management programmes?

Q2. For people with the following primary headaches (migraine with or without aura, menstrual related migraine, chronic migraine, tension type headache), what is the clinical evidence and cost-effectiveness of non-pharmacological management with psychological therapies?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Headaches – all (section D.2.1) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Non-pharmacological terms for: education and self management programmes and psychological therapies combined using the 'OR' boolean operator (sections D.4.7.6 & D.4.7.7)	Not part of search	RCTs or SRs (sections D.5.1 & D.5.2) [Medline, Embase, PsycINFO, & Cinahl only]	All years - 13/03/2012 Medline, Embase, Cochrane, PsycINFO, Cinahl & AMED

D.1.13 Treatment of medication overuse headaches

Q1. 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?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Medication overuse headache (section D.2.7) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Not applicable	Not part of search	RCTs, SRs & observational studies (sections D.5.1. D.5.2 & D.5.3). [Medline, Embase & PsycInfo only]	All years - 13/03/2012 Medline, Embase, Cochrane & PsycINFO.

D.1.14 Fetal adverse events - oxygen

Q1. What is the evidence for adverse fetal events in females using oxygen during pregnancy?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
No population terms used. Search 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Oxygen therapy and fetal adverse events terms (section D.4.8.1)	Not applicable	Observational studies (section D.5.3) [for all searched databases]	All years - 13/03/2012 Medline & Embase.

D.1.15 Fetal adverse events - triptans

Q1. What is the evidence for adverse fetal events in females with primary headaches during pregnancy using triptans?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
Headaches – all (section D.2.1) 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Triptans and fetal adverse events terms (section D.4.8.2)	Not applicable	Not used	All years - 13/03/2012 Medline & Embase.

D.1.16 Fetal adverse events - verapamil

Q1. What is the evidence for adverse fetal events in females using verapamil during pregnancy?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention/ Exposure	Comparison	Study filter used	Date parameters & databases searched
No population terms used. Search 'NOT'ed with exclusion filter in Medline & Embase (section D.3)	Verapamil and fetal adverse events terms (section D.4.8.3)	Not applicable	Observational studies (section D.5.3) [for all searched databases]	All years - 13/03/2012 Medline & Embase.

D.1.17 Health economic searches

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Study filter used	Date parameters & databases searched
Headache – all (section D.2.1)	Economic [Medline only] (section D.5.5)	• 2008 – 13/03/2012 (Medline) • All years - 13/03/2012 (NHS EED, HTA and HEED)

D.1.18 Quality of life studies

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Study filter used	Date parameters & databases searched
Headache – all (section D.2.1)	Quality of Life [Medline only] (section D.5.6)	All years - 13/03/2012

D.2 Population search strategies

D.2.1 Headache – all

Medline search terms

1.	Headache/
2.	exp Headache Disorders/
3.	(headache* or migraine*).ti,ab.
4.	or/1-3

Embase search terms

1.	exp "headache and facial pain"/
2.	(headache* or migraine*).ti,ab.
3.	or/1-2

Cinahl search terms

S1.	(MH "Headache+")
S2.	headache* or migraine*
S3.	S1 or S2

Cochrane search terms

#1.	MeSH descriptor Headache explode all trees
#2.	MeSH descriptor Headache Disorders explode all trees
#3.	(migraine* or headache*):ti,ab
#4.	#1 OR #2 OR #3

PsycINFO search terms

1.	exp Headache/
2.	(headache* or migraine*).ti,ab.
3.	or/1-2

HEED search terms

1.	ax= headache* or migraine*

NHS EED & HTA CRD search terms

1.	MeSH DESCRIPTor HEADACHE EXPLODE ALL TREES
2.	MeSH DESCRIPTor HEADACHE disorders
3.	MeSH DESCRIPTor Headache Disorders, Primary EXPLODE ALL TREES
4.	(headache) or (headaches) or (migraine) or (migraines)
5.	#1 or #2 or #3 or #4

D.2.2 Primary Headaches

Medline search terms

1.	Headache/
2.	Headache Disorders/ or exp Headache Disorders, Primary/
3.	(headache* or migraine*).ti,ab.
4.	or/1-3

Embase search terms

1.	headache/ or migraine/ or primary headache/ or chronic daily headache/ or migraine/ or migraine aura/ or migraine with aura/ or migraine without aura/
2.	(headache* or migraine*).ti,ab.

3.	or/1-2

D.2.3 Migraine

Medline search terms

1.	exp Migraine Disorders/
2.	migraine*.ti,ab.
3.	or/1-2

Embase search terms

1.	exp migraine/
2.	migraine*.ti,ab.
3.	or/1-2

Cinahl search terms

S1.	(MH "Migraine")
S2.	migraine*
S3.	S1 or S2

Cochrane search terms

#1.	MeSH descriptor Migraine Disorders explode all trees
#2.	migraine*:ti,ab
#3.	#1 OR #2

D.2.4 Tension type headache

Medline search terms

1.	Tension-Type Headache/
2.	(headache* adj3 (tension or tension type or muscle contraction or psychomyogenic or stress or ordinary or essential or idiopathic or psychogenic)).tw.
3.	((chronic adj2 daily adj2 headache*) or (daily adj2 persistent adj2 headache*)).ti,ab.
4.	or/1-3

Embase search terms

1.	exp tension headache/
2.	(headache* adj3 (tension or tension type or muscle contraction or psychomyogenic or stress or ordinary or essential or idiopathic or psychogenic)).tw.
3.	((chronic adj2 daily adj2 headache) or (daily adj2 persistent adj2 headache*)).ti,ab.
4.	or/1-3

Cinahl search terms

S1.	(MH "Tension Headache")
S2.	(headache* n3 tension*) or (headache* n3 "muscle contraction") or (headache* n3 psychomyogenic) or (headache* n3 stress) or (headache* n3 ordinary) or (headache* n3 essential) or (headache* n3 idiopathic) or (headache* n3 psychogenic) or (headache* n3 daily
S3.	S1 or S2

Cochrane search terms

#1.	MeSH descriptor Tension-Type Headache, this term only
#2.	(headache near3 (tension or "tension type" or "muscle contraction" or idiopathic or ordinary or psychogenic or psychomyogenic or daily or essential)):ti,ab
#3.	#1 OR #2

D.2.5 Cluster headache

Medline search terms

1.	cluster headache/
2.	(cluster adj4 headache*).tw.
3.	((ciliary or migrain* or petrosal or sluder* or spheno-palatine or vidian) adj4 neuralgi*).tw.
4.	or/1-3

Embase search terms

1.	exp cluster headache/
2.	(cluster adj4 headache*).tw.
3.	((ciliary or migrain* or petrosal or sluder* or spheno-palatine or vidian) adj4 neuralgi*).tw.
4.	or/1-3

Cinahl search terms

S1.	(MH "Cluster Headache")
S2.	cluster n4 headache*
S3.	(ciliary n4 neuralgi*) or (migrain* n4 neuralgi*) or (petrosal n4 neuralgi*) or (sluder* n4 neuralgi*) or (spheno-palatine n4 neuralgi*) or (vidian n4 neuralgi*)
S4.	(Harris-Horton* N2 disease) or (Harris-Horton* N2 headache*) or (Harris-Horton* N2 syndrome*) or (horton N2 disease) or (horton N2 headache*) or (horton N2 syndrome*)
S5.	S1 or S2 or S3 or S4

Cochrane search terms

#1.	MeSH descriptor Cluster Headache, this term only
#2.	cluster near4 headache*:ti,ab
#3.	((ciliary or migrain* or petrosal or sluder* or spheno-palatine or vidian) near4 neuralgi*):ti,ab
#4.	((Harris-Horton* or horton) near2 (disease or headache* or syndrome*)):ti,ab
#5.	(#1 OR #2 OR #3 OR #4)

PsycINFO search terms

1.	(cluster adj4 headache*).tw.
2.	((ciliary or migrain* or petrosal or sluder* or spheno-palatine or vidian) adj4 neuralgi*).tw.
3.	((Harris-Horton* or horton) adj2 (disease or headache* or syndrome*)).tw.
4.	or/1-3

D.2.6 Menstrual and menstrual related migraine

Medline search terms

1.	exp Migraine Disorders/
2.	migraine*.ti,ab.
3.	or/1-2
4.	menstrua*.ti,ab.
5.	3 and 4

Embase search terms

1.	exp migraine/
2.	migraine*.ti,ab.

3.	or/1-2
4.	menstrua*.ti,ab.
5.	3 and 4

Cochrane search terms

#1.	MeSH descriptor Migraine Disorders explode all trees
#2.	migraine*:ti,ab
#3.	#1 or #2
#4.	menstrua*:ti,ab
#5.	#3 and #4

Cinahl search terms

S1.	(MH "Migraine")
S2.	Migraine*
S3.	S1 or S2
S4.	menstrua*
S5.	S3 and S4

D.2.7 Medication overuse headache

Medline search terms

1.	((rebound or transformed) adj5 (headache* or migrain*)).ti,ab.
2.	((medication or drug or pain?killer* or ergot* or analges* or triptan* or opioid or caffeine) adj5 (over?use or mis?use or associated or induced or abuse) adj5 (headache* or migrain*)).ti,ab.
3.	or/1-2

Embase search terms

1.	((rebound or transformed) adj5 (headache* or migrain*)).ti,ab.
2.	((medication or drug or pain?killer* or ergot* or analges* or triptan* or opioid or caffeine) adj5 (over?use or mis?use or associated or induced or abuse) adj5 (headache* or migrain*)).ti,ab.
3.	or/1-2

Cochrane search terms

#1.	((rebound or transformed) near5 (headache* or migrain*)):ti,ab
#2.	((medication or drug or painkiller* or pain-killer* or pain killer* or ergot* or analges* or triptan* or opioid or caffeine) near5 (overuse or over-use or misuse or mis-use or associated or induced or abuse) near5 (headache* or migrain*)):ti,ab
#3.	#1 or #2

PsycINFO search terms

1.	((rebound or transformed) adj5 (headache* or migrain*)).ti,ab.
2.	((medication or drug or pain?killer* or ergot* or analges* or triptan* or opioid or caffeine) adj5 (over?use or mis?use or associated or induced or abuse) adj5 (headache* or migrain*)).ti,ab.
3.	or/1-2

D.3 Exclusions

Medline search terms

1.	letter/
2.	editorial/

3.	exp historical article/
4.	Anecdotes as Topic/
5.	comment/
6.	case report/
7.	animals/ not humans/
8.	exp Animals, Laboratory/
9.	exp Animal Experimentation/
10.	exp Models, Animal/
11.	exp Rodentia/
12.	or/1-11

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	animal/ not human/
6.	nonhuman/
7.	animals, laboratory/
8.	exp experimental animal/
9.	exp animal experiment/
10.	animals, laboratory/
11.	exp animal model/
12.	exp rodent/
13.	or/1-12

D.4 Intervention or exposure terms

D.4.1 Indications for consideration of additional investigation

Medline search terms

1.	(red flag* or warning).ti,ab.
2.	((intracranial or key or serious or significant) adj2 (abnormal* or characteristic* or patholog* or cause* or symptom* or feature*)).ti,ab.
3.	or/1-2
4.	exp HIV/
5.	(human immunodeficiency virus or human immuno-deficiency virus or HIV or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome).ti,ab.
6.	or/4-5
7.	exp Neoplasms/
8.	(cancer* or neoplasm* or tumo?r*).ti,ab.
9.	or/7-8
10.	(early adj3 (day or morning) adj3 (migraine* or headache*)).ti,ab.
11.	(new adj3 (onset or daily) adj3 (migraine* or headache*)).ti,ab.
12.	3 or 6 or 9 or 10 or 11

Embase search terms

1.	(red flag* or warning).ti,ab.
2.	((intracranial or key or serious or significant) adj2 (abnormal* or characteristic* or patholog* or cause* or symptom* or feature*)).ti,ab.

3.	or/1-2
4.	exp Human immunodeficiency virus/
5.	(human immunodeficiency virus or human immuno-deficiency virus or HIV or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome).ti,ab.
6.	or/4-5
7.	exp neoplasm/
8.	(cancer* or neoplasm* or tumo?r*).ti,ab.
9.	or/7-8
10.	(early adj3 (day or morning) adj3 (migraine* or headache*)).ti,ab.
11.	(new adj3 (onset or daily) adj3 (migraine* or headache*)).ti,ab.
12.	3 or 6 or 9 or 10 or 11

D.4.2 Screening questionnaires

Medline search terms

1.	exp Questionnaires/
2.	questionnaire*.ti,ab.
3.	Mass Screening/
4.	screen*.ti,ab.
5.	or/1-4

Embase search terms

1.	exp questionnaire/
2.	questionnaire*.ti,ab.
3.	mass screening/ or screening/ or screening test/
4.	screen*.ti,ab.
5.	or/1-4

Cochrane search terms

#1.	MeSH descriptor Questionnaires explode all trees
#2.	questionnaire*:ti,ab
#3.	MeSH descriptor Mass Screening, this term only
#4.	screen*:ti,ab
#5.	#1 or #2 or #3 or #4

D.4.3 Headache diaries

Medline AND Embase search terms

6.	(diary or diaries).ti,ab.
7.	(chronicle* or patient log* or daily record* or daily log*).ti,ab.
8.	or/1-2

Cinahl search terms

S1.	diary or diaries
S2.	chronicle or chronicles or patient log or patient logs or daily record or daily records or daily recording or daily log or daily logs or daily logging
S3.	S1 or S2

Cochrane search terms

#6.	(diary or diaries or chronicle*):ti,ab
#7.	((patient next log*) or (daily next log*) or (daily next record*)):ti,ab
#8.	#1 OR #2

D.4.4 Imaging

Medline search terms

1.	exp tomography, x-ray computed/
2.	exp Magnetic Resonance Imaging/
3.	(neuroimag* or neuro-imag*).ti,ab.
4.	(compute* adj2 tomograph*).ti,ab.
5.	(ct or cat).ti,ab.
6.	((MR or magnetic resonance or NMR) adj2 (imag* or tomograph* or angiograph*)).ti,ab.
7.	MRI.ti,ab.
8.	or/1-7

Embase search terms

1.	neuroimaging/
2.	exp computer assisted tomography/
3.	exp nuclear magnetic resonance imaging/
4.	(neuroimag* or neuro-imag*).ti,ab.
5.	(compute* adj2 tomograph*).ti,ab.
6.	(ct or cat).ti,ab.
7.	((MR or magnetic resonance or NMR) adj2 (imag* or tomograph* or angiograph*)).ti,ab.
8.	MRI.ti,ab.
9.	or/1-8

D.4.5 Acute pharmacological treatments

D.4.5.1 Antiemetics

Medline search terms

1.	antiemetics/ or domperidone/ or metoclopramide/ or cinnarizine/ or cyclizine/
2.	antiemetic*.mp.
3.	Domperidone.mp.
4.	Metoclopramide.mp.
5.	Cinnarizine.mp.
6.	Cyclizine.mp.
7.	Phenothiazines/ or prochlorperazine/ or perphenazine/ or trifluoperazine/ or promethazine/
8.	Phenothiazine*.mp.
9.	Prochlorperazine.mp.
10.	Perphenazine.mp.
11.	Trifluoperazine.mp.
12.	Promethazine.mp.
13.	exp Histamine Antagonists/
14.	antihistamine*.mp.
15.	Cyproheptadine.mp.
16.	migraleve.mp.
17.	migramax.mp.
18.	paramax.mp.
19.	or/1-18

Embase search terms

1.	exp antimigraine agent/
2.	antiemetics/ or domperidone/ or metoclopramide/ or cinnarizine/ or cyclizine/
3.	antiemetic*.mp.
4.	Domperidone.mp.
5.	Metoclopramide.mp.
6.	Cinnarizine.mp.
7.	Cyclizine.mp.
8.	phenothiazine derivative/ or prochlorperazine/ or perphenazine/ or trifluoperazine/ or promethazine/
9.	Phenothiazine*.mp.
10.	Prochlorperazine.mp.
11.	Perphenazine.mp.
12.	Trifluoperazine.mp.
13.	Promethazine.mp.
14.	exp antihistaminic agent/
15.	antihistamine*.mp.
16.	Cyproheptadine.mp.
17.	migraleve.mp.
18.	migramax.mp.
19.	paramax.mp.
20.	or/1-19

Cochrane search terms

#1.	(antiemetic* or cyclizine or domperidone or metoclopramide or cinnarizine):ti,ab,kw
#2.	(phenothiazine* or prochlorperazine or perphenazine or trifluoperazine or promethazine):ti,ab,kw
#3.	MeSH descriptor Histamine Antagonists explode all trees
#4.	(antihistamine* or cyproheptadine):ti,ab
#5.	(migraleve or migramax or paramax):ti,ab
#6.	#1 or #2 or #3 or #4 or #5

D.4.5.2 Aspirin, paracetamol & opioids

Medline search terms

1.	(acetylsalicylic acid or aspirin).mp.
2.	(paracetamol or acetaminophen or panadol).mp.
3.	exp Analgesics, Opioid/
4.	(Buprenorphine or Codeine or Diamorphine or Dihydrocodeine or Dipipanone or Fentanyl or Hydromorphone or Meptazinol or Morphine or Oxycodone or Papaveretum or Pentazocine or Pethidine or Tramadol).mp.
5.	or/1-4

Embase search terms

1.	(acetylsalicylic acid or aspirin).mp.
2.	(paracetamol or acetaminophen or panadol).mp.
3.	exp narcotic analgesic agent/
4.	(Buprenorphine or Codeine or Diamorphine or Dihydrocodeine or Dipipanone or Fentanyl or Hydromorphone or Meptazinol or Morphine or Oxycodone or Papaveretum or Pentazocine or Pethidine or Tramadol).mp.
5.	or/1-4

Cochrane search terms

#1.	(acetylsalicylic acid or aspirin):ti,ab,kw
#2.	(paracetamol or acetaminophen or panadol):ti,ab,kw
#3.	MeSH descriptor Analgesics, Opioid explode all trees
#4.	(Buprenorphine or Codeine or Diamorphine or Dihydrocodeine or Dipipanone or Fentanyl or Hydromorphone or Meptazinol or Morphine or Oxycodone or Papaveretum or Pentazocine or Pethidine or Tramadol):ti,ab,kw
#5.	#1 or #2 or #3 or #4

D.4.5.3 Corticosteroids

Medline search terms

1.	exp Adrenal Cortex Hormones/
2.	adrenal cortex hormone*.mp.
3.	exp Steroids/
4.	(corticosteriod* or glucocorticoid*).mp.
5.	exp Prednisolone/
6.	exp Dexamethasone/
7.	(prednisolone or prednisone or dexamethasone).mp.
8.	or/1-7

Embase search terms

1.	exp corticosteroid/
2.	(corticosteriod* or glucocorticoid*).mp.
3.	exp steroid/
4.	adrenal cortex hormone*.mp.
5.	prednisolone/
6.	dexamethasone/
7.	(prednisolone or prednisone or dexamethasone).mp.
8.	or/1-7

Cochrane search terms

#1.	MeSH descriptor Adrenal Cortex Hormones explode all trees
#2.	("Adrenal Cortex Hormones" or "Adrenal Cortex Hormone"):ti,ab
#3.	MeSH descriptor Steroids explode all trees
#4.	(corticosteriod* or glucocorticoid*):ti,ab
#5.	MeSH descriptor Prednisolone explode all trees
#6.	MeSH descriptor Dexamethasone explode all trees
#7.	(prednisolone or prednisone or dexamethasone):ti,ab,kw
#8.	#1 or #2 or #3 or #4 or #5 or #6 or #7

D.4.5.4 Ergots

Medline search terms

1.	(ergotamine or dihydroergotamine).mp.
2.	(cafergot or migril).mp.
3.	or/1-2

Embase search terms

1.	(ergotamine or dihydroergotamine).mp.
2.	(cafergot or migril).mp.
3.	or/1-2

Cochrane search terms

#1.	(ergotamine or dihydroergotamine):ti,ab,kw
#2.	(cafergot or migril):ti,ab,kw
#3.	(ergotamine or dihydroergotamine):ti,ab,kw
#4.	#1 OR #2 OR #3

D.4.5.5 Hormonal contraception

Medline search terms

1.	contraceptive agents/ or contraceptive agents, female/ or exp contraceptives, oral/ or exp menstruation-inducing agents/
2.	(Loestrin20 or Mercilon or Femodette or Brevinor or Cilest or Eugynon30 or Loestrin30 or Microgynon30 or Norimin or Norinyl-1 or Ovranette or Ovysmen or Yasmin or Femodene or Marvelon or Minulet or BiNovum or Logynon or Qlaira or Synphase or Triadene or Tri-Minulet or Trinordial or TriNovum or Evra patch or Cerazette or Femulen or Micronor or Microval or Neogest or Norgeston or Noriday or Medroxyprogesterone acetate or Depo-provera or Norethisterone enantate or Noristerat or Etonogestrel-releasing implant or Implanon or Mirena).mp.
3.	((progestogen* or progestin* or progestagen* or estrogen* or oestrogen* or combined) adj3 contraceptive*).ti,ab.
4.	or/1-3

Embase search terms

1.	contraceptive agent/ or ethinylestradiol plus etonogestrel/ or ethinylestradiol plus norelgestromin/ or injectable contraceptive agent/ or menstruation inducing agent/ or oral contraceptive agent/
2.	(Loestrin20 or Mercilon or Femodette or Brevinor or Cilest or Eugynon30 or Loestrin30 or Microgynon30 or Norimin or Norinyl-1 or Ovranette or Ovysmen or Yasmin or Femodene or Marvelon or Minulet or BiNovum or Logynon or Qlaira or Synphase or Triadene or Tri-Minulet or Trinordial or TriNovum or Evra patch or Cerazette or Femulen or Micronor or Microval or Neogest or Norgeston or Noriday or Medroxyprogesterone acetate or Depo-provera or Norethisterone enantate or Noristerat or Etonogestrel-releasing implant or Implanon or Mirena).mp.
3.	((progestogen* or progestin* or progestagen* or estrogen* or oestrogen* or combined) adj3 contraceptive*).ti,ab.
4.	or/1-3

Cochrane search terms

#1.	MeSH descriptor Contraceptive Agents, this term only
#2.	MeSH descriptor Contraceptive Agents, Female, this term only
#3.	MeSH descriptor Contraceptives, Oral explode all trees
#4.	(Loestrin20 or Mercilon or Femodette or Brevinor or Cilest or Eugynon30 or Loestrin30 or Microgynon30 or Norimin or Norinyl-1 or Ovranette or Ovysmen or Yasmin or Femodene or Marvelon or Minulet or BiNovum or Logynon or Qlaira or Synphase or Triadene or Tri-Minulet or Trinordial or TriNovum or Evra patch or Cerazette or Femulen or Micronor or Microval or Neogest or Norgeston or Noriday or "Medroxyprogesterone acetate" or Depo-provera or "Norethisterone enantate" or Noristerat or "Etonogestrel-releasing implant" or Implanon or Mirena):ti,ab
#5.	((progestogen* near3 contraceptive*) or (progestin* near3 contraceptive*) or (progestagen* near3 contraceptive*) or (estrogen* near3 contraceptive*) or (oestrogen* near3 contraceptive*) or (combined near3 contraceptive*)):ti,ab
#6.	#1 or #2 or #3 or #4 or #5

D.4.5.6 NSAIDs

Medline search terms

1.	exp Anti-Inflammatory Agents, Non-Steroidal/
2.	(((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or NSAID*).tw.
3.	(Aceclofenac or Acemetacin or Celecoxib or Dexibuprofen or Dexketoprofen or Diclofenac or Etodolac or Etoricoxib or Fenbufen or Fenoprofen or Flurbiprofen or Ibuprofen or Indometacin or Ketoprofen or Mefenamic acid or Meloxicam or Nabumetone or Naproxen or Piroxicam or Sulindac or Tenoxicam or Tiaprofenic acid or tolfenamic acid or clotam rapid).mp.
4.	or/1-3

Embase search terms

1.	exp nonsteroid antiinflammatory agent/
2.	(((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or NSAID*).tw.
3.	(Aceclofenac or Acemetacin or Celecoxib or Dexibuprofen or Dexketoprofen or Diclofenac or Etodolac or Etoricoxib or Fenbufen or Fenoprofen or Flurbiprofen or Ibuprofen or Indometacin or Ketoprofen or Mefenamic acid or Meloxicam or Nabumetone or Naproxen or Piroxicam or Sulindac or Tenoxicam or Tiaprofenic acid or Tolfenamic acid or clotam rapid).mp.
4.	or/1-3

Cochrane search terms

#1.	MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees
#2.	("nonsteroidal antinflammatory" or "non-steriodal antinflammatory" or "non steroidal antinflammatory" or "nonsteroidal anti-inflammatory" or "non-steriodal anti-inflammatory" or "non steroidal anti-inflammatory" or "nonsteroidal anti inflammatory" or "non-steriodal anti inflammatory" or "non steroidal anti inflammatory" or NSAID*):ti,ab
#3.	(Aceclofenac or Acemetacin or Celecoxib or Dexibuprofen or Dexketoprofen or Diclofenac or Etodolac or Etoricoxib or Fenbufen or Fenoprofen or Flurbiprofen or Ibuprofen or Indometacin or Ketoprofen or Mefenamic acid or Meloxicam or Nabumetone or Naproxen or Piroxicam or Sulindac or Tenoxicam or "Tiaprofenic acid" or "tolfenamic acid" or "clotam rapid"):ti,ab,kw
#4.	#1 or #2 or #3

D.4.5.7 Triptans

Medline search terms

1.	Tryptamines/ or Sumatriptan/
2.	(triptan* or Almotriptan or Eletriptan or Frovatriptan or Naratriptan or Rizatriptan or Sumatriptan or Zolmitriptan).mp.
3.	(almogran or relpax or migard or naramig or maxalt or imigran or zomig).mp.
4.	or/1-3

Embase search terms

1.	exp triptan derivative/
2.	(triptan* or Almotriptan or Eletriptan or Frovatriptan or Naratriptan or Rizatriptan or Sumatriptan or Zolmitriptan).mp.
3.	(almogran or relpax or migard or naramig or maxalt or imigran or zomig).mp.
4.	or/1-3

Cochrane search terms

#1.	MeSH descriptor Tryptamines, this term only
#2.	(triptan* or Almotriptan or Eletriptan or Frovatriptan or Naratriptan or Rizatriptan or Sumatriptan or Zolmitriptan):ti,ab,kw
#3.	(almogran or relpax or migard or naramig or maxalt or imigran or zomig):ti,ab,kw
#4.	#1 or #2 or #3

D.4.6 Prophylactic pharmacological interventions

Medline search terms

1.	exp Calcium Channel Blockers/
2.	(calcium adj3 (blocker* or antagonist* or inhibitor*)).ti,ab.
3.	(nimodipine or diltiazem or verapamil).ti,ab.
4.	Angiotensin-Converting Enzyme Inhibitors/
5.	angiotensin receptor antagonists/ or angiotensin ii type 1 receptor blockers/ or angiotensin ii type 2 receptor blockers/
6.	(Captopril or Cilazapril or Enalapril maleate or Fosinopril sodium or Imidapril hydrochloride or Lisinopril or Moexipril hydrochloride or Perindopril erbumine or Perindopril arginine or Quinapril or Ramipril or Ramipril with felodipine or Trandolapril).mp.
7.	(Angiotensin-Converting Enzyme Inhibitor* or ACE inhibitor* or angiotensin receptor blocker* or ARB or ARBS).ti,ab.
8.	(candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan).ti,ab.
9.	exp Serotonin Uptake Inhibitors/
10.	(selective serotonin reuptake inhibitor* or selective serotonin uptake inhibitor* or SSRI*).ti,ab.
11.	(paroxetine or citalopram or escitalopram or fluoxetine or fluvoxamine or sertraline or mirtazapine).ti,ab.
12.	(SNRI* or serotonin norepinephrine reuptake inhibitor*).ti,ab.
13.	venlafaxine.ti,ab.
14.	exp Antidepressive Agents, Tricyclic/
15.	tricyclic*.ti,ab.
16.	(amitryptyline or amitriptiline or imipramine or nortriptyline or desipramine or dosulepin).ti,ab.
17.	exp Adrenergic beta-Antagonists/
18.	(beta-blocker* or beta?blocker*).ti,ab.
19.	(propranolol or metoprolol or nadolol or timolol or atenolol).ti,ab.
20.	methysergide/ or pizotyline/
21.	Ergotamine/
22.	Cyproheptadine/
23.	(serotonergic adj2 modulator*).ti,ab.
24.	(methysergide or pizotifen or pizotyline or ergotamine or cyproheptadine).ti,ab.
25.	exp Anticonvulsants/
26.	(anticonvulsant* or antiepileptic or anti-epileptic*).ti,ab.
27.	(sodium valproate or valproic acid or topiramate or gabapentin).ti,ab.
28.	or/1-27

Embase search terms

1.	(calcium adj3 (blocker* or antagonist* or inhibitor*)).ti,ab.
2.	(nimodipine or diltiazem or verapamil).ti,ab.
3.	exp calcium channel blocking agent/

4.	exp dipeptidyl carboxypeptidase inhibitor/
5.	exp angiotensin receptor antagonist/
6.	(Angiotensin-Converting Enzyme Inhibitor* or ACE inhibitor* or angiotensin receptor blocker* or ARB or ARBS).ti,ab.
7.	(captopril or cilazapril or enalapril maleate or fosinopril sodium or imidapril hydrochloride or lisinopril or moexipril hydrochloride or perindropril or quinapril or ramipril or trandolapril).mp.
8.	(candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan).ti,ab.
9.	exp serotonin uptake inhibitor/
10.	(selective serotonin reuptake inhibitor* or selective serotonin uptake inhibitor* or SSRI*).ti,ab.
11.	(paroxetine or citalopram or escitalopram or fluoxetine or fluvoxamine or sertraline or mirtazapine).ti,ab.
12.	(SNRI* or serotonin norepinephrine reuptake inhibitor*).ti,ab.
13.	venlafaxine.ti,ab.
14.	exp tricyclic antidepressant agent/
15.	tricyclic*.ti,ab.
16.	(amitryptyline or amitriptiline or imipramine or nortriptyline or desipramine or dosulepin).ti,ab.
17.	exp *beta adrenergic receptor blocking agent/
18.	(beta-blocker* or beta?blocker*).ti,ab.
19.	(propranolol or metoprolol or nadolol or timolol or atenolol).ti,ab.
20.	(serotonergic adj2 modulator*).ti,ab.
21.	(methysergide or pizotifen or pizotyline or ergotamine or cyproheptadine).ti,ab.
22.	methysergide/ or methysergide maleate/
23.	pizotifen/ or pizotifen maleate/
24.	ergotamine/ or ergotamine tartrate/
25.	cyproheptadine/
26.	exp anticonvulsive agent/
27.	(anticonvulsant* or antiepileptic or anti-epileptic*).ti,ab.
28.	(sodium valproate or valproic acid or topiramate or gabapentin).ti,ab.
29.	or/1-28

Cochrane search terms

#1.	MeSH descriptor Calcium Channel Blockers explode all trees
#2.	MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees
#3.	MeSH descriptor Angiotensin II Type 1 Receptor Blockers explode all trees
#4.	MeSH descriptor Serotonin Uptake Inhibitors explode all trees
#5.	MeSH descriptor Antidepressive Agents, Tricyclic explode all trees
#6.	MeSH descriptor Adrenergic beta-Antagonists explode all trees
#7.	MeSH descriptor Anticonvulsants explode all trees
#8.	MeSH descriptor Ergotamine explode all trees
#9.	MeSH descriptor Pizotyline explode all trees
#10.	MeSH descriptor Methysergide explode all trees
#11.	MeSH descriptor Cyproheptadine explode all trees
#12.	(calcium near3 (blocker* or antagonist* or inhibitor*)):ti,ab
#13.	(nimodipine or diltiazem or verapamil):ti,ab
#14.	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril):ti,ab
#15.	("angiotensin-converting enzyme inhibitor*"):ti,ab

#16.	("ace inhibitor*"):ti,ab
#17.	(arb or arbs):ti,ab
#18.	(angiotensin near receptor near blocker*):ti,ab
#19.	(ssri* or "selective serotonin reuptake inhibitor*" or "selective serotonin uptake inhibitor*"):ti,ab
#20.	(snri* or "serotonin norepinephrine reuptake inhibitor*"):ti,ab
#21.	(venlafaxine or paroxetine or citalopram or escitalopram or fluoxetine or fluvoxamine or sertraline or mirtazapine):ti,ab
#22.	(tricyclic* or amitryptyline or amitriptiline or imipramine or nortriptyline or desipramine or dosulepin):ti,ab
#23.	(beta-blocker* or "beta blocker*"):ti,ab
#24.	(propranolol or metoprolol or nadolol or timodol or atenolol or methysergide or pizotyline or pizotifen or ergotamine or cyproheptadine or "sodium valproate" or "valproic acid" or topiramate or gabapentin or anticonvulsant* or antiepileptic* or anti-epileptic*):ti,ab
#25.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

D.4.7 Non-pharmacological treatments

D.4.7.1 Acupuncture

Medline search terms

1.	Acupuncture/
2.	exp Acupuncture Therapy/
3.	(acupunctur* or needling or electroacupunctur*).ti,ab.
4.	or/1-3

Embase search terms

1.	exp Acupuncture/
2.	(acupunctur* or needling or electroacupunctur*).ti,ab.
3.	or/1-2

Cochrane search terms

#1.	MeSH descriptor Acupuncture, this term only
#2.	MeSH descriptor Acupuncture Therapy explode all trees
#3.	(acupunctur* or needling or electroacupunctur*):ti,ab
#4.	#1 or #2 or #3

Cinahl search terms

S1.	(MH "Acupuncture+") OR (MH "Acupuncturists")
S2.	acupunctur* or electroacupunctur* or needling
S3.	S1 or S2

D.4.7.2 Dietary supplements

Medline search terms

1.	exp Dietary Supplements/
2.	vitamins/ or vitamin b complex/ or exp riboflavin/ or exp vitamin b 12/
3.	magnesium compounds/ or magnesium chloride/ or magnesium hydroxide/ or magnesium oxide/ or magnesium sulfate/
4.	Magnesium/
5.	exp Ubiquinone/

6.	(vitamin B12 or vitamin B 12).ti,ab.
7.	(cobalamin* or cyanocobalamin* or cobamide* or hydroxo-cobalamin* or hydroxycobalamin* or hydroxocobalamin*).ti,ab.
8.	(riboflavin or vitamin B2 or vitamin B 2 or vitamin g).ti,ab.
9.	(magnesium adj2 (supplement* or salt* or carbonate or oxide or chloride or sulphate or sulfate or maleate or citrate or lactate or aspartate or chelate)).ti,ab.
10.	(coenzyme Q10 or ubiquinone or ubidecarenone).ti,ab.
11.	or/1-10

Embase search terms

1.	diet supplementation/
2.	Vitamin B complex/ or Vitamin/ or Vitamin B group/
3.	exp riboflavin/
4.	exp cobalamin derivative/
5.	magnesium/ or magnesium aspartate/ or magnesium carbonate/ or magnesium chloride/ or magnesium citrate/ or magnesium derivative/ or magnesium hydroxide/ or magnesium oxide/ or magnesium salt/ or magnesium sulfate/
6.	ubidecarenone/
7.	(vitamin B12 or vitamin B 12).ti,ab.
8.	(cobalamin* or cyanocobalamin* or hydroxycobalamin* or hydroxo-cobalamin* or cobamide* or hydroxocobalamin*).ti,ab.
9.	(riboflavin or vitamin B2 or vitamin B 2 or vitamin g).ti,ab.
10.	(magnesium adj2 (supplement* or salt* or carbonate or oxide or chloride or sulphate or sulfate or maleate or citrate or lactate or aspartate or chelate)).ti,ab.
11.	(coenzyme Q10 or ubiquinone or ubidecarenone).ti,ab.
12.	or/1-11

Cochrane search terms

#1.	MeSH descriptor Dietary Supplements, this term only
#2.	MeSH descriptor Vitamins, this term only
#3.	MeSH descriptor Vitamin B Complex, this term only
#4.	MeSH descriptor Riboflavin explode all trees
#5.	MeSH descriptor Vitamin B 12 explode all trees
#6.	MeSH descriptor Magnesium explode all trees
#7.	MeSH descriptor Magnesium Compounds, this term only
#8.	MeSH descriptor Magnesium Chloride, this term only
#9.	MeSH descriptor Magnesium Hydroxide, this term only
#10.	MeSH descriptor Magnesium Oxide, this term only
#11.	MeSH descriptor Magnesium Sulfate, this term only
#12.	MeSH descriptor Ubiquinone, this term only
#13.	(Vitamin B12 or vitamin B 12):ti,ab
#14.	(cobalamin* or cyanocobalamin* or hydroxycobalamin* or hydroxo-cobalamin* or cobamide* or hydroxocobalamin*):ti,ab
#15.	(riboflavin or vitamin B2 or vitamin B 2 or vitamin G):ti,ab
#16.	(magnesium near/2 (supplement* or salt* or carbonate or oxide or chloride* or sulphate or sulfate or maleate or citrate or lactate or asparate or chelate)):ti,ab
#17.	("coenzyme Q10" or ubiquinone or ubidecarenone):ti,ab
#18.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17

Cinahl search terms

S1.	(MH "Dietary Supplementation") or (MH "Dietary Supplements") or (MH "Vitamins")

	or (MH "Vitamin B Complex") or (MH "Vitamin B12") or (MH "Riboflavin") or (MH "Magnesium") or (MH "Magnesium Compounds") or (MH "Magnesium Sulfate") or (MH "Coenzyme Q")
S2.	"vitamin B 12" or "Vitamin B12" or cobalamin* or cyanocobalamin* or cobamide* or hydroxo-cobalamin* or hydroxocobalamin or hydroxycobalamin or riboflavin or "vitamin B 2" or "Vitamin B2" or "vitamin G"
S3.	coenzyme Q-10 or coenzyme Q10 or ubiquinone or ubidecarenone
S4.	magnesium N2 supplement* or magnesium N2 salt* or magnesium N2 carbonate or magnesium N2 oxide or magnesium N2 chloride or magnesium N2 sulphate or magnesium N2 sulfate or magnesium N2 maleate or magnesium N2 citrate or magnesium N2 lactate or magnesium N2 aspartate or magnesium N2 chelate
S5.	S1 or S2 or S3 or S4

D.4.7.3 Herbal remedies

Medline search terms

1.	Herbal Medicine/ or Drugs,chinese herbal/
2.	Tanacetum parthenium/
3.	Petasites/
4.	Phytotherapy/
5.	Plants, Medicinal/
6.	plant preparations/ or plant extracts/
7.	feverfew*.ti,ab.
8.	((chrysanthemum or tanacetum) adj2 parthenium*).ti,ab.
9.	(butterbur* or petasite*).ti,ab.
10.	or/1-9

Embase search terms

1.	herbal medicine/ or herb/ or herbaceous agent/
2.	phytotherapy/
3.	medicinal plant/
4.	plant extract/
5.	plant medicinal product/
6.	tanacetum parthenium/ or tanacetum parthenium extract/
7.	butterbur/
8.	petasites/ or exp petasites hybridus extract/
9.	Petasites extract/
10.	feverfew*.ti,ab.
11.	((chrysanthemum or tanacetum) adj2 parthenium*).ti,ab.
12.	(butterbur* or petasite*).ti,ab.
13.	or/1-12

Cochrane search terms

#1.	MeSH descriptor Herbal Medicine, this term only
#2.	MeSH descriptor Phytotherapy, this term only
#3.	MeSH descriptor Plants, Medicinal, this term only
#4.	MeSH descriptor Plant Preparations, this term only
#5.	MeSH descriptor Plant Extracts, this term only
#6.	MeSH descriptor Drugs, Chinese Herbal, this term only
#7.	(feverfew* or butterbur* or petasites):ti,ab
#8.	((chrysanthemum or tanacetum) NEXT parthenium):ti,ab
#9.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

Cinahl search terms

S1.	(MH "Medicine, Herbal") or (MH "Plant Extracts") or (MH "Drugs, Chinese Herbal") or (MH "Plants, Medicinal") or (MH "Butterbur") or (MH "Feverfew") or (MH "Herbalists")
S2.	feverfew* or butterbur* or petasite* or chrysanthemum N2 parthenium or tanectum N2 parthenium
S3.	S1 or S2

D.4.7.4 Exercise

Medline search terms

1.	exp Exercise/
2.	exp Exercise Therapy/
3.	"Physical Education and Training"/
4.	exp Exercise Movement Techniques/
5.	(exercise adj3 (session* or training or technique* or physical or isometric or aerobic or therap* or program* or class*)).ti,ab.
6.	(tai chi or tai ji or pilates or yoga).ti,ab.
7.	(physical adj2 (training or education or program*)).ti,ab.
8.	or/1-7

Embase search terms

1.	exp exercise/
2.	kinesiotherapy/
3.	physical education/
4.	(exercise adj3 (session* or training or technique* or physical or isometric or aerobic or therap* or program* or class*)).ti,ab.
5.	(tai chi or tai ji or pilates or yoga).ti,ab.
6.	(physical adj2 (training or education or program*)).ti,ab.
7.	or/1-6

Cochrane search terms

#1.	MeSH descriptor Exercise explode all trees
#2.	MeSH descriptor Exercise Therapy explode all trees
#3.	MeSH descriptor Physical Education and Training, this term only
#4.	MeSH descriptor Exercise Movement Techniques explode all trees
#5.	(exercise near/3 (session* or training or technique* or physical or isometric or aerobic or therap* or program* or class*)):ti,ab
#6.	("tai chi" or "tai ji" or pilates or yoga):ti,ab
#7.	(physical next (training or education or program*)):ti,ab
#8.	#1 or #2 or #3 or #4 or #5 or #6 or #7

Cinahl search terms

S1.	(MH "Exercise+") or (MH "Therapeutic Exercise+") or (MH "Physical Education and Training")
S2.	tai chi or tai ji or pilates or yoga or physical N2 training or physical N2 education or physical N3 program* or exercise N2 session* or exercise N2 training or exercise N2 technique* or exercise N2 therap* or therapeutic n2 exercise or exercise N2 program* or exercise N2 class* or physical N2 exercise* or isometric N2 exercise* or aerobic N2 exercise*
S3.	S1 or S2

D.4.7.5 Manual therapies

Medline search terms

1.	exp Musculoskeletal Manipulations/ or "Physical Therapy (Speciality)"/ or Physical Therapy Modalities/
2.	Chiropractic/
3.	Manipulation, Orthopedic/
4.	Osteopathic Medicine/
5.	((lumbar or cervical or spinal or musculoskeletal) adj2 manipulat*).ti,ab.
6.	(osteopath* or chiropractic* or reflexolog* or massage or acupressure or shiatsu or shiatzu).ti,ab.
7.	((movement or manual or manipulat* or trigger point or motion or passive or cpm) adj2 therap*).ti,ab.
8.	(stretching adj2 (exercise* or relaxed or dynamic or passive or muscle or active or isometric)).ti,ab.
9.	or/1-8

Embase search terms

1.	exp manipulative medicine/ or physiotherapy/ or joint mobilization/
2.	((lumbar or cervical or spinal or musculoskeletal) adj2 manipulat*).ti,ab.
3.	(osteopath* or chiropractic* or reflexolog* or massage or acupressure or shiatsu or shiatzu).ti,ab.
4.	((movement or manual or manipulat* or trigger point or motion or passive or cpm) adj2 therap*).ti,ab.
5.	(stretching adj2 (exercise* or relaxed or dynamic or passive or muscle or active or isometric)).ti,ab.
6.	or/1-5

Cochrane search terms

#1.	MeSH descriptor Musculoskeletal Manipulations explode all trees
#2.	MeSH descriptor Chiropractic, this term only
#3.	MeSH descriptor Manipulation, Orthopedic, this term only
#4.	MeSH descriptor Osteopathic Medicine, this term only
#5.	((lumbar or cervical or spinal or musculoskeletal) next manipulat*):ti,ab
#6.	(osteopath* or chiropractic* or reflexolog* or massage or acupressure or shiatsu or shaitzu):ti,ab
#7.	((movement or manual or manipulat* or "trigger point" or motion or passive or cpm) NEXT therap*):ti,ab
#8.	(stretching near/3 (exercise* or relaxed or dynamic or passive or active or muscle or isometric)):ti,ab
#9.	MeSH descriptor Physical Therapy (Specialty), this term only
#10.	MeSH descriptor Physical Therapy Modalities, this term only
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or # 8 or #9 or #10

Cinahl search terms

S1.	(MH "Physical Therapy") or (MH "Manual Therapy+") or (MH "Joint Mobilization") or (MH "Osteopathy") or (MH "Osteopathic Medicine") or (MH "Osteopaths") or (MH "Chiropractic") or (MH "Chiropractic Assessment") or (MH "Chiropractic Practice") or (MH "Chiropractors")
S2.	lumbar N2 manipulat* or cervical N2 manipulat* or spinal n2 manipulat* or musculoskeletal N2 manipulat* or osteopath* or chiropractic* or reflexolog* or massage* or acupressure* or shiatsu or shaitzu or movement N2 therap* or manual N2 therap* or manipulat* N2 therap* or "trigger point" N2 therap* or motion N2

	therap* or cpm or stretch* N2 exercise* or relaxed N2 stretch* or dynamic n2 stretch* or passive N2 stretch* or muscle N2 stretch* or active N2 stretch* or isometric N2 stretch*
S3.	S1 or S2

D.4.7.6 Education and self management programmes

Medline search terms

1.	Self Care/ or Social Support/ or Counseling/
2.	Self-Help Groups/ or exp Patient participation/
3.	health education/ or exp consumer health information/ or patient education as topic/ or Communication/ or Health Communication/
4.	patient education handout/
5.	teaching/ or exp Programmed Instruction as Topic/
6.	exp communications media/ or Hotlines/ or exp Internet/
7.	information centers/ or information services/ or learning/
8.	Information Dissemination/ or Health Knowledge, Attitudes, Practice/
9.	(self care or self-care or selfcare or selfhelp or self-help or self help or self-management or self management).ti,ab.
10.	(social support or support group*).ti,ab.
11.	((education* or learn* or training or teach*) adj2 (program* or patient* or consumer* or material* or resource* or aid*)).ti,ab.
12.	(information adj2 (resource* or leaflet* or pamphlet* or handout*)).ti,ab.
13.	(patient adj (information or knowledge or website*)).ti,ab.
14.	(workshop* or counse?ling or seminar* or discussion group*).ti,ab.
15.	(factsheet* or advice line* or advice-line* or help line* or help-line* or helpline*).ti,ab.
16.	or/1-15

Embase search terms

1.	self care/ or self help/ or social support/
2.	health education/ or patient education/ or patient participation/
3.	consumer health information/ or patient information/
4.	teaching/ or counseling/ or patient counseling/
5.	exp mass communication/ or interpersonal communication/
6.	information center/ or information dissemination/ or information service/
7.	learning/ or lifelong learning/ or self-directed learning/
8.	(self care or selfcare or self-care or selfhelp or self-help or self help or self-management or self management).ti,ab.
9.	(support group* or social support).ti,ab.
10.	((education* or learn* or training or teach*) adj2 (program* or patient* or consumer* or material* or resource* or aid*)).ti,ab.
11.	(information adj2 (resource* or leaflet* or pamphlet* or handout*)).ti,ab.
12.	(patient adj (information or knowledge or website*)).ti,ab.
13.	(workshop* or counse?ling or seminar* or discussion group*).ti,ab.
14.	(factsheet* or advice line* or advice-line* or help line* or help-line* or helpline*).ti,ab.
15.	or/1-14

Cochrane search terms

#1.	MeSH descriptor Self Care, this term only
#2.	MeSH descriptor Social Support explode all trees

#3.	MeSH descriptor Counseling, this term only
#4.	MeSH descriptor Self-Help Groups, this term only
#5.	MeSH descriptor Patient Participation, this term only
#6.	MeSH descriptor Health Education, this term only
#7.	MeSH descriptor Consumer Health Information explode all trees
#8.	MeSH descriptor Patient Education as Topic, this term only
#9.	MeSH descriptor Communication, this term only
#10.	MeSH descriptor Teaching, this term only
#11.	MeSH descriptor Programmed Instruction as Topic explode all trees
#12.	MeSH descriptor Communications Media explode all trees
#13.	MeSH descriptor Hotlines, this term only
#14.	MeSH descriptor Internet explode all trees
#15.	MeSH descriptor Information Centers, this term only
#16.	MeSH descriptor Information Services, this term only
#17.	MeSH descriptor Learning, this term only
#18.	MeSH descriptor Information Dissemination explode all trees
#19.	MeSH descriptor Health Knowledge, Attitudes, Practice explode all trees
#20.	(selfcare or "self care" or self-care or selfhelp or self-help or "self help" or self-management or "self management"):ti,ab
#21.	("social support" or "support group*"):ti,ab
#22.	((education* or training or teach* or learn*) near/2 (program* or consumer* or material* or aid* or resource* or patient*)):ti,ab
#23.	(information NEXT (resource* or leaflet* or pamphlet* or handout*)):ti,ab
#24.	(patient NEXT (information or knowledge or website*)):ti,ab
#25.	(workshop* or counseling or counselling or seminar* or "discussion group*"):ti,ab
#26.	(factsheet* or "advice line*" or advice-line* or help-line* or helpline* or "help line*"):ti,ab
#27.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 or #22 or #23 or #24 OR #25 OR #26

Cinahl search terms

S1.	(MH "Self Care") or (MH "Support, Psychosocial") or (MH "Counseling") or (MH "Support Groups") or (MH "Consumer Participation") or (MH "Health Education") or (MH "Health Information") or (MH "Consumer Health Information") or (MH "Libraries, Consumer Health") or (MH "Patient Education") or (MH "Communication")
S2.	(MH "Teaching") or (MH "Self Directed Learning") or (MH "Teaching Materials") or (MH "Programmed Instruction+") or (MH "Seminars and Workshops") or (MH "Communications Media+") or (MH "Information Centers") or (MH "Telephone Information Services") or (MH "Library Services") or (MH "Information Services") or (MH "Pamphlets")
S3.	(MH "Learning") or (MH "Lifelong Learning") or (MH "Health Knowledge") or (MH "Information Needs")
S4.	(self-care or selfcare or self care or selfhelp or self-help or self help or self-management or self management) or (social support or support group* or workshop* or counseling or counselling or seminar* or discussion group*) or (factsheet* or advice line* or advice-line* or help line* or help-line* or helpline*)
S5.	(education N2 material* or education N2 resource* or education N2 aid*) or (learn* N2 material* or learn* n2 resource* or learn N2 aid*) or (training N2 resource* or training n2 aid* or training n2 material* or teach* N2 aid*or teach n2 resource* or teach N2 material*)
S6.	(education N2 program* or patient n2 education or consumer N2 education) or

	(learn* N2 program* or training n2 program* or consumer n2 program* or patient N2 program*) or (training N2 program* or patient n2 train* or consumer n2 train*)
S7.	information n2 resource* or information n2 leaflet* or information N2 pamphlet* or information N2 handout* or patient N2 information or patient n2 knowledge or patient N2 website*
S8.	S1 or S2 or S3 or S4 or S5 or S6 or S7

PsycINFO search terms

1.	exp self help techniques/
2.	social support/
3.	counseling/
4.	support groups/
5.	client participation/
6.	health education/ or client education/ or health knowledge/
7.	communication/ or information dissemination/
8.	computer assisted instruction/ or individualized instruction/ or programmed instruction/
9.	exp Communications Media/
10.	Teaching/
11.	hot line services/
12.	exp communication systems/
13.	information services/
14.	learning/
15.	(self care or selfcare or self-care or selfhelp or self-help or self help or self-management or self management).ti,ab.
16.	(support group$ or social support).ti,ab.
17.	((education$ or learn$ or training or teach$) adj2 (program$ or patient$ or consumer$ or material$ or resource$ or aid$)).ti,ab.
18.	(information adj2 (resource$ or leaflet$ or pamphlet$ or handout$)).ti,ab.
19.	(patient adj2 (information or knowledge or website$)).ti,ab.
20.	(workshop$ or counselling or seminar$ or discussion group$).ti,ab.
21.	(factsheet$ or advice line$ or advice-line$ or help line$ or help-line$ or helpline$).ti,ab.
22.	or/1-21

D.4.7.7 Psychological therapies

Medline search terms

1.	Cognitive Therapy/
2.	exp Biofeedback, Psychology/ or feedback/ or feedback, psychological/ or autogenic training/
3.	Breathing Exercises/
4.	relaxation therapy/
5.	Muscle Relaxation/
6.	Relaxation/
7.	"Imagery (Psychotherapy)"/
8.	Meditation/
9.	Mind-Body Therapies/ or Mind-Body Relations, metaphysical/
10.	Psychotherapy/
11.	(cognitive adj behavio?r adj (therap* or treatment or technique*)).ti,ab.
12.	(neurofeedback or biofeedback).ti,ab.
13.	((controlled or paced or therap* or exercise*) adj2 breathing).ti,ab.

14.	(respirat* adj3 (training or exercise* or therap*)).ti,ab.
15.	(CBT or qigong).ti,ab.
16.	(guided adj2 (imagery or visuali*)).ti,ab.
17.	(mindfulness or meditation or attention* control training).ti,ab.
18.	((finger or hand) adj2 warming).ti,ab.
19.	(handwarming or fingerwarming).ti,ab.
20.	(relaxation adj2 (therap* or training)).ti,ab.
21.	(relaxation adj2 (muscle* or progressive or therap* or exercis* or technique* or training)).ti,ab.
22.	or/1-21

Embase search terms

1.	cognitive therapy/
2.	psychophysiology/
3.	feedback system/ or autogenic training/
4.	neurofeedback/ or neurofeedback training/
5.	breathing exercise/
6.	relaxation training/
7.	smooth muscle relaxation/ or muscle relaxation/
8.	guided imagery/
9.	meditation/
10.	psychotherapy/
11.	warming/
12.	(cognitive adj behavio?r* adj (therap* or treatment or technique*)).ti,ab.
13.	CBT.ti,ab.
14.	(neurofeedback or biofeedback).ti,ab.
15.	((controlled or paced or exercise* or therap*) adj2 breathing).ti,ab.
16.	(respirat* adj3 (training or exercise* or therap*)).ti,ab.
17.	qigong.ti,ab.
18.	(guided adj2 (imagery or visuali*)).ti,ab.
19.	(mindfulness or meditation or attention* control training).ti,ab.
20.	(finger warming or fingerwarming or hand warming or handwarming).ti,ab.
21.	(relaxation adj2 (muscle* or progressive or therap* or exercis* or technique* or training)).ti,ab.
22.	or/1-21

Cochrane search terms

#1.	MeSH descriptor Psychotherapy, this term only
#2.	MeSH descriptor Cognitive Therapy, this term only
#3.	MeSH descriptor Feedback, Psychological explode all trees
#4.	MeSH descriptor Feedback, this term only
#5.	MeSH descriptor Autogenic Training, this term only
#6.	MeSH descriptor Breathing Exercises, this term only
#7.	MeSH descriptor Relaxation, this term only
#8.	MeSH descriptor Relaxation Therapy explode all trees
#9.	MeSH descriptor Muscle Relaxation, this term only
#10.	MeSH descriptor Imagery (Psychotherapy), this term only
#11.	MeSH descriptor Mind-Body Therapies, this term only
#12.	MeSH descriptor Mind-Body Relations, Metaphysical, this term only
#13.	(cognitive NEXT (behaviour* or behavior* or therap* or technique*)):ti,ab
#14.	(neurofeedback or biofeedback or CBT or qigong or handwarming or fingerwarming or hand-warming or finger-warming):ti,ab

#15.	((controlled or paced or therap* or exercis*) near/3 breathing):ti,ab
#16.	(respirat* NEXT (training or exercis* or therap*)):ti,ab
#17.	(guided NEXT (imagery or visuali*)):ti,ab
#18.	(mindfulness or meditation or " attention* control training"):ti,ab
#19.	((finger or hand) NEXT warming):ti,ab
#20.	(relaxation near/2 (muscle* or progressive or therap* or exercis* or technique* or training)):ti,ab
#21.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

Cinahl search terms

S1.	(MH "Biofeedback") or (MH "Cognitive Therapy") or (MH "Autogenic Training (Iowa NIC)") or (MH "Biofeedback (Iowa NIC)") or (MH "Breathing Exercises+") or (MH "Simple Relaxation Therapy (Iowa NIC)") or (MH "Progressive Muscle Relaxation (Iowa NIC)") or (MH "Relaxation Techniques") or (MH "Muscle Relaxation") or (MH "Guided Imagery") or (MH "Simple Guided Imagery (Iowa NIC)") or (MH "Psychotherapy")
S2.	(MH "Mind Body Techniques") or (MH "Meditation") or (MH "Qigong") or (MH "Meditation (Iowa NIC)")
S3.	(cognitive N3 therap* or cognitive N2 behaviour or cognitive n3 technique* or cognitive N2 behavior) or (neurofeedback or biofeedback or CBT or qigong or guided n2 imagery or visualization or guided n2 visuali*) or (mindfulness or meditation or attention* control training)
S4.	(controlled n2 breathing or paced n2 breathing or breathing n2 therap* or breathing n2 exercise* or respirat* N3 training or respirat* n3 exercise* or respirat* N3 therap*) or (finger n2 warming or hand n2 warming or handwarming or fingerwarming or hand-warming or finger-warming) or (relaxation n2 therap*or relaxation n2 training or progressive n3 relaxation or relaxation n3 exercise* or relaxation n3 technique*)
S5.	S1 or S2 or S3 or S4

PsycINFO search terms

1.	exp cognitive behavior therapy/
2.	exp biofeedback/
3.	autogenic training/
4.	respiration/
5.	exp relaxation therapy/
6.	muscle relaxation/ or relaxation/
7.	imagery/ or guided imagery/
8.	mindfulness/ or meditation/
9.	*behavior therapy/
10.	*psychotherapeutic techniques/
11.	(cognitive adj behavio?r adj (therap$ or treatment or technique$)).ti,ab.
12.	(neurofeedback or biofeedback).ti,ab.
13.	((controlled or paced or exercise$ or therap$) adj2 breathing).ti,ab.
14.	(respirat$ adj3 (training or exercise$ or therap$)).ti,ab.
15.	(CBT or qigong).ti,ab.
16.	(guided adj2 (imagery or visuali$)).ti,ab.
17.	(mindfulness or meditation or attention$ control training).ti,ab.
18.	(finger warming or fingerwarming or hand warming or handwarming).ti,ab.
19.	((finger or hand) adj2 warming).ti,ab.
20.	(relaxation adj2 (therap$ or muscle$ or progressive or exercis$ or technique$ or training)).ti,ab.
21.	or/1-20

D.4.8 Fetal adverse events

D.4.8.1 Fetal adverse events – oxygen

Medline search terms

1.	exp Oxygen Inhalation Therapy/
2.	oxygen.ti,ab.
3.	or/1-2
4.	(pregnan* or prenatal).mp.
5.	3 and 4
6.	Abnormalities, Drug-Induced/
7.	3 and 6
8.	exp Oxygen Inhalation Therapy/ae, ct [Adverse Effects, Contraindications]
9.	or/5,7-8
10.	Pregnancy Outcome/
11.	((pregnan* or birth) adj2 outcome*).mp.
12.	exp Pregnancy Complications/
13.	exp Congenital Abnormalities/
14.	((f?etal or f?etus or birth or neonatal or congenital or pregnan*) adj3 (complication* or abnormal* or defect* or malformation*)).mp.
15.	or/10-14
16.	9 and 15

Embase search terms

1.	exp oxygen therapy/
2.	oxygen*.ti,ab.
3.	or/1-2
4.	(pregnan* or prenatal).mp.
5.	3 and 4
6.	drug induced disease/
7.	exp adverse drug reaction/
8.	exp side effect/
9.	or/6-8
10.	3 and 9
11.	oxygen therapy/ae [Adverse Drug Reaction]
12.	or/5,10-11
13.	pregnancy outcome/
14.	((pregnan* or birth) adj2 outcome*).mp.
15.	exp pregnancy complication/
16.	exp congenital disorder/
17.	((f?etal or f?etus or birth or neonatal or congenital or pregnan*) adj3 (complication* or abnormal* or defect* or malformation*)).mp.
18.	or/13-17
19.	12 and 18

D.4.8.2 Fetal adverse events – triptans

Medline search terms

1.	(pregnan* or prenatal).mp.
2.	Tryptamines/ or Sumatriptan/
3.	(triptan$ or Almotriptan or Eletriptan or Frovatriptan or Naratriptan or Rizatriptan or Sumatriptan or Zolmitriptan).mp.

4.	(almogran or relpax or migard or naramig or maxalt or imigran or zomig).mp.
5.	or/2-4
6.	1 and 5
7.	Abnormalities, Drug-Induced/
8.	5 and 7
9.	Sumatriptan/ae, ct, po, to
10.	or/6,8-9
11.	Pregnancy Outcome/
12.	((pregnan* or birth) adj2 outcome*).mp.
13.	exp Pregnancy Complications/
14.	exp Congenital Abnormalities/
15.	((f?etal or f?etus or birth or neonatal or congenital or pregnan*) adj3 (complication* or abnormal* or defect* or malformation*)).mp.
16.	or/11-15
17.	10 and 16

Embase search terms

1.	exp triptan derivative/
2.	(triptan$ or Almotriptan or Eletriptan or Frovatriptan or Naratriptan or Rizatriptan or Sumatriptan or Zolmitriptan).mp.
3.	(almogran or relpax or migard or naramig or maxalt or imigran or zomig).mp.
4.	or/1-3
5.	(pregnan* or prenatal).mp.
6.	4 and 5
7.	triptan derivative/ae, to [Adverse Drug Reaction, Drug Toxicity]
8.	drug induced disease/
9.	exp adverse drug reaction/
10.	exp side effect/
11.	or/8-10
12.	4 and 11
13.	or/6-7,12
14.	pregnancy outcome/
15.	((pregnan* or birth) adj2 outcome*).mp.
16.	exp pregnancy complication/
17.	exp congenital disorder/
18.	((f?etal or f?etus or birth or neonatal or congenital or pregnan*) adj3 (complication* or abnormal* or defect* or malformation*)).mp.
19.	or/14-18
20.	13 and 19

D.4.8.3 Fetal adverse events – verapamil

Medline search terms

1.	exp Verapamil/
2.	(Verapamil or Calan or Cordilox or Dexverapamil or Falicard or Finoptin or Iproveratril or Isoptin or Isoptine or Izoptin or Lekoptin).ti,ab.
3.	or/1-2
4.	(pregnan* or prenatal).mp.
5.	3 and 4
6.	Abnormalities, Drug-Induced/
7.	3 and 6
8.	Verapamil/ae, ct, po, to [Adverse Effects, Contraindications, Poisoning, Toxicity]

9.	or/5,7-8
10.	Pregnancy Outcome/
11.	((pregnan* or birth) adj2 outcome*).mp.
12.	exp Pregnancy Complications/
13.	exp Congenital Abnormalities/
14.	((f?etal or f?etus or birth or neonatal or congenital or pregnan*) adj3 (complication* or abnormal* or defect* or malformation*)).mp.
15.	or/10-14
16.	9 and 15

Embase search terms

1.	verapamil/
2.	(verapamil or Calan or Cordilox or Dexverapamil or Falicard or Finoptin or Iproveratril or Isoptin or Isoptine or Izoptin or Lekoptin).mp.
3.	or/1-2
4.	(pregnan* or prenatal).mp.
5.	3 and 4
6.	drug induced disease/
7.	exp adverse drug reaction/
8.	exp side effect/
9.	or/6-8
10.	3 and 9
11.	verapamil/ae [Adverse Drug Reaction]
12.	or/5,10-11
13.	pregnancy outcome/
14.	((pregnan* or birth) adj2 outcome*).mp.
15.	exp pregnancy complication/
16.	exp congenital disorder/
17.	((f?etal or f?etus or birth or neonatal or congenital or pregnan*) adj3 (complication* or abnormal* or defect* or malformation*)).mp.
18.	or/13-17
19.	12 and 18

D.5 Study filter search terms

D.5.1 Systematic review (SR) search terms

Medline search terms

1.	"review"/ or review.pt. or review.ti.
2.	(systematic or evidence* or methodol* or quantitativ*).ti,ab.
3.	1 and 2
4.	Meta-Analysis/
5.	Meta-Analysis as Topic/
6.	(meta-analy* or metanaly* or metaanaly* or meta analy*).ti,ab.
7.	((systematic* or evidence* or methodol* or quantitativ*) adj3 (review* or overview*)).ti,ab.
8.	((pool* or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
9.	or/3-8

Embase search terms

1.	"review"/ or review.pt. or review.ti.

2.	(systematic or evidence* or methodol* or quantitativ* or analys* or assessment*).ti,sh,ab.
3.	1 and 2
4.	Meta-Analysis/
5.	"systematic review"/
6.	(meta-analy* or metanaly* or metaanaly* or meta analy*).mp.
7.	((systematic* or evidence* or methodol* or quantitativ*) adj5 (review* or survey* or overview*)).ti,ab,sh.
8.	((pool* or combined or combining) adj (data or trials or studies or results)).ti,ab.
9.	or/3-8

PsycINFO search terms

1.	(meta analysis or systematic review).sh,md.
2.	literature review.sh,md.
3.	(metaanal* or meta anal* or metasynthes* or meta synthes*).tw.
4.	((systematic or quantitative or methodologic*) adj5 (overview* or review*)).tw.
5.	((quantitativ* or data) adj (extraction or synthesis)).tw.
6.	((bids or cinahl or cochrane or embase or index medicus or isi citation or medlars or psyclit or psychlit or scisearch or science citation or (web adj2 science)) and review*).tw.
7.	(pooled or pooling).tw.
8.	(research adj (review* or integration)).tw.
9.	(handsearch* or ((hand or manual) adj search*)).tw.
10.	((electronic or bibliographic) adj database*).tw.
11.	(mantel haenszel or peto or dersimonian or der simonian).ti,ab.
12.	(fixed effect* or random effect*).ti,ab.
13.	reference list*.ab.
14.	bibliograph*.ab.
15.	published studies.ab.
16.	relevant journals.ab.
17.	selection criteria.ab.
18.	or/1-17

Cinahl search terms

S1.	(MH "Literature Review") or TI review or PT review
S2.	TX systematic or TX evidence* or TX methodol* or TX quantitativ* or TX analys* or TX assessment*
S3.	(MH "Meta Analysis") or (TX pool* N2 data or TX pool* N2 trials or TX pool* N2 studies or TX pool* N2 results or TX combined N2 data or TX combined N2 trials or TX combined N2 studies or TX combined N2 results or TX combining N2 data or TX combining N2 trials or TX combining N2 studies or TX combining N2 results) or PT systematic review
S4.	(S1 and S2) or S3

D.5.2 Randomised controlled studies (RCTs) search terms

Medline search terms

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ab.
4.	placebo.ab.
5.	randomly.ab.

6.	Clinical Trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	Randomized-Controlled-Trial/
2.	Crossover-Procedure/
3.	Single-Blind-Procedure/
4.	Double-Blind-Procedure/
5.	random*.ti,ab.
6.	factorial*.ti,ab.
7.	(crossover* or cross over* or cross-over*).ti,ab.
8.	((doubl* or singl*) adj blind*).ti,ab.
9.	(assign* or allocat* or volunteer*).ti,ab.
10.	or/1-9

PsycINFO search terms

1.	exp Clinical Trial/
2.	randomi*.ti,ab.
3.	((clinical* or control*) adj3 trial*).ti,ab.
4.	((singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)).ti,ab.
5.	Placebos/ or placebo*.ti,ab.
6.	(volunteer* or "control group" or controls).ti,ab.
7.	((crossover or cross-over or cross over) adj2 (design* or stud* or procedure* or trial*)).ti,ab.
8.	or/1-7

Cinahl search terms

S1.	((MH "Random Assignment") or (MH "Random Sample+") or (MH "Crossover Design") or (MH "Clinical Trials+") or (MH "Comparative Studies") or (MH "Control (Research)+") or (MH "Control Group") or (MH "Factorial Design") or (MH "Quasi-Experimental Studies+") or (MH "Placebos") or (MH "Meta Analysis") or (MH "Sample Size") or (MH "Research, Nursing") or (MH "Research Question") or (MH "Research Methodology+") or (MH "Evaluation Research+") or (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") or (MH "Nursing Practice, Research-Based") or (MH "Solomon Four-Group Design") or (MH "One-Shot Case Study") or (MH "Pretest-Posttest Design+") or (MH "Static Group Comparison") or (MH "Study Design") or (MH "Clinical Research+")) or (clinical nursing research or random* or cross?over or placebo* or control* or factorial or sham* or meta?analy* or systematic review* or blind* or mask* or trial*)

D.5.3 Observational studies search terms

Medline search terms

1.	Epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	Cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective) and (study or studies or review or

	analys* or cohort*)).ti,ab.
9.	cross sectional.ti,ab.
10.	or/1-9

Embase search terms

1.	epidemiology/
2.	exp case control study/
3.	cohort analysis/
4.	cross-sectional study/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	cross sectional.ti,ab.
10.	or/1-9

D.5.4 Diagnostic accuracy search terms

Medline search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or PPV or NPV).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	likelihood function/
7.	(ROC curve* or AUC).ti,ab.
8.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	or/1-9

Embase search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or PPV or NPV).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	(ROC curve* or AUC).ti,ab.
7.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8.	diagnostic accuracy/
9.	diagnostic test accuracy study/
10.	gold standard.ab.
11.	or/1-10

D.5.5 Health economic search terms

Medline search terms

1.	exp "Costs and Cost Analysis"/
2.	Economics/

3.	Economics, Nursing/ or Economics, Medical/ or Economics, Hospital/ or Economics, Pharmaceutical/
4.	exp "Fees and Charges"/
5.	exp Budgets/
6.	budget*.tw.
7.	cost*.ti.
8.	(cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab.
9.	(economic* or pharmacoeconomic* or pharmaco-economic*).ti.
10.	(price* or pricing*).tw.
11.	(financial or finance or finances or financed).tw.
12.	(fee or fees).tw.
13.	(value adj2 (money or monetary)).tw.
14.	or/1-13
15.	exp models, economic/
16.	models, theoretical/ or models, organizational/
17.	economic model*.tw.
18.	markov chains/
19.	markov*.tw.
20.	Monte Carlo Method/
21.	monte carlo.tw.
22.	exp Decision Theory/
23.	(decision* adj2 (tree* or analy* or model*)).tw.
24.	or/15-23
25.	14 or 24

D.5.6 Quality of life search terms

Medline search terms

1.	quality adjusted life.tw.
2.	(qaly* or qald* or qale* or qtime*).tw.
3.	disability adjusted life.tw.
4.	daly*.tw.
5.	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
6.	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
7.	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
8.	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
9.	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
10.	(euroqol or euro qol or eq5d or eq 5d).tw.
11.	(hql or hqol or h qol or hrqol or hr qol).tw.
12.	(hye or hyes).tw.
13.	health* equivalent* year*.tw.
14.	(hui or hui1 or hui2 or hui3).tw.
15.	health utilit*.tw.
16.	disutilit*.tw.
17.	rosser.tw.

18.	(quality of wellbeing or quality of well being).tw.
19.	qwb.tw.
20.	willingness to pay.tw.
21.	standard gamble*.tw.
22.	time trade off.tw.
23.	time tradeoff.tw.
24.	tto.tw.
25.	or/1-24

Embase search terms

1.	quality adjusted life.tw.
2.	(qaly* or qald* or qale* or qtime*).tw.
3.	disability adjusted life.tw.
4.	daly*.tw.
5.	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
6.	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
7.	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
8.	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
9.	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
10.	(euroqol or euro qol or eq5d or eq 5d).tw.
11.	(hql or hqol or h qol or hrqol or hr qol).tw.
12.	(hye or hyes).tw.
13.	health* equivalent* year*.tw.
14.	(hui or hui1 or hui2 or hui3).tw.
15.	health utilit*.tw.
16.	disutilit*.tw.
17.	rosser.tw.
18.	(quality of wellbeing or quality of well being).tw.
19.	qwb.tw.
20.	willingness to pay.tw.
21.	standard gamble*.tw.
22.	time trade off.tw.
23.	time tradeoff.tw.
24.	tto.tw.
25.	or/1-24

D.6 Patient information (complete search strategies)

Medline search terms

1.	*Headache/
2.	*headache disorders/ or exp *headache disorders, primary/
3.	(headache* or migraine*).ti.
4.	or/1-3
5.	"patient acceptance of health care"/ or exp patient satisfaction/
6.	Patient Education as Topic/

7.	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
8.	((client* or patient* or user* or carer* or consumer* or customer*) adj2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)).ti,ab.
9.	or/5-8
10.	qualitative research/
11.	exp Interviews as Topic/
12.	exp Questionnaires/
13.	health care surveys/
14.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
15.	or/10-14
16.	4 and 9 and 15

Embase search terms

1.	exp *chronic daily headache/ or *headache/ or exp *migraine/ or *primary headache/ or exp *tension headache/
2.	(headache* or migraine*).ti.
3.	or/1-2
4.	patient attitude/ or patient preference/ or patient satisfaction/ or consumer attitude/
	patient information/ or consumer health information/
5.	patient education/
6.	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
7.	((client* or patient* or user* or carer* or consumer* or customer*) adj2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*)).ti,ab.
8.	or/4-8
9.	qualitative research/
10.	exp interview/
11.	exp questionnaire/
12.	health care survey/
13.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
14.	or/10-14
15.	3 and 9 and 15

Cinahl search terms

S1.	(MH "Headache+")
S2.	headache* or migraine*
S3.	S1 or S2
S4.	(MH "Patient Satisfaction")
S5.	(MH "Patient Attitudes")
S6.	((client* or patient* or user* or carer* or consumer* or customer*) n2 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform* or experience or experiences or opinion*))
S7.	information* n3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)
S8.	S4 or S5 or S6 or S7
S9.	(MH "Qualitative Studies+")
S10.	(MH "Qualitative Validity+")

S11.	(MH "Interviews+") or (MH "Focus Groups") or (MH "Surveys")
S12.	(MH "Questionnaires+")
S13.	qualitative or interview* or focus group* or theme* or questionnaire* or survey*
S14.	S9 or S10 or S11 or S12 or S13
S15.	S3 and S8 and S14

Appendix E: Evidence tables – Clinical evidence

E.1 Assessment and diagnosis

E.1.1 Indications for consideration of additional investigation

HIV positive with new onset headache

Study details	Patients	Cohorts	Outcome measures	Effect size	Comments
Author & Year: Gifford and Hecht, 2001[320] **Study design:** Retrospective cohort study **Setting:** 2 hospitals in San Francisco, USA. Department NR. **Length of follow up:** Over 10 years (January 1986 to June 1996)	**Patient group:** HIV infected adults presenting with headache and undergoing head CT scan. **Inclusion criteria:** Patients with HIV/AIDS; had received a head CT with contrast to evaluate headache; were HIV infected at the time of the CT scan. **Exclusion criteria:** Prior history of *Toxoplasma gondii*, primary brain lymphoma or other intracranial mass lesions; had brain imaging (head CT or MRI) or meningitis during the previous 30 days. **All patients** **N**: 364 **M**=342; **F**=22 **Age:** <30 years: n=71, 30-39 years: n= 204, ≥40 years: n=89 **Low risk group** (n)=35 **Intermediate risk group (**n)=242 **High risk group** (n)=87	Study cohort receiving head CT was classified into the following risk categories of having an intracranial mass lesion. **Low risk** (no focal neurological signs, no altered mental status, no seizure, CD4 count> 200 cells/µl) **Intermediate risk** (no focal neurological signs, no altered mental status, no seizure, CD4 count< 200 cells/µl) **High risk** (focal neurological signs, altered mental status, or seizure)	**Presence of intracranial mass lesions**	**1.Low risk group**: 0(0%, 95% CI 0% to 10%); n=35 **2. Intermediate risk group:** 22 (9%, 95% CI 2% to 16%); n=242 **3. High risk group:** 18 (21%, 95% CI 12% to 29%); n=87 P values 1v2, p<0.05 2v3, p<0.01	**Funding:** California University-wide AIDS Research Program and Department of Veteran affairs **Limitations:** No control group. Age range not specified. Study does not list the confounding factors *a priori*. **Additional outcomes**: Clinical variables independently associated with abnormal head CT result.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, HIV= human immunodeficiency virus, AIDS= Acquired immune deficiency syndrome, CT= computed tomography, MRI= Magnetic resonance imaging

Study details	Patients	Cohorts	Outcome measures	Effect size	Comments
Author & Year: Singer et al, 1993 & 1996[734,735] **Study design:** Prospective cohort study **Setting:** Outpatient setting, Los Angeles, USA	**Patient group:** Adult HIV+ ambulatory male volunteers recruited through advertisements and local sources. **Exclusion criteria:** Inability to give informed consent, medical contraindication to lumbar puncture or CNS opportunistic infection or tumour identified prior to evaluation **All patients** **N:** 229 **Group 1:** Had HIV-1 associated headache **N:** 98 **Age (mean):** 38.1±9.7 years **History of non-HIV related neurologic disease:** 35/98 (36%) HIV related neurologic disease: **Group 2 :** Did not have HIV-1 associated headache **N:** 131 **Age (mean):** 39.9±10.6 years **History of non-HIV related neurologic disease:** 30/130 (23%)	**Group 1:** HIV-1 associated headache Patients were classified as having HIV-1 associated headache if headaches: • first occurred after the known date of HIV seropositivity, • did not have a clear-cut cause for example, trauma, AZT use • were associated with HIV-1 alone or an associated CNS opportunistic infection or tumour. Also included were patients who had headaches prior to HIV-1 seropositivity but developed a new type of headache that met the above criteria. **Group 2 :** No HIV-1 associated headache Patients were classified as not having an HIV-1 associated headache if: • they reported no headaches • reported headaches that antedated the time of HIV-1 seropositivity and were unchanged since onset • reported headaches that had another clear-cut cause.	**CNS opportunistic infection (at baseline evaluation)** **New HIV-1 associated neurologic disease (at 1 year evaluation)**	**HIV+ with headache:** 2/98(2%) **HIV+ without headache:** 4/131(3%) **New HIV-1 associated headache:** 7/34 (20.5%) **HIV+ without headache:** 8/109 (7.33%)	**Funding:** National Institutes of Mental Health; Department of Veteran affairs; Neurologic AIDS research consortium and AIDS regional Education and Training Centre **Limitations:** 39% of all HIV+ subjects had primary HIV-1 associated neurologic disease (cognitive dysfunction, myelopathy, peripheral neuropathy); headache not in isolation of other symptoms. No confounding factors identified *a priori.* **Additional outcomes:** Association of headaches with systemic disease progression. **Notes:** Study also reported outcomes for another group of 53 seronegative controls.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, HIV= Human immunodeficiency virus, AZT= Zidovudine, CNS=Central nervous system

History of malignancy with new onset headache

Study Details	Patients	Cohorts	Outcome measures	Effect size	Comments
Author & Year: Antunes & De Angelis, 1999 [40] **Study design:** Cohort study **Setting:** Department of neurology, Memorial Sloan-Kettering Cancer Center, New York	**Patient group:** Patients with systemic cancer, aged 20 or younger. **All patients** **N:** 157 (patients with systemic cancer who underwent neurologic consultations between January 1993 and December 1996.) 21 (patients with isolated headache without focal signs) **Age (median):** 14 years **M:F**= 90:67 **Cancer types:** Leukemia: 59 Hodgkin's lymphoma:8 Non-Hodgkin's lymphoma: 26 Neuroblastoma: 13 Ewing's sarcoma: 10 Rhabdomyosarcoma:10 Osteogenic sarcoma: 9 Germ cell: 5 Teratoma: 3 Primitive neuroectodermal tumor:2 Other: 16	157 patients with 161 malignancies who underwent 206 neurologic consultations in total. Cohort was divided into two groups according to the presence or absence of lateralizing signs.	**Occurrence of intracranial abnormalities**	Brain metastasis: 3/21 (14.3%)	**Funding: NR** **Limitations:** No information on outcomes in patients with cancer without headaches. No listing of confounding factors *a priori.* **Additional outcomes:** Etiology of headaches associated with focal signs and symptoms.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval

E.1.2 Identifying people with primary headache

Migraine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Brighina et al. 2007[108] **Study design:** Validation study (cross-sectional) **Setting:** 8 headache centres in Sicily (tertiary care)	**Patient group:** Headache patients aged 18-65 **Inclusion criteria:** Patients referred to the headache centres and reporting at least 2 headache attacks in the last 3 months. Must have experienced at least one headache that interfered with their life. **Exclusion criteria:** NR **All patients** **N:** 222 **Age (mean):** 38.68±12.02 **F/M:** 163/59 **Drop outs:** 0	**Group 1 – ID migraine** Italian version of the ID Migraine (translated by Pfizer who own original copyright). Response to each item treated as a binary variable: 'no' assigned to responses of 'never' or 'rarely' and 'yes' assigned to 'less than half the time' or 'half the time or more'. **Group 2 – ICHD II** Complete clinical evaluation according to the ICHD II criteria. Patients were evaluated by a board-qualified headache specialist (always the same in each centre), blind to the result of the ID migraine. Full assessment included medical history, physical examination including additional diagnostic tests if clinically indicated.	**Sensitivity** (95%CI)	Migraine (2 items positive): 0.95 (0.91-0.98) Other primary headache: 0.20 (0.09-0.32) Secondary headache: 0.48 (0.29-0.67)	**Funding:** Pfizer (copyright holders of ID Migraine) **Limitations:** No serious limitations **Additional outcomes:** Diagnostic outcomes for nausea, photophobia and disability as individual measures. Accuracy. Sub-groups of age and sex. **2x2 table:** completed by NCGC
			Specificity (95%CI)	Migraine (2 items positive): 0.72 (0.62-0.82) Other primary headache: 0.12 (0.08-0.17) Secondary headache: 0.22 (0.16-0.28)	
			Positive predictive value (95%CI)	Migraine (2 items positive): 0.88 (0.82-0.93) Other primary headache: 0.05 (-0.02-0.09) Secondary headache: 0.08 (0.04-0.13)	
			Negative predictive value (95%CI)	Migraine (2 items positive): 0.87 (0.78-0.95) Other primary headache: 0.39 (0.26-0.51) Secondary headache: 0.75 (0.64-0.87)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, ICHD II=2nd edition of the International Classification of Headache Disorders

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Ertas et al. 2009[263] **Study design:** Validation study (cross-sectional) **Setting:** Multicentre outpatients; opthalmology, ENT and neurology. 11 centres in Turkey	**Patient group:** > 17 years old with headache **Inclusion criteria:** > 17 year old, presenting to neurology, ear nose and throat (ENT) or ophthalmology clinics, passing the pretest screening questions for headache: if one was affirmative the participants were enrolled for the ID migraine test and examination by a neurologist: (i) Do your headaches limit your ability to work, study or enjoy life? (ii) Do you want to talk to your healthcare professional about your headaches? **Exclusion criteria: <**18 years old, or not capable of communicating. **All patients (with headache)** N: 1585 Drop outs: 564 (did not pass pretest questions) **Neurology clinic** N: 530 (after pretest) Age, mean (SD): 46.5 (17) F (%): 63.8 **ENT Clinic**	**Group 1 – ID migraine** Including three screening questions: during the last 3 months, (i) Did you feel nauseated or sick to your stomach with your headache? (ii) Did light bother you when you had a headache (drastically more than when you did not have headaches)? (iii) Did your headache limit your ability to work, study or do what you needed to do for at least 1 day? The cut off point for diagnosis of migraine was 2 or more positive responses. **Group 2 – ICHD II** Neurologists or trained neurology residents interviewed patients using a symptom checklist based on a diagnostic headache evaluation prepared according to IHS criteria (ICHD II).	**Sensitivity** Migraine (>2 items positive) **Specificity** Migraine (>2 items positive) **Positive predictive value** Migraine (>2 items positive) **Negative predictive value** Migraine (>2 items positive)	Neurology: 87.87 ENT: 86.62 Opthalmology: 79.87 Neurology: 73.96 ENT: 74.38 Opthalmology: 75.95 Neurology: 0.86 ENT: 0.80 Opthalmology: 0.86 Neurology: 0.76 ENT: 0.83 Opthalmology: 0.67	**Funding:** Pfizer **Limitations:** Original data not reported Not clear if patients could be diagnosed with more than one headache type (assumed they could due to n values reported). Headache not always the primary complaint (no data presented separately for those in which it was). Not specifically stated that diagnosis was made blinded to other test result, but assumed. **Additional outcomes:** Localization of headache. Severity of headache. Breakdown of ID migraine items. Headache characteristics. Trigger factors. Percentage using medication for headaches. **2x2 table:** Completed by NCGC

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 263 (after pretest) Age, mean (SD): 47.3 (18) F (%): 58.1 **Opthalmology clinic** N: 228 (before pretest) Age, mean (SD): 43.3 (16) F (%): 52.9				

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, IHS=International Headache Society, ICHD II=2nd edition of the International Classification of Headache Disorders, ENT=Ear Nose & Throat

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Gil-Gouveia et al. 2010[321] **Study design:** Validation study (cross-sectional) **Setting:** 2 headaches outpatient clinics in Portugal	**Patient group:** Adults with headache **Inclusion criteria:** Adults reporting at least 2 headache attacks in the last 3 months attending headache outpatient clinics. **Exclusion criteria:** Age <18 years, current uncontrolled medical or psychiatric illness, illiteracy, headache syndromes with no clear diagnosis or not fulfilling definite ICHD-II diagnostic criteria and the presence of more than one headache type or current medication overuse headache (MOH). **All patients** N: 142 Age, mean (SD): 39.2 (13.9) F/M: 119/23 (83.8% F) Drop outs: 11 excluded due to MOH or not fulfilling ICHD criteria **Included in analysis** N: 131 Age mean (SD): 38.2 (13.2) F/M: 110/21 (84% F) Disease duration, mean(SD) yrs: 13.6(10.8)	**Group 1 – ID migraine** Portuguese version obtained by consensus translation process. Participants asked to complete the questionnaire before the first clinical visit to the headache specialist. 1 point scored for each affirmative answer, ≥2 considered a positive diagnostic test. **Group 2 – ICHD II** Headache specialist blinded to ID-migraine results performed medical and neurological history and examination. ICHD-II diagnosis made and other demographic factors recorded.	**Sensitivity** (95%CI) Migraine (>2 items positive)	0.94 (0.87-0.97)	**Funding:** Pfizer approved use of ID migraine, not mention of funding. **Limitations:** Patients not fulfilling definite ICHD-II criteria excluded from analysis. **Additional outcomes:** Age at symptom onset. Headache frequency, duration and intensity. Use of prophylactic treatment. **2x2 table**: Yes
			Specificity (95%CI) Migraine (>2 items positive)	0.60 (0.46-0.73)	
			Positive predictive value (95%CI) Migraine (>2 items positive)	0.80 (0.71-0.87)	
			Negative predictive value (95%CI) Migraine (>2 items positive)	0.85 (0.70-0.94)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, ICHD II=2nd edition of the International Classification of Headache Disorders, MOH=Medication overuse headache

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Karli et al. 2007[420] **Study design:** Validation study (cross-sectional) **Setting:** 41 neurology outpatient clinics in Turkey	**Patient group:** Adults with headache **Inclusion criteria:** Adults presenting to neurological outpatients clinics over 17 years of age and able to communicate. Must have had 2 or more headaches in the last 3 months and answer yes to at least one of the following questions: (i) Do your headaches limit your ability to work, study or enjoy life? (ii) Do you want to talk to your healthcare professional about your headaches? **Exclusion criteria:** Not capable to communicate, younger than 17 years of age. **All patients** N: 3683 screened, 1816 included (answering pre-screening questions positively) Age, mean (SD): 45.2 (17) F/M(%): 62.9/37.1 Headache as primary cause of admission: 35.1%	**Group 1 – ID migraine** Completed by all patients passing the pre-test questions. Migraine was diagnosed if there were at least 2 positive responses to the 3 ID migraine questions. **Group 2 – ICHD II** All patients who completed the ID migraine were interviewed by a neurologist or trained neurology resident using a symptom checklist based on a semi-structured diagnostic headache evaluation according to the ICHD-II criteria, and assigned a clinical diagnosis of migraine, tension type or other headache.	**Sensitivity** Migraine (2 items positive)	91.82	**Funding:** Pfizer **Limitations:** No serious limitations **Additional outcomes:** Diagnostic outcomes for all three questions of ID migraine. Subgroup analysis based on gender and years of education. Numbers diagnosed with each headache type separated by subgroup according to diagnosis and reason for admission. **2x2 table:** Completed by NCGC
			Specificity Migraine (2 items positive)	63.40	
			Positive predictive value (ratio) Migraine (2 items positive)	0.72	
			Negative predictive value (ratio) Migraine (2 items positive)	0.88	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, ICHD II=2nd edition of the International Classification of Headache Disorders

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Khu et al. 2008[435] **Study design:** Cross-sectional **Setting:** 57 GP clinics in Singapore	**Patient group**: Patients presenting to GP clinics with headache (aged >8) **Inclusion criteria:** Primary complaint of headache **Exclusion criteria:** Non-consenting **All patients** **N:** 584 **Age, mean (SD):** 37 (11) Range 8-74 (5% under 20yrs) **F/M (%):** 74.5/24.5 **Duration of headaches** (%): <1 yr 20.7, 1-5yrs 28.6, >5yrs 49.1 **MIDAS:** minimal disability 53.9%, mild 22.6%, moderate 19.7%, severe 11.6% **Drop outs:** 0	**Group 1 – ID migraine** Completed by patients after instruction by clinician or clinic assistant. Also included questions on demographics, headache duration, frequency, MIDAS, doctor-hopping behaviour, headache treatment and social burden of headaches. >2 positive answers on ID migraine confirmed diagnosis. **Group 2 – ICHD II** Questionnaire completed by physician according to study coordinator instruction. Included headache feature, clinical diagnosis and management details. Attention was paid to overusage of acute pain medication and perceived need for prophylactic treatment.	**Sensitivity*** Migraine (2 items positive)	0.50 (0.45-0.55)	**Funding:** Janssen-Cilag **Limitations:** Results reported as percentage diagnosed – diagnostic outcomes calculated by NCGC. Assumed questionnaires interpreted independently, but only states they were collected independently. Physician diagnosis considered as a separate item to IHS diagnosis. Not clear who assigns IHS diagnosis. **Additional outcomes**: Reasons for dissatisfaction with current headache treatments. Prophylaxis and indications for taking. Headache profile. **Notes:** * Calculated by NCGC from % prevalence values presented **2x2 table completed**:Yes
			Specificity* Migraine (2 items positive)	0.84 (0.78-0.88)	
			Positive predictive value* Migraine (2 items positive)	0.85	
			Negative predictive value* Migraine (2 items positive)	0.52	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, ICHD II=2nd edition of the International Classification of Headache Disorders

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Kim & Kim 2006[436] **Study design:** Diagnostic (cross-sectional) **Setting:** TMJ and orofacial pain clinic in Korea	**Patient group:** Adults with TMD or orofacial pain and headache **Inclusion criteria:** Adults attending TMJ and orofacial pain clinic who reported two or more headaches in the previous 3 months. In addition, the subjects had to either wish to consult a doctor about their headaches or report that the headaches interfered with their lives. Patients had to be able to read and write Korean. **Exclusion criteria:** NR **All patients** N: 176 Age, mean(SD): 30.7 (9.3) F/M: 143/33 Drop outs: 0	**Group 1 – ID migraine** Self-administered questionnaire consisting of nine questions referring to the severity and nature of their headache pain and the presence of associated migraine symptoms. **Group 2 – IHS criteria** A headache specialist completed the semistructured diagnostic questionnaires and examined the patients and assigned clinical diagnosis of migraine according to IHS criteria.	**Sensitivity** (95%CI) Migraine (2 items positive)	0.58 (0.45-0.72)	**Funding:** NR **Limitations:** NPV not presented. †PPV presented differed to that calculated by NCGC (paper reported 93.9%). Unclear if interpretation of results made blinded to other test results. Patients have TMD and orofacial pain as primary complaint (indirect). NPV not presented. **Additional outcomes:** Sensitivity and specificity of each of the 9 items on the original ID-Migraine. **2x2 table:** Completed by NCGC * calculated by NCGC
			Specificity (95%CI) Migraine (2 items positive)	0.98 (0.76-1)	
			Positive predictive value (95%CI) Migraine (2 items positive)	*†86%	
			Negative predictive value (95%CI) Migraine (2 items positive)	*91%	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, IHS =International Headache Society, TMJ=temporomandibular joint, TMD=temporomandibular disorders

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Lipton et al. 2003[505] **Study design:** Development study **Setting:** Primary care practice (21 practices in the US)	**Patient group:** Adults aged 18-55 with headache **Inclusion criteria:** Men and women aged 18-55 visiting a primary care practice office for any reason. Patients had to be able to read and write English, and not have participated in a previous Pfizer-sponsored migraine study. They must report 2 or more headaches in the previous 3 months. In addition, eligible subjects had to indicate that they had experienced a headache that had limited their ability to work, study, or enjoy life, or that they might wish to speak with a healthcare professional about their headaches. **Exclusion criteria:** Participation in previous Pfizer-sponsored migraine study. After one third of the sample had been enrolled, an additional entry criterion was added that excluded patients with a previous diagnosis of migraine (to ensure that a high proportion of patients had not previously been diagnosed with migraine). **All patients**	**Group 1 – ID migraine** In the primary care practice patients were asked to complete the migraine screener (on questionnaire). Consisting of 9 questions developed by consensus panel based on IHS criteria. There were additional questions on age, sex, race, previous diagnosis and frequency of headache, not used for diagnosis. Questionnaire was reviewed for completeness by the primary care practitioner or a member of their staff. **Group 2 – IHS** The patient was referred to a headache specialist for a structured diagnostic headache evaluation within 2 weeks of the screening. Results of the screening questionnaire were not available to the headache specialist. The appointment included a medical history, physical examination, comprehensive neurologic history and examination and a semi-structured interview that included the IHS features of migraine supplemented by	**Sensitivity (95%CI)** Migraine (2 items positive) **Specificity (95%CI)** Migraine (2 items positive) **Positive predictive value (95%CI)** Migraine (2 items positive) **Negative predictive value (95%CI)** Migraine (2 items positive)	0.81 (0.77-0.85) 0.75 (0.64-0.84) 93.3 (89.9-98.5) *51.08%	**Funding:** Pfizer **Limitations:** Additional exclusion criteria added after 1/3 of patients had been recruited. Reasons for the 8 patients with missing data not stated. **Additional outcomes**: Diagnostic outcomes on each item of the questionnaire individually. MSQ MIDAS Migraine-related work productivity questionnaire. Henry Ford Hospital headache disability inventory. Test-retest reliability (on a subset of patients). **Notes:** 9 item version of screener used initially. NB. Study included for information rather than analysis. **2x2 table:** Completed by NCGC

	N: 563 eligible, 550 screened, 451 completed both index test and reference standard (validation sample) **Age mean (SD):** 39.3 (10.1) **F/M:** 341/110 (75.6/24.4%) **Drop outs**: 99 completed screener but did not attend their neurology appointment (for reference standard) 17.7% 8 Missing data from one test (1.4%)	additional questions relating to family history and medical treatment history. The headache expert was encouraged to probe for clinical information necessary to clarify the differential diagnosis.			* Calculated by NCGC

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, IHS=International Headache Society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Mostardini et al. 2009[574] **Study design:** Validation study (cross sectional) **Setting:** Headache clinic, post ED discharge (Italy)	**Patient group:** Patients discharged from ED with a diagnosis of primary headache **Inclusion criteria:** Attending headache clinic within 48 hours of discharge from ED with a diagnosis of primary headache. **Exclusion criteria:** Those who did not speak Italian fluently and subjects with an ICHD-II diagnosis of probably migraine. **All patients** **N**: 254† (199 calculated by NCGC) **Age mean (SD): 37 (15)** **F/M:** 2:1 (ratio) **Drop outs**: 0	**Group 1 – ID migraine** Self-administered and dichotomic questionnaire based on three questions regarding the presence of nausea, photophobia and disability during headache. Defined as positive when the answer to at least two out of the three questions is yes. **Group 2 – ICHD II** A headache expert blinded to the test made a diagnosis according to the ICHD-II criteria. The data used by the ED to make a diagnosis before discharging the patients were obtained.	**Sensitivity†** Migraine (2 items positive) For primary headaches	0.94 (0.94)	**Funding:** NR **Limitations:** †Discrepancies in results reported for primary headaches only – wrong total n used in paper (both values reported here). Patients with ICHD-II diagnosis of probably migraine excluded because ID-Migraine not validated for this category (but TTH etc included) **Additional outcomes**: Data analysed for those with IHS diagnosis of primary headache, and the whole population (including secondary headache). **Notes:** Analysis of those with primary headaches only reported here. **2x2 table:** Completed by NCGC
			Specificity† Migraine (2 items positive) For primary headaches	0.81 (0.83)	
			Positive predictive value† Migraine (2 items positive) For primary headaches	0.98 (0.99)	
			Negative predictive value† Migraine (2 items positive) For primary headaches For all of the above data is NCGC calculated value (study value)	0.54 (0.31)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, ICHD II=2nd edition of the International Classification of Headache Disorders

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Samaan et al. 2010[682] **Study design:** Validation study (cross sectional) **Setting:** Specialist headache clinic	**Patient group:** Patients referred to specialist headache clinic with significant headaches not managed by other health care providers. **Inclusion criteria:** All patients registered for the clinic eligible to participate. **Exclusion criteria:** NR **All patients** **N**: 200 randomised, 170 analysed **Age (mean):** NR **F/M:** NR **Drop outs**: 30 Not stated if they did not attend appointment or were unable to be diagnosed.	**Group 1 – The structured migraine interview (SMI)** Designed to answer the question 'did this person suffer from migraine at any time in his/her life'. 10 questions formed from ICHD criteria. The questionnaire was mailed to all patients at the migraine clinic. Responses from SMI were scored usinga computerised coding algorithm to generate migraine diagnosis. **Group 2 – Clinician diagnosis** A random sample of 200 subjects were selected from the respondents using a random list of ID numbers which concealed the participants' identity. These people were invited to see a migraine clinic headache specialist to provide the clinical diagnosis. They were blind to the SMI diagnosis.	**Sensitivity** **Specificity** **Positive predictive value** **Negative predictive value**	0.87 0.58 0.97 0.26	**Funding: NR** **Limitations:** Very specific patient group with significant headaches that could not be managed by other healthcare providers. Study does not specifically state that ICHD criteria used for reference standard, but assumed it would be in this clinic. Missing data for 30 patients, no reason given. **Additional outcomes**: Correlation with seld-reported migraine, migraine treatment and analgesic use. Comparison of face to face interview the SMI telephone interview. **Notes:** Clinical diagnosis only included migraine with aura, migraine without aura and non-migraine headache. There were no cases of probably migraine. For analysis the diagnoses were grouped as migraine (with or without aura) and non-migraine headache. **2x2 table:** Yes (in paper, verified by NCGC)

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, ICHD II=2nd edition of the International Classification of Headache Disorders

Cluster headache

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Dousset et al. 2009[232] **Study design:** Validation study (cross-sectional) **Setting:** Outpatients headache clinic, France	**Patient group:** People aged >15 with cluster headache or migraine **Inclusion criteria:** Age >15 years, good knowledge of French, an history of episodic or chronic cluster headache or migraine with or without aura for over a year, an history of at least 2 active cluster periods for patients with episodic cluster headache. All diagnoses were made buy one of 3 headache specialists according to 2004 IHS criteria. **Exclusion criteria:** Possible organic causes of headache were excluded through a general and a neurological examination and if needed complementary exams. **All patients** **N**: 96 **Age mean (SD):** 41.3 (12.5) **F/M:** 54/42 **Drop outs**: 0	**Group 1 – Cluster headache screening questionnaire** Based on 3 most prevalent criteria of ICHD-II for cluster headache: (i) Strictly unilaterality of pain; (ii) Attack duration ≤180 minutes if untreated; (iii) Ipsilateral conjunctival injection, and/or lacrimation. The questionnaire was formed so that they could be quickly filled out and easily understood. At the end of the visit, the nurse of the headache centre explained the objective study and the patients filled the questionnaire out unaided. **Group 2 – ICHD II** Diagnosis made by the headache specialist based on the ICHD-II criteria. This included a medical history and examination. The specialist completed a symptom checklist based on IHS criteria and assigned a clinical diagnosis of migraine, cluster headache or probably cluster headache.	**Sensitivity (%)**	**All 3 questions:** 78.4 **Q 1:** 94.6 **Q2:** 91.1 **Q3:** 89.2 **Q2+3:** 81.1 **Q 1+2:** 86.5 **Q1+3:** 86.5	**Funding:** NR **Limitations:** Original data not reported. Does not specifically say that results were interpreted blind to the other test results – but different assessors completed each. **2x2 table completed:** No
			Specificity (%)	**All 3 questions:** 100 **Q 1:** 44.1 **Q2:** 91.4 **Q3:** 82.5 **Q2+3:** 100 **Q 1+2:** 94.9 **Q1+3:** 88.1	
			Positive predictive value (%)	**All 3 questions:** 100 **Q 1:** 51.5 **Q2:** 87.2 **Q3:** 76.7 **Q2+3:** 100 **Q 1+2:** 91.4 **Q1+3:** 82.1	
			Negative predictive value (%)	**All 3 questions:** 88.1 **Q 1**: 92.9 **Q2:** 94.6 **Q3:** 92.2 **Q2+3**: 89.4 **Q 1+2**: 91.8 **Q1+3:** 91.2	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, ICHD II=2nd edition of the International Classification of Headache Disorders

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ref ID: Torelli et al 2005[794] **Study design:** Validation study **Setting:** Outpatients headache centre, Italy	**Patient group:** Aged over 14 with migraine, tension type headache or cluster headache **Inclusion criteria:** Age 14 years; Good knowledge of Italian; A history of migraine with or without aura, episodic or chronic tension type headache, or chronic cluster headache for over a year; and a history of at least two active cluster periods for patients with episodic cluster headache. **Exclusion criteria:** Possible organic causes of headache were excluded through a general and a neurological examination and, if needed, through instrumental tests. **All patients** **N**: 71 **Age (mean):** 37.5 (15.1) **F/M:** 32/39 (45.1/54.9%) **Drop outs**: 0	**Group 1 – Cluster headache screening questionnaire** Consisted of 16 questions to be answered as 'yes' 'no or 'don't know'. Full questionnaire is available in study. It was designed to be self-administered, easily understood and quick to fill out. At the end of their visit, a diagnosis-blind neurologist explained the objective of the study and they were asked to fill out the questionnaires unaided. **Group 2 – IHS criteria** Initially the 1988 IHS criteria were used, however the second edition (the ICHD-II) was publicised while the study was under-way. All diagnoses established according to 1988 criteria were reviewed applying the 2004 criteria.	**Sensitivity**	**Excrutiating pain:** 100 **Unilaterality:** 100 **Location of pain:** 100 **Conjunctival injection:** 63.3 **Lacrimation**: 80.0 **Nasal congestion:** 63.3 **Rhinorrhea:** 70.0 **Restlessness:** 90.0 **Duration of attacks:** 100 **Frequency of attacks**: 73.3 **Attacks for at least 7 days:** 96.7 **Attacks at fixed hours:** 63.3 **Night attacks:** 63.3 **Remission periods:** 56.7 **Use of preventive treatment:** 66.7	**Funding:** Glaxo Smith Klein **Limitations:** Original data not reported. **Additional outcomes**: Diagnostic outcomes for episodic cluster headache and chronic cluster headache. This seems to be a post-hoc analysis. Not included here. **Notes:** Full questionnaire available in publication **2x2 table completed:** No
			Specificity	**Excrutiating pain:** 34.1 **Unilaterality:** 61.0 **Location of pain:** 58.5 **Conjunctival injection:** 90.2 **Lacrimation**: 75.6 **Nasal congestion:** 90.2 **Rhinorrhea:** 90.2 **Restlessness:** 92.7 **Duration of attacks:** 90.2 **Frequency of attacks**: 73.2 **Attacks for at least 7 days:** 68.3 **Attacks at fixed hours:** 78.0 **Night attacks:** 78.0 **Remission periods:** 95.1 **Use of preventive treatment:** 97.6	

			Positive predictive value	**Excrutiating pain:** 52.6 **Unilaterality:** 65.2 **Location of pain:** 63.8 **Conjunctival injection:** 82.6 **Lacrimation**: 70.6 **Nasal congestion:** 82.6 **Rhinorrhea:** 84.0 **Restlessness:** 90.0 **Duration of attacks:** 88.2 **Frequency of attacks**: 66.7 **Attacks for at least 7 days:** 69.0 **Attacks at fixed hours:** 67.9 **Night attacks:** 67.9 **Remission periods:** 89.5 **Use of preventive treatment:** 95.2	
			Negative predictive value	**Excrutiating pain:** 100 **Unilaterality:** 100 **Location of pain:** 100 **Conjunctival injection:** 77.1 **Lacrimation**: 83.8 **Nasal congestion:** 77.1 **Rhinorrhea:** 80.4 **Restlessness:** 92.7 **Duration of attacks:** 100 **Frequency of attacks**: 78.9 **Attacks for at least 7 days:** 96.6 **Attacks at fixed hours:** 74.4 **Night attacks:** 74.4 **Remission periods:** 75.0 **Use of preventive treatment:** 80.0	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, CI=Confidence interval, ICHD II=2nd edition of the International Classification of Headache Disorders

E.1.3 Headache diaries for the diagnosis and management of primary headaches and medication overuse headache

Headache diaries as an aid to diagnosis

Study details	Patients	Interventions	No. correctly diagnosed	Sensitivity	Specificity	PPV	NPV	Comments
Author & Year: Russell et al, 1992[679] **Study design:** Diagnostic study **Section of question:** Diagnosis **Setting:** Headache research unit, University hospital, Denmark. **Duration of follow-up:** Four weeks or more	**Patient group:** Adults with migraine **Inclusion criteria:** Migraine patients who used the diary for four weeks or more **All patients** **N:** 61 47 F, 14M **Age (median [range], years):** 44 [21-65] **Drop outs:** none	**Index test:** Diagnostic headache diary developed by one study author. Patients received diary at the end of first visit and were instructed on its use. Diary completed every evening on days in which a headache occurred. Questions included: headache duration, visual or sensory disturbances; location, character and intensity of pain, aggravation by routine physical activity, accompanying symptoms, precipitating factors and medication. Diaries blindly examined by different observers and a diagnosis of headache was made. **Reference standard:** Physician diagnosis of headache classified according to operational diagnostic criteria of the IHS following detailed semi-structured headache history, physical and neurological examination. Physician diagnosis was made prior to use of diary.	**Migraine without aura**					**Funding:** NR **Limitations:** Lag period of four weeks between physician diagnosis and diary diagnosis. Period of use of diary may not have allowed enough time for diagnosis of episodic/chronic TTH. Study was conducted in a specialised headache research unit in a university hospital; may not be representative sample. *Calculated by NCGC
			54*	94.3% (50/53)*	50% (4/8)*	92.5% (50/54)*	57.1% (4/7)*	
			Migraine with aura					
			44*	72.7% (8/11)*	72% (36/50)*	36.3% (8/22)*	92.3% (36/39)*	
			Episodic Tension-type Headache					
			35*	84.2% (16/19)*	45.2% (19/42)*	41% (16/39)*	86.3% (19/22)*	
			Chronic Tension-type Headache					
			46*	21% (4/19)*	100% (42/42)*	100% (4/4)*	73.6% (42/57)*	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, TTH=tension type headache, PPV=positive predictive value, NPV=negative predictive value

Study details	Patients	Intervention	No. correctly diagnosed	Sensitivity	Specificity	PPV	NPV	Comments
Author & Year: Phillip et al, 2007[628] **Study design:** Diagnostic study **Section of question**: Diagnosis **Setting:** Glostrup university hospital, Denmark **Duration of follow-up**: Diaries kept for 24 headache days for a maximum of 2 months	**Patient group:** Adults with difficult to diagnose headaches. **Inclusion criteria:** Living in Denmark. Able to answer written and verbal questions. **Patient characteristics:** Participants were part of an epidemiological study of headache conducted in general population in 1989 and another cohort of young adults (aged 25-36 years). **N:** 1175 eligible for inclusion; 848 participated (555 clinical interview, 293 telephone interview); 106 identified to receive diary if the interviewer found it difficult to diagnose headaches on based on history alone (unable to characterise headache quality, frequency and/or associated symptoms).	**Index test:** Diagnostic headache diary, based on IHS criteria. Questions focussed on characteristics necessary to diagnose and distinguish between migraine and tension- type headache. Participants were instructed to complete the diary at the end of each headache day. Diaries were examined by two independent observers who were blinded to the clinical diagnosis and the diagnosis of the other observer and a diagnosis was made based upon diary findings. **Reference standard:** Structured clinical headache interview, physical and neurological examination and self administered questionnaire . Headache disorders were diagnosed and coded according to IHS criteria. In cases where subjects did not participate in a clinical interview, a headache diagnostic interview was conducted over the telephone to make a diagnosis of headache.	**Migraine**:					**Funding:** NR **Limitations:** Some clinical interviews were conducted over the telephone and no physical examination was conducted. Selection of participants for diary use was made on the basis of level of difficulty of clinical diagnosis and may have resulted in a selection bias. Period of use of diary may not have allowed enough time for diagnosis of episodic/chronic TTH. Study was conducted in a university hospital and may not be a representative sample. Small sample size. **Notes:** *Calculated at NCGC. ‡Sensitivity of clinician diagnosis taking diary as reference standard (reported in paper):
			37*	84.8%*‡	75%*‡	90%*	64%*	
			Tension-type headache:					
			39*	88%*‡	66%*‡	97.3%*	29%*	
			Chronic Tension-type headache:					
				77%*				

Study details	Patients	Intervention	No. correctly diagnosed	Sensitivity	Specificity	PPV	NPV	Comments
	All patients **N:** 106 (received a diary), 49 (returned diary), 41(clinical interview), 8 (telephone interview), 4 (incomplete diary), 45 (analysed) **Age (mean, range):** 44, 26-70 years **Sex M:F** 1:3.1 **Dropouts:** 57	Physician diagnosis was made prior to use of diary.						Migraine (90%) and Tension-type headache (97%); Specificity of clinician diagnosis taking diary as reference standard (reported in paper): Migraine (64%) and Tension-type headache (29%).

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, IHS=international headache society, TTH=tension type headache, PPV=positive predictive value, NPV=negative predictive value

Study details	Patients	Intervention	No. correctly diagnosed	Sensitivity	Specificity	PPV	NPV	Comments
Author & Year: Tassorelli et al, 2008[772] **Study design:** Diagnostic study **Section of question:** Diagnosis **Setting:** Headache centres at Copenhagen, Denmark and Pavia, Italy **Duration of follow-up:** Four weeks	**Patient group:** People aged >11 with undiagnosed headache **Inclusion criteria:** New headache patients awaiting consultation at 2 headache centres. **All patients:** **N:** 84 (received diary), 78 (completed diary), 2 (excluded as diagnosed as cluster headache patients at clinical interview), 76 (analysed) Sex M/F: 21/55 (1:2.6) **Mean age (yrs [range]):** 39.1 [11-85] **Duration of headache (mean [range]):** 17.5 [1-70]	**Index test:** Diagnostic headache diary using ICHD-II diagnostic criteria for migraine, tension type headache and medication overuse headache. Diary contained detailed instructions and was required to be filled up on a daily basis by the patients. Diary was mailed to participants at least 4 weeks prior to their first consultation. Diary was assessed by two senior physicians who were blinded to the patients' history and to the diagnosis based on clinical interview and examination and a diagnosis of headache was made. **Reference standard:** Clinical interview obtaining headache history and physical examination leading to diagnosis of headache. Physician diagnosis was made after use of diary.	**Migraine**					**Funding:** NR **Limitations:** Clinical interviews were conducted by two separate physicians in different centres. Period of use of diary may not have allowed enough time for diagnosis of episodic/chronic TTH. Study was conducted in a specialised headache research unit in a university hospital and may not be representative sample. **Notes:** *Calculated by reviewer at NCGC. ‡Sensitivity of diary taking clinician diagnosis as reference standard reported in paper as 92% (59/66). † Specificity of diary taking clinician diagnosis as reference standard reported in paper as 87% (54/62).
			66*	92.1%*‡ (59/64)	58.3%	92.1%*	58.3%*	
			Tension–type headache					
			49*	75%	58.3%	51.2%*	80%*	
			Medication overuse headache					
			64*	75%	86.6%*† (52/60)	60%*	92.8%*	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, TTH=tension type headache, PPV=positive predictive value, NPV=negative predictive value

Headache diaries as an aid to management of people with primary headaches

Study details	Patients	Methods	Outcomes	Effect size	Comments
Author & Year: Baos et al, 2005[58] **Study design:** Open label prospective study, survey **Section of question:** Patient and physician experience **Setting:** Primary care setting in urban Spain **Duration of follow-up:** One and half months	**Patient group:** Adults with migraine, previous clinical trial participants **Inclusion criteria:** Aged ≥18 years with experienced migraine, with or without aura as defined by International Headache Society criteria. Never used a triptan. Recruited by 22 primary care physicians from group practices in 12 cities in Spain. Each physician could enrol 10 patients. Patients originally recruited for a open label study comparing rizatriptan with non-triptan therapy for migraine. **Exclusion criteria:** Current use of propranolol. Any contradiction to triptan use. **All patients** **N:** 118 (enrolled); 97 (completed the study and included in the analysis) **Age (mean±SD, range):** 39±12(18-73) **Drop outs:** 19	Patients used a diary to record clinical responses and satisfaction with therapy for three consecutive migraine attacks during the study, the first and third treated with rizatriptan 10-mg wafer and the second with usual non-triptan therapy. Patients completed a self- administered questionnaire regarding migraine history and the most recent pre-study migraine attack at baseline visit. They were given a diary containing three self administered questionnaires one for each of the three study migraine attacks. At each migraine attack patients recorded: • Headache pain intensity (mild/moderate/severe). • Grade of functional disability (none/mild/ severe/ require bed rest) • Associated symptoms (photophobia, phonophobia, nausea and vomiting) at time of taking migraine medication. • Timing. • Type and amount of medication and any additional medications taken after 24 hours of taking migraine medication. • Response to the medication (onset of pain relief and pain free, associated symptoms and return to usual activities) • Impact of attack on work hours (hours worked with migraine, hours of work	**Patient more satisfied with level of care provided by doctor as compared to before the study** Positive response/Number responded; (Percentage)	59/84 (70%)	**Funding:** Merck Sharpe and Dohme de Espana, S.A) **Limitations:** Small sample size. No control group. Recruited from an ongoing study, therefore, effects observed may be influenced by treatment given. Study may not be generalisable to population. Participants were known to physicians and this may have influenced responses.
			Migraine diary helped patient communicate better with physicians Positive response/Number responded; (Percentage)	70/80 (88%)	
			Of the patients who reported the diary to be useful, 80% were more satisfied with present medical care than pre-study care Of the patients who did not find the diary to be useful, or who did not answer, 11% were more satisfied with present medical care as compared to pre-study care		
			Diary enabled physician to communicate better with patients about migraine Positive response/Number responded; (Percentage)	20/22 (91%)	
			Diary enabled physician to assess differences in pain intensity and disability across attacks within the same patient	100%	
			Difference in evaluation and differentiation between headaches pre and post study	10/22 (46%)	

Study details	Patients	Methods	Outcomes	Effect size	Comments
	Gender (F): 80 (83%) **Headache pain intensity at baseline:** Moderate 36 (38%), Severe 60 (63 %)	missed, amount of difficulty working and rating of job effectiveness on a scale of 0-100%) • Impact on quality of life and satisfaction with treatment Questions on work related disability and quality of life were selected from validated questionnaires. Physicians also completed a baseline migraine history and treatment questionnaire for each patient at first visit. At the end of the study after evaluating 10 patients, physicians completed a questionnaire regarding the usefulness of the migraine diary.	Positive response/Number responded; (Percentage) **Diary influenced decisions regarding prescription medication for migraine** Positive response/Number responded; (Percentage)	 15/22 (68%)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation

Study details	Patients	Methods	Outcomes	Comments
Author & Year: Coeytaux et al, 2007[155] **Study design:** Qualitative study, focus groups **Section of question:** Patient experience **Setting:** University-based, tertiary care headache clinic in USA **Duration of follow-up:** 12 weeks for clinical trial	**Patient characteristics:** Adults with frequent headaches **Inclusion criteria:** Experienced 15 or more days of headache prior to clinical trial. Participants had recently participated in a clinical trial evaluating the effectiveness of medical management plus acupuncture compared to medical management without acupuncture. **Exclusion criteria:** NR **All patients** **N:** 34 Number attending 1 out of 4 scheduled focus group discussions: 19 **Age (range):** 22-83 years **Sex M/F:** 20/14 (26/74%) **Drop outs:** 14	Objective of the study was to identify clinical outcomes considered to be most important by patients who experience frequent headaches to help inform clinicians which of available headache assessment instruments may be most appropriate in assessing change over time. Patients were asked to keep a daily pain diary during the 12 week trial and had to record 'the pain severity of your worst headache that day, with 0=no headache and 10=very severe pain'. Focus group discussions were facilitated by two of the study authors and social scientists who were not directly involved in the RCT. Discussion focused on 5 topics: • Severity of pain associated with headaches • Definition of meaningful symptom relief • Uncertainty regarding timing and severity of headaches • Devaluation of the impact of headaches on sufferers, especially by health care professionals • Assessments of pain and its effects meaningful to participants	**Patients views:** Pain diary was useful and not overly burdensome to complete. Diary provided a meaningful expression of their level of pain and was useful in measuring pain severity and frequency. Diary allowed them to see improvement of which they might have been otherwise unaware.	**Funding:** National Institute of Health and GlaxoSmithKline **Limitations:** Participants were recruited from a clinical trial, may not be generalisable to the population. No information provided on whether participants were known to study authors. Focus group discussions may not have been able to elicit individual experiences. No mention of validation of the diary. Participants also completed the HIT-6, SF-36 and MIDAS questionnaires simultaneously and this may have influenced their understanding of the questions in the diary and their responses.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, HIT6=headache impact test, SF-36=short form-36, MIDAS=migraine disability assessment

Study details	Patients	Methods	Outcomes	Effect size	Comments
Author & Year: Jensen et al, 2011[400] **Study design:** Randomised study; survey **Section of question:** Patient and physician experience **Setting:** 16 headache centres in 9 countries (Europe and Latin America). **Duration of follow-up:** Four weeks or more	**Patient characteristics:** Adults with headache awaiting consultation at headache clinics **Inclusion criteria:** Age 18-65 years **All patients** **N:** 626 **Group 1- Diary +clinical interview** **N:**321 **Age (median, range):** 37 (16-74) **M/F:** 250/71 **Years with headache(median, range):** 11 (1-52) **Headache days per month(median, range):** 9(1-30) **Days with drug intake per month(median, range):** 7 (0-30) **Group 2- Clinical interview** **N:** 305 **Age (median, range):** 37 (17-72) **M/F:** 238/67 **Years with headache(median, range):**12 (1-50**)** **Headache days per month(median, range):** 10(2-30) **Days with drug intake per month(median, range):** 6 (0-30)	**Group 1** A basic diagnostic headache diary was developed based on ICHD-II criteria and tested in a pilot study. Based on results of pilot study the diary was modified slightly to collect information relevant to ICHD-II diagnostic criteria for migraine, TTH and medication overuse headache and on the consumption of symptomatic medication and also included a set of simple detailed instructions. Patients were sent the diary by post a month before first consultation; were asked to complete it every day for 4 weeks and bring it along for their first consultation. Diagnosis was made on the basis of data from diary +clinical interview. **Group 2** Patients did not receive diary. Diagnosis was made on the basis of clinical interview alone. **All** All patients and physicians were given separate questionnaires at the end of the first visit to assess usability and usefulness of the diary.	**Adequacy of information for diagnosis** (% who found information adequate for diagnosis) **Patient experiences:** • 97.5% of patients reported no difficulty in understanding the diary and providing information. • Patients evaluated diary as useful for making them aware of medication usage and less useful for understanding headache triggers or deciding when to treat headache. **Physician experiences:** • 97% of physicians reported no difficulty in understanding the diary and interpreting information. • Physicians evaluated diary as being helpful in diagnosing medication overuse headache and informing patients about medication intake; regarded it as less useful in informing about headache triggers.	**Group 1:** 97.7% **Group 2:** 86.8%	**Funding:** Grant from the European commission (Eurohead project) and the Italian ministry of health (Ricerca Corrente 2008) **Limitations:** •Period of use of diary may not have allowed enough time for diagnosis of episodic/chronic headache. •Study was conducted in a specialised headache research unit in a university hospital and the study sample may not be representative of all headache patients. **Notes:** As in the pilot study, the criteria for chronic TTH and MOH were modified on account of the short recording period; chronic TTH was diagnosed when TTH was present on ≥50% of days in the recording period; MOH was diagnosed when headache was present on ≥15 days per month and when the medication overuse criteria was met.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ICHD=international classification of headache disorders, TTH=tension type headache, MOH=medication overuse headache

Study Details	Patients	Interventions	Outcomes	Effect size	Comments
Author & Year: Porter et al, 1981[635] **Study design:** Survey **Section of question:** Patient experience **Setting:** Specialist care, Boston, USA **Duration of follow-up:** Four weeks	**Patient group**: Patients who had sought specialised headache care **Inclusion criteria:** Patients who had been in contact with the study authors during the previous four years for specialised headache care. Patients had varied diagnosis (not specified) which are thought to account for most recurrent headaches. **All patients** **N:** 1148 (total number of chronicles mailed); **Sex M/F:** 57/177 **Age (mean):** 49 years **Drop outs:** Returned and usable chronicles (n): 234. Not returned (n): 798. Returned but not usable: 47 (27 refused, 12 had no name, 4 had no consent form, 4 did not follow directions). Returned undelivered by the postal service: 69 (3 died, 66 address unknown).	Headache chronicle with letter of invitation for participation in study and consent form was mailed to all participants. Headache chronicle consisted of one self- reporting page for each week followed with open ended questions. The chronicle had sections reporting pain intensity, how much the pain interfered with participants' usual activities, whether they experienced nausea, and when and what did participants do for prevention and relief of headache. The chronicle also reported to what extent the participants felt a range of negative emotions. Participants completed the headache chronicles on a day-to-day basis over a period of four weeks. To evaluate how completing the chronicle affected the description of headaches, the severity and occurrence reported in the chronicles was compared between the first and second two-week periods.	**Percentage who thought the chronicle was helpful**	38%	**Funding:** Government **Limitations:** No mention of validation or piloting of the questionnaire. Participants were known to the study authors previously, may have influenced their answers and response rate. Sample not representative of all those who suffer from headache. No mention of any medication/ treatment regime/additional care that was provided for the management of migraine. Relationship between negative feelings and headache intensity cannot be classified as causal due to cross sectional nature of survey.
			Percentage who thought the chronicle was a hindrance	8%	
			Percentage who thought the chronicle would be helpful to their physician	69%	
			Headache intensity Average level of headache pain over second two weeks as compared to first two weeks	Decreased: 127/234 (54.2%) Increased: 95/234 (40.5%) Unchanged: 12/234 (5.1%)	
			Headache frequency Number of days with any level of headache over second two-week period	Increased: 96/234 (41%) Decreased: 53/234 (22.6%) Unchanged: 85/234 (36.3%)	
			Average level of negative feelings Over second two week period	Increased: 96/234 (41%) Decreased: 118/234 (50.4%) Unchanged: 20/234 (8.5%)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised

E.1.4 Imaging for diagnosis in people with suspected primary headache

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Cull, 1995[175] **Study design:** Retrospective **Setting:** Neurology outpatient clinics, UK and Holland **Duration of follow-up:** N/A	**Patient group:** Patients with migraine with or without aura. **Inclusion criteria:** Patients presenting with 1st attacks of migraine with or without aura after the age of 40. **Exclusion criteria:** NR **All patients** **N:** 69 **Age of onset (mean, SD):** 51.6 (8.9) **F/M:** 46 (66.6%)/ 23 (33.3%) **Migraine with aura:** 59/69 (86%) **Migraine without aura:** 10/ 69 (14%) **Family history of migraine**: 15/69 (22%)	**All patients** Clinical and investigation data were collected on patients at neurology outpatients clinics between 1988 and 1994. Participating physicians were asked to record patient history clinical examination and non invasive investigations. CT or MRI was performed in all cases and where possible Doppler US. Clinical neurological examination was normal in 65 cases (94%) CT scanning carried out on 67 patients. MRI scanning in 2 patients.	**Arterio- venous malformations** (n)	0/65	**Funding:** NR **Limitations:** Only includes patients with migraine. **Additional outcomes:** Routine haematology and auto-antibodies were assessed. **Notes:** Carotid Doppler US studies carried out in 38 patients. 1 patient had MS. 1 patient had migraine related to head injury. Patients had CT or MRI.
			Tumours (n)	0/65	
			Abnormal CT (n)	5/67 (7.69%) 1 moderate atrophy (MS) 4= 1 or more cerebral infarctions	

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Demaerel et al, 1996[190] **Study design:** Retrospective **Setting:** Department of radiology, University hospital, Belgium. **Duration of follow-up:** N/A	**Patient group:** Patients complaining of headache **Inclusion criteria:** Normal clinical neurological examination **Exclusion criteria:** Patients with dizziness, vertigo, migraine and epilepsy. **All patients** **N:** 363 **Age (mean, range):** 35 (3-83) **Drop outs:** N/A **F/M:** 212 (58.4%)/ 151 (41.6%)	**Group 1** Consecutive patients with chronic headache examined by cranial CT before and after intravenous contrast enhancement. Patients divided into 3 groups: **Group 1 -** (321/ 363) normal CT findings **Group 2 -** (31/363) patients with non significant abnormalities **Group 3 -** (11/363) significant abnormality. All had a space occupying lesion. MRI undertaken in 8/11 patients in this group.	**Tumour / neoplasm**	9/363 (2.18%) **Meningioma:** 4 **Multiple metastases** (originating from an oat cell carcinoma in the lung): 1 The following patients were treated surgically and pathological findings were: **Oligodendrioma** (grade 2): 1 **Astrocytoma** (grade 3): 1 **Ganglioma**: 1 **Undifferentiated carcinoma with neuroendocrine features**: 1	**Funding:** NR **Limitations:** Patients with migraine excluded. In 2 patients a developmental venous anomaly on CT could not be confirmed. One patient had a developmental venous anomaly that could be seen on MRI but not on CT. Unclear on what basis patients in group 3 were referred for MRI. **Additional outcomes:** NR **Notes:** Intraventricular cysts recorded as significant abnormality. An additional brain MRI requested in 29/363 (8%) patients. Additional MRI carried out in 8/11 patients in group 3. CT was carried out both with and without contrast material, some patients had MRI.
			Intraventricular cyst	2/363 (0.55%)	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Grimaldi et al, 2009[342] **Study design:** Prospective cohort **Setting:** 8 emergency departments (ED) in northern Italy **Duration of follow-up:** 3 months after emergency department admission	**Patient group:** Adults >18 with headache **Inclusion criteria:** Patients >18 years presenting to ED with headache as the chief complaint. **Exclusion criteria:** Head trauma in previous 30 days, complaint of visual aura not followed by headache and re-admission to ED after recruitment into the study. **All patients** **N:** 120* **Age (mean):** 40 (14) **Drop outs:** 17 (14.1%) **F:** 77 (64.2%)	Detailed history and examination of the patient, ED physician assigned patient to 1 of 4 clinical scenarios to each patient. An indeterminate clinical scenario was used if the patient did not fit one of the 4 scenarios or if they met the criteria for more than 1. Once the scenario was assigned physician was suggested to follow the recommended diagnostic procedures (previously published) but physician was free to select best care for patient. Scenario 1, 2 and 3: classified as malignant headaches Adult patients admitted to ED for severe headache (acute onset, focal signs, fever/ neck stiffness, progressively worsening). Scenario 4: classified as benign headaches (previous history of headache- complaining of a headache very similar to previous in terms of intensity, duration and associated symptoms). There was also an indeterminate group, which either fitted more than one of the 4 scenarios, or did not match any of them. Head CT scan without contrast with 3mm slices through posterior fossa of brain and a follow up structured telephone interview by a neurologist expert in headache management at least 3 months after ED admission.	**Serious abnormalities**	0/103	**Funding:** NR **Limitations:** Only 80/120 patients assigned to scenario 4 were included in the analysis, stated that 17 dropped out. Discrepancy in numbers. There was an indeterminate group- unclear whether these should be included. Does not state type of primary headaches that included patients diagnosed with. **Additional outcomes:** N/A **Notes:** *256 included, but only looking at scenario 4 therefore n=120. Head CT scan assessed by a trained neuroradiologist. Interviewer was unaware of scenario assignment by ED physician at recruitment. Interview performed using a structured questionnaire.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Jordan et al, 2000[406] **Study design:** Retrospective **Setting:** Long beach memorial medical centre, USA **Duration of follow-up:** N/A	**Patient group:** Patients presenting for MRI of headache at institution over a 3 year period **Inclusion criteria:** NR **Exclusion criteria:** Patients with focal findings on physical examination, prior brain surgery, head trauma or immunocompromise. **All patients** **N:** 328 **Age (mean):** 42 (6-84) **M/F:** 106 (32.3%)/ 222 (67.7%) **Drop outs:** N/A	Patients had MRI for headache. Patients categorised as: Group 0= negative study, (n-163) Group 1= positive study without any significance, (n=158) Group 2= positive study with clinically significant result. (n=5)	**Tumour / neoplasm**	1/ 328 (0.30%) (low grade glioma)	**Funding:** NR **Limitations:** Unclear if patients previously had CT. Unclear whether study includes secondary headaches. -Does not state what type of primary headache the patient is diagnosed with. **Additional outcomes:** Referral speciality and motivation for referral for imaging. **Notes:** Discrepancy between total included in study(n=328), and group totals (n=326) *cysts were considered as group 1 as they were small and had a lack of mass effect.
			Arteriovenous malformations	1/328 (0.30%) (dural)	
			Cysts	9/328 (2.74%) (7 arachnoid, 2 pineal)*	

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Sempere et al, 2005[712] **Study design:** Prospective **Setting:** Neurology clinics, Spain. **Duration of follow-up:** At least 3 months	**Patient group:** >15 years with non-acute headache **Inclusion criteria:** Consecutive patients >15 years attending neurology clinic with non acute headache as main symptom. Defined as any headache which began at least 4 weeks before. Referred by family physician working in the health area. **Exclusion criteria:** Patients with facial pain alone and pregnant women. **All patients** **N:** 1876 **Age (mean, range):** 38 (15-95) **F/M:** 1243 (66.3%)/ 633 (33.7%) **Drop outs:** NR **Migraine:** 919 /1876 (49%)* **TTH**: 664/1876 (35.4%)* **Cluster:** 21/1876 (1.1%)* **Indeterminate:** 203/1876 (10.8%)* **New-onset headache:** 629 (33.5%) **Headache for >1 year:** 1247 (66.5%) **Normal neurological examination:** 1857 (99.2%) **CT scan:** 1432/ 1876 (76.3%) **MRI:** 580/ 1876 (30.9%)	Every patient received CT or MRI- choice made on individual basis. MRI performed with 1.5-T imagers (sagital and axial T1 weighted and axial T2 weighted imaging with 6mm thickness. CT studies performed with high resolution scanners- slice thickness was 5mm in posterior fossa and 10mm in the supratentorial cavity. Choice of contrast medium made on individual basis by radiologist. Neuroimaging results classified as significant abnormalities, non-significant abnormalities or normal. MRI performed after a normal CT if patient's headache did not respond to treatment or in patients with abnormalities on CT to improve their diagnosis.	**Tumour / neoplasm**	7/1857 (0.37%) (3 pituitary adenomas, 1 low grade astrocytomas, 2 meningioma, 1 brain stem glioma) 1 new onset common migraine, 1 indeterminate type headache, 1 history of episodic cluster headache	**Funding:** NR **Limitations:** MRI carried out in 119 patients with normal CT and revealed 1 meningioma and 1 acoustic neurinoma. Unclear why MRI carried out in this subgroup and whether results reported with main results. Dropouts NR **Additional outcomes:** Likelihood ratios for a significant abnormality on neuroimaging. **Notes:** Radiologist who performed evaluation of CT and MRI did not access patients' clinical history. Results from patients with normal neurological examinations only.
			Hydrocephalus	2/1857 (0.11%) 1 had history of episodic migraine, 1 had chronic indeterminate type headache	
			Arteriovenous malformation	1/1857 (0.05%) Episodic migraine for previous 6 years	
			Cyst	2 /1857 (0.11%) (1 colloid, 1 arachnoid) 1 chronic indeterminate and 1 new onset migraine	
			Stroke	1 /1857 (0.05%) (acute stroke) New onset headache of indeterminate type.	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Tsushima & Endo, 2005[805] **Study design:** Retrospective **Setting:** Department of radiology, Japan. **Duration of follow-up:** N/A	**Patient group:** Adults with chronic or recurrent headache **Inclusion criteria:** Chief complaint of chronic or recurrent headache with duration of 1 month or more. No other neurologic symptoms or focal findings on examination, no prior head surgery, head trauma, or seizure. **Exclusion criteria:** NR **All patients** **N:** 306 **Age (mean, SD):** 54.2 (15.2) **Drop outs:** N/A **M/F:** 136 (40%)/170 (50%)	All patients underwent examination with MR imager. Transverse T1 weighted spin echo, proton density weighted and T2 weighted fast spin echo image were obtained. Section thickness was 5mm with a gap of 2.5mm for all sequences.. Contrast material enhanced transverse T1 weighted images were obtained by using gadopentetate dimeglutamine if a more detailed examination was recommended by the patient's physician or demanded by the patient. MR imaging results were divided into 3 groups: those with no abnormality, those with minor abnormality, those with clinically important intracranial abnormality	**Tumour / neoplasm** **Subdural haematoma**	1 /306 (0.33%) (pituitary macroadenoma) 1 /306 (0.33%)	**Funding:** NR **Limitations:** 23 patients underwent repeat MRI scans due to patient demand-no abnormality found in any scan. Does not state type of headache that included patients were diagnosed with. **Additional outcomes:** N/A **Notes:** All MRI images were interpreted by one of the authors with 15 years experience as a general radiologist. The images were not reinterpreted for this study.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Wang et al, 2001[836] **Study design:** Retrospective **Setting:** Patients referred to department of radiology, New York, USA. **Duration of follow-up:** N/A	**Patient group:** Adults referred for MRI evaluation of headache. **Inclusion criteria:** Primary complaint of headache with a duration of 3 months or more who have had an evaluation by the neurology service. **Exclusion criteria:** Other neurologic symptom **All patients** **N:** 402 **Age (range):** 18-85 **Drop outs:** N/A **M/F:** 116 (28.9%)/ 286 (71.1%) **Migraine:** 161/402 **TTH:** 71/402 **Mixed:** 27/402 **Atypical:** 64/402 **Other:** 79/402	Sagittal T1 weighted, axial proton density weighted and axial T2 weighted images were obtained. In 84 patients, iv gadolinium-based contrast material was administered and additional axial and coronal images were obtained. MRI findings categorised as negative or positive for major abnormality.	**Tumour / neoplasm**	4 /402 (1%) (1 glioma, 1 meningioma, 1 pituitary macroadenoma, 1 metastases) All had atypical headache	**Funding:** NR **Limitations:** Paper also includes patients with secondary headaches, but separates results for primary headache. **Additional outcomes:** N/A **Notes:** Abnormality defined as major if it was a mass, caused mass effect or was believed to be the likely cause of the patient's headache.
			Cyst	2 /402 (0.5%) (1 petrous apex cholesterol cyst, 1 large arachnoid cyst) 1 had migraine 1 had atypical headache	
			Arteriovenous malformation	1/402 (0.25%) Atypical headache	
			Subdural haematoma	1/402 (0.25%) Atypical headache	
			Hydrocephalus	3/402 (0.75%) 2 had atypical headache 1 tension type headache	

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

E.1.5 Imaging as a management strategy for people with primary headaches

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Howard et al, 2005[385] **Study design:** RCT **Setting:** Headache clinic in secondary care, London **Duration of follow-up:** 1 year	**Patient group:** Patients with chronic daily headache **Inclusion criteria**: Consecutive English-speaking patients who fulfilled the criteria for chronic daily headache (CDH); at least 15 days per month of headache for >6 months, including tension-type headache, migraine and secondary headache due to excessive medication consumption, presenting as new patients to the headache clinic at King's College Hospital in London. **Exclusion criteria:** Clinical justification for neuroimaging (with the exception of solely providing reassurance). Medical contraindication to an MRI scan. **All patients** **N:** 150 **Age (mean):** 38.1 (S.D. 12.4) years **Drop outs:** 8, but unclear **HADS positive:** 66/150 (44%) **Group 1 (offered scan)**	**Group 1** Received an offer of a screening MRI scan using a sagittal localiser image followed by a double echo axial series. **Group 2** No scan / treatment as usual **All patients** Asked to take part in interviews and follow up questionnaires with data from primary care case notes. Given a letter providing information on CDH. Completed a semi-structured interview for their medical and psychiatric history. Completed the following scales: HADS (hospital anxiety and depression scale) Visual analogue scales (VAS) of level of worry about health (0-100) and level of	**Resource use - GP** Number of patients using services during year following randomisation	**Group1:** 67/68 (99%) **Group 2:** 66/69 (96%) **Relative risk:** 0.99 * **95% CI:** 0.88-1.11 * **p value:** 0.619 (0.84*)	**Funding:** The Wellcome Trust **Limitations:** Randomisation unclear. Patients swapped groups. Allocation concealment unclear. Single-blind (assessor only). Response rate was lower than expected which meant there was a lack of statistical power for some of the outcome measures. 1/3 of HADS positive patients not offered a scan had scans elsewhere in the following year. Incomplete reporting of data. **Additional outcomes:** Likert five point scales for anxiety about serious underlying illness. Revised illness perception questionnaire (IPQ-R). Medical outcome study
			Resource use - neurologist Number of patients using services during year following randomisation	**Group1**: 1/68 (1.5%) **Group 2:** 17/69 (25%) **Relative risk:** 0.06 * **95% CI:** 0.01-0.42 * **p value:** <0.001 (0.005*)	
			Resource use - psychiatrist/therapist Number of patients using services during year following randomisation	**Group1:** 1/68 (1.5%) **Group 2:** 8/69 (12%) **Relative risk:**0.12 * **95% CI:**0.02-0.95 * **p value:** 0.033 (0.04*)	
			Resource use – outpatient Number of patients using services during year following randomisation	**Group1:** 30/68 (44%) **Group 2:** 32/69 (46%) **Relative risk:**0.91* **95% CI:** 0.62-1.34 * **p value:** 0.864 (0.64*)	
			Resource use – other imaging Number of patients using services during year following randomisation	**Group1:** 13/68 (19%) **Group 2:** 21/69 (30%) **Relative risk:**0.60* **95% CI:**0.33-1.11* **p value:** 0.166 (0.11*)	
			Resource use – tests Number of patients using services during year	**Group1:** 21/68 (31%) **Group 2:** 29/69 (42%) **Relative risk:**0.71*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 76 **Age (mean):**37 (11.4%) **Drop outs:** not clear, 5 did not have scan **Group 2 (not offered scan)** **N:** 74 **Age (mean):** 40 (13.2) **Drop outs:** unclear, 3 demanded a scan.	illness belief (0-100) Likert five point scales of anxiety about serious underlying illness. Health anxiety questionnaire (HAQ) of 21 questions with 4 subscales. Service use over a retrospective 1 year period prior to consultation (Client Service Receipt Inventory). Revised illness perception questionnaire (IPQ-R). Medical outcome study short form 36 (SF-36). Headache diary 6 weeks before the consultation and headache index calculated. All patients received usual clinical care: explanation of symptoms, verbal reassurance of no serious pathology and CDH advice.	following randomisation	**95% CI:**0.44-1.12* **p value:** 0.215 (0.14*)	short form 36 (SF-36), data not reported. **Notes:** CDH defined as: at least 15 days per month of headache for more than 6 months (which can include tension type headache, migraine, and secondary headache due to extensive medication consumption). Headache index= no. of hours with headache x intensity / no. of days recorded. * Based on ITT analysis in paper – other data reported here is available case analysis. †calculated by NCGC
			Resource use – inpatient care Number of patients using services during year following randomisation	**Group1:** 5/68 (7%) **Group 2:** 10/69 (14%) **Relative risk:** 0.49* **95% CI:**0.17-1.36* **p value:** 0.274 (0.17*)	
			Resource use – other services Number of patients using services during year following randomisation	**Group1**: 6/68 (9%) **Group 2:** 6/69 (9%) **Relative risk:** 0.97* **95% CI:**0.33-2.88* **p value:** 1 (0.96*)	
			Resource use – sick notes Number of patients using services during year following randomisation	**Group1:** 6/68 (9%) **Group 2:** 7/69 (10%) **Relative risk:** 0.83* **95% CI:** 0.29-2.37* **p value:** 1 (0.73*)	
			Change in anxiety and depression VAS worry (at 1 year, scan-no scan) (n Gp1: 54, Gp2: 42)	**Adjusted difference:** -4.47 **95% CI:**-15.27 to 6.33 **SE:** 5.51 †	
			Change in anxiety and depression HAQ health, worry and preoccupation (at 1 year, scan-no scan) (n Gp1: 48, Gp2: 34)	**Adjusted difference:** 0.22 **95% CI:**-1.26 to 1.70 **SE:** 0.76 †	
			Change in anxiety and depression	**Adjusted difference:** 0.31 **95% CI:**-0.84 to 1.45	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			HAQ fear of illness (at 1 year, scan-no scan) (n Gp1: 50, Gp2: 33)	**SE:** 0.58 †	
			Change in anxiety and depression HAQ reassurance seeking behaviour (at 1 year, scan-no scan) (n Gp1: 50, Gp2: 35)	**Adjusted difference:** -0.39 **95% CI:**-0.93 to 0.16 **SE:** 0.28 †	
			Change in anxiety and depression HAQ life interference (at 1 year, scan-no scan) (n Gp1: 51, Gp2: 33)	**Adjusted difference:** -0.20 **95% CI:** -1.12 to 0.72 **SE:** 0.47 †	
			Incidental neurological findings (%)	97% normal 2 abnormal (a posterior fossa arachnoid cyst and a hypothalamic signal flair, neither clinically significant).	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CDH=chronic daily headache, HADS=hospital anxiety and depression scale, VAS=Visual analogue scale

E.2 Management

E.2.1 Information and support for people with primary headache

Study	Adelman et al, 2000[8]	
Aim	To assess migraine sufferers' choice and use of physicians, their experiences in obtaining an accurate diagnosis, and their current treatment practices. Intended to provide physicians a better understanding of their patients' need and behaviours, which will lead to better overall disease management.	
Population	801 people with migraine (IHS criteria) recruited from a consumer database mail questionnaire (diagnosis confirmed by phone screening) in the USA.	
Methods	Telephone questionnaire containing 64 questions. Several measures were open-ended queries which allowed for spontaneous responses. The majority of the reporting in the study is descriptive statistics only. Open ended question results are grouped into logical categories.	
Themes with findings	<u>Sources of information</u> [Poor quality study. Only information directly relevant to the question on patient information and support reported here].	When asked if they felt they had the most current information about treating their migraine, most answered 'no.
		Current consulters most often relied on their physicians as their source of information, lapsed consulters and non consulters most often relied on magazine news stories for their migraine information.
		The type of information they wish they had known earlier and think other migraine sufferers might find useful to know was most often related to medication.
		34% said they would like to have more information on medications, such as what new prescription medication was available and what worked best.
		20% felt seeing a physician for a diagnosis and/or treatment was important.
		14% felt that information about other treatments was important, such as how bed rest in a dark room can help a migraine sufferer.
		12% believe information related to the cause of migraine is important to know, especially what can trigger a migraine and that migraine can be hereditary.
Limitations	• Structured interview – not clear how many questions were open ended. • Interview by telephone, including confirming diagnosis of migraine according to IHS criteria. May lead to doubt in diagnosis. • Descriptive statistics only used, no formal qualitative analysis.	

Study	Belam et al, 2005[66]	
Aim	• To develop a research partnership between migraine sufferers and healthcare professionals who had an interest in the area with the objective of synthesizing tacit and explicit knowledge in the area. • To identify and raise awareness of what it is to suffer from migraines from patients' perspectives, in order to improve the management of migraine. • To inform the development of a local primary care headache intermediate care clinic and contribute to the dialogue of how headache services should be delivered.	
Population	8 patients with migraine who had attended an intermediate care headache clinic in the UK. Age range 30 to 61. 6 women and 2 men. Headache impact test (HIT) disability score ranged from 64 to 80. (HIT score reflects the impact of headache on daily activities with a score over 56 indicating a 'substantial impact'.	
Methods	Interviews were carried out by two headache patient researchers based around a question framework relating to key milestones in the headache journey as identified by patient researchers. Modified into focused conversations. Interviews carried out at a health centre with GP researcher available for support. Interviews were taped but not transcribed. Patient researchers were recruited from the same headache clinic, advertisements in the local press and word of mouth and through a migraine organisation. A core group of 5 patients were selected and formed a research team with 3 professionals: a clinical psychologist; a GP who led a local headache clinic; and a research manager who administered the research unity of the general practice where the project was undertaken. There was a debrief after each interview followed by a process of consensus qualitative data analysis at a later date. The research team listened to each tape as a group. Key statements relevant to the research focus or meaningful to a team member were transcribed and grouped into categories based on group discussion about their meaning. The categories were collectively reviewed, cross-references, refined and defined into core themes with typical quotes for each theme.	
Themes with findings	<u>Impact on life (everyone is different)</u> Three aspects were identified:	**Physical and psychological impact** – all participants identified severe impact on the physical side of their life. Accompanying thoughts of death due to physical impact were thoughts around suicide. There were other physical and psychological implications other than pain.
		Impact on family and social life – the impact of migraine extends beyond the individual to family, friends and colleagues. Study reports that many employers are not sympathetic
		Impact on career – migraine impacts upon career choice and development.
		All patients researchers and participants emphasized the personal and individual nature of migraine. It is recognised that each patient experiences the themes differently.
		A recurring theme is that the impact of migraine is not understood by non-sufferers.
		Metaphor that emerged during the research was "handling the beast". Produced by one of the patient researchers during the latter stages of analysis and resonated strongly with all researchers and participants during feedback of our findings.

Study	Belam et al, 2005[66]	
	Making sense of the problem	There was a need to understand what was happening and to place the problem in the context of their lives.
		A recurring theme was the value of talking to others, sharing experiences and exploring meaning.
		All participants and patient researchers found the opportunity of talking to a healthcare professional with an interest in the subject valuable.
	Putting up with it	The majority of migraine sufferers are not under regular medical care and are fatalistic about their problem. (The reasons for this not explored in this study).
	Doing something about it	Participants engaged in a great deal of self-help, both in terms of managing their lives and looking for remedies, particularly within the field of complementary medicine. Self-help was frequently a result of poor experience within the medical service. In many cases, patients felt that GPs and other doctors did not take the condition seriously and that they were unhelpful.
		The experience was not all negative and we were able to identify some positive benefits particularly from the intermediate care headache clinical that all participants had attended.
		An important theme was the advice to other sufferers to read up about their condition before they go to the doctor.
		Overall the advice to doctors was to take the condition seriously and sympathetically, acknowledging that migraine is more than just a headache.
		The recurring theme was that the medical profession does not address the needs of sufferers adequately, but that satisfactory outcomes can be achieved by delivering care from a doctor with a special interest in the area.
Limitations	• Only one method of data collection used. • Interviews weren't transcribed and study does not state in detail the methods used to code or identify themes. Authors recognise a lack of rigour in the traditional methods of qualitative analysis but state that the consensual, reiterative methodology used including stakeholder brings different insights and yields a valuable approach that traditional research may have overlooked. • All patients are from an intermediate care headache clinic – the impact of their headache was greater than the population presenting to primary care. • Patients acting as researchers interpreting interviews could introduce bias.	

Study	Henderson 1999[368]	
Aim	To illuminate the experiences of women living with migraine as it relates to the impact on their quality of life.	
Population	20 women aged 26-45 with migraine (according to ICHD criteria) in Australia. Participants identified through networking with existing support groups established by the Australian Brain Foundation and also from members of groups which had been disbanded.	
Methods	Semi-structured, informal style interviews. Interviews were taped and lasted approximately 1 hour. Interviews transcribed, then tapes were erased. All transcripts were anonymised. Follow up telephone interview lasting approximately 15 minutes to clarify some aspects or issues and validate the emerging themes. Ethnographic data analysis methods used: Notes rewritten, coded and compared. 1 researcher involved. Themes derived.	
Themes with findings	Recognition of migraine as a biological disorder	All except 2 reflected a tendency to blame themselves. Health professionals and others in the community tended to reinforce this concept.
	Inadequate pain relief	Effective pain relief was the most important result women hoped to receive from treatment in order to decrease the severity and frequency of migraines. Pain resulted, in the majority of cases, with a total lost of time and activities.
	Physical and social incapacity	Participants reported markedly decreased physical functioning, with many suffering total incapacity and bed rest. Participants also reported that migraine interfered with their social functioning in a profound manner. There was a strong feeling among many women that other people did not understand their migraine as a valid illness.
	Changes in work role and self esteem	Many were forced to give up work, work part time or work from home. Some experienced a total loss of career.
	Uncertain future	Concerns regarding the unpredictability of the nature of migraine in relation to severity and frequency, and the threat of it being a long term and recurrent illness with no relief or conclusion, excepting between attacks. Long term planning was deemed to be impossible mainly because of the unpredictability.
	Isolation	Began with the process of responding negatively to the chronicity of pain and disability when they who relatives doubted the reality of body pain, blamed the victim and minimised the need for help. Isolation was characterised by negative interactive processes that filled women's lives with unrelieved pain, loneliness and despair. However, many of the women described experiences of shifting their focus to development of coping mechanisms.
	Stressful emotions and development of coping strategies.	Most commonly expressed emotions ere anger, frustration, despair, depression, anxiety, acceptance, new hope and determination. The women focussed on fulfilling their lives despite the limitations imposed by migraine. They attempted to define themselves through their own choices and values rather than the migraine or negative perception of others. The most frequently used category of coping was optimistic, followed by self-reliant, supportive, confrontive,

Study	Henderson 1999[368]	
		evasive, and finally emotive. Participants viewed their migraine as a burden, threat or challenge.
	Dissatisfaction with healthcare	An overwhelming response. Characterised in 2 major ways: a lack of understanding and support coupled with ineffective treatments; a lack of education and information combined with little or no help in the development of coping strategies. Little attention has been given to the active role many patients assume when seeking help. Each woman referred in some way to the part she played in actively seeking help. All except one sought help from professional and non-professional healers.
	Lack of understanding and support	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.
	Lack of information, education and development of coping strategies.	All were frustrated by lack of adequate information and explanation of migraine and its treatment. They stressed that no attention was 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. The found it difficult to locate sources of information, and health professionals were described as giving no guidance or direction to the sufferers.
	Need for education programs for health professionals and the community	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.
Limitations	• Only one researcher undertaking interviews and interpreting themes • No quotes given. • Role of the researcher and setting not stated. No patient details stated except for age range.	

Study	Loder et al, 2005[512]	
Aim	To gain a more complete understanding of cluster headaches	
Population	8 cluster headache patients who were of had been receiving treatment in the Spaulding Rehabilitation Hospital Headache Management Program in the USA.	
Methods	Mailed questionnaires with some open ended questions. Spelling and punctuation were corrected when necessary to improve readability and abbreviations spelled out in full. Potentially identifiable information was deleted or disguised. Otherwise, no changes were made to the choice or order of words. Only selected representative or especially informative answers or portions of answers were included in report.	
Themes with findings	What would you like to say to the doctor [Poor quality study that does not present a thematic analysis. Only information directly relevant to the question on patient information and support reported here]	Positive view of 2 helpful specialists: "Both listened intently to what I had to say as I described my symptoms. Both discussed their diagnosis in detail while seeking my input and comment. Both included me in developing an appropriate course of action, explaining pain models and alternate treatments. I always felt I was being listened to, taken seriously, and treated with dignity and respect. I was convinced that my headaches were being addressed by knowledgeable and competent professional, focusing on my problem." Suggestions: "I would suggest having the person's family come in to talk with the doctor or clinic because that can be a source of stress at home… I wish my husband had come in with me to the doctor appointments early on. I really did feel I was going out of my mind… feeling out of control is scary and it is important to recognize that".
Limitations	• No details of participants other than their diagnosis. • Mailed questionnaire only. • No thematic analysis. • Only selected responses reported, states that these were the representative or especially informative answers.	

Study	Meyer 2002[557]	
Aim	To explore, describe and analyse the process of vigilance in women who had migraine headaches to develop a substantive theory of the phenomenon.	
Population	22 females >18years (range 18-61) with migraine in the USA.	
Methods	Purposive and theoretical sampling used for selection of participants. Purposive sample of 9 women of the researcher's acquaintance initially asked to participate. As the theory began to develop, theoretical sampling used and subsequent participants selectedto help fully define emerging categories. Semi-structured interviews. Data collection and analysis proceeded simultaneously. Transcripts of taped oral interviews. Initial interview questions were open ended and asked about: background to migraines, when they started; what a typical headache is like; how participants felt at the onset of a migraine; how participants recognised it as migraine; how participants decide what to do if they think a migraine is likely to start; how participants know if what they decided is working; things participants do or don't do because of migraine; how they take care of their migraines; any other experiences. Only appears to involve one researcher in interviews and primary analysis but peer debriefing was used to review coding and categories, interpretations and conclusions were tested with members of the group from whom the data was collected.	
Themes with findings	Owning the label	Women needed to learn to think of themselves as individuals who had migraine headaches. Women typically got a label for their condition with input from others. Searching for a name was one sub-category, the other was accepting the label.
	- Searching for a name	Women sought a diagnosis that could explain the frequency and severity of their headaches.
	- Accepting the label	Once they had a name for their condition, they needed to accept it to develop their capacity for vigilance. The woman 'tried on' the label of migraine to see how it fit. They looked for the reinforcement of the label from experts, but it was their own sense of its correctness that led them to accept it. This sense of correctness was reinforced each time the woman successfully named and treated each individual headache episode or identified a trigger.
	Making the connections	The process women used to learn about their personal experience of migraine contained two sub-processes: recognizing the patterns and knowing the options. Required continued use of the strategies of learning from self and others. They continued to get information from experts, other people who had migraines and the media. They saw this as critical to 'keeping on top' of the latest developments in treatments. The more frequent or bothersome their headache, the more actively they attempted to make connections that would allow them to increase control and maximise function.
	- Recognizing the patterns	When women learned to associate internal sensations with the onset of a migraine headache and identifying headache triggers.
	- Knowing the options	The awareness of pharmacological and non-pharmacological forms of treatment.
	Watching out	Women take what they know and apply it to the here and now. There are four subcategories: assigning meaning to what is, calculating the risk, staying ready and monitoring the results.

Study	Meyer 2002[557]	
	- Assigning meaning to what is	Women take what they know about their headache and trigger patterns (the connections they have made) and compare it to what they encounter at the present time.
	- Calculating the risk [This section of the paper reports a lot of information specifically about triptans. These data are not reported here]	A strategy used to determine whether the benefits of treatment or trigger avoidance outweighed the negative aspects. The women then used this determination in deciding the course of action. The main issue was the maintenance of function. Sometimes the need to function optimally led to the women to consider intervening more rapidly or to think about going to their second line treatments more quickly. However the intervention itself could be a risk to function. Side effects other than those that affected functioning were also a risk considered. Some women discussed the benefits of avoiding triggers versus their reluctance to five up things they enjoyed.
	- Staying ready	Almost all stated they thought about the importance of keeping their medication available to them. Readiness for encountering triggers was also discussed.
	- Monitoring the results	They needed to be in tune to the sensations that indicated their chosen treatment was working.
	Deciding what to do	Three subcategories are included: determining the actions to be taken, selecting the actions to be avoided, and optimising benefits over risks.
	- Determining actions to be taken	Action to be taken was usually pharmacological. Women talked about a variety of decisions available to them and how decisions changed as circumstances changed. Very few had only one course of action that they always followed.
	- Selecting actions to be avoided	Two basic categories: Things that exacerbate a headache were to be avoided –bright lights and noise, several women thought lying down exacerbated the problem and made a point to try and sit up even if the headache started in the middle of the night, one women avoided bending down to pick something up or walking up steps. Things that might trigger a headache – one woman had eliminated chocolate from her diet; several talked about avoiding alcohol or some types of alcohol (e.g. red wine); some women eliminated perfumes or candle odours, or were very selective about which scents they used; one woman avoided big action films because of the loud noise and flickering lights.
	- Optimising benefits over risks	Women who decided to refrain from drinking alcohol described as “not being worth it”. Other women accepted the risk associated with triggers because they felt avoiding the trigger was worse than the possibility of getting a headache. The acceptance of the risk was especially true when the trigger was inconsistent in causing the migraine.
	Acting to maximise function	All of the previous steps in the cascade led to this point. Women maintained vigilance because it allowed them to choose actions they believed would maximise their functioning. After implementing a course of action, the

Study	Meyer 2002[557]	
		woman monitored the results and if necessary, the decision process began anew. Action also led to learning about what worked and what didn't. This knowledge reinforces the label and was incorporated into the woman's set of connections for future decision making.
Limitations	• Unclear how participants were selected. Researcher describes initial 9 participants as "acquaintances" with migraine. • Unclear what setting the interviews were performed in and the role of the researcher. • Only appears to involve 1 researcher in data collection and first analysis.	

Study	Moloney 2006[566]	
Aim	To obtain the perceptions of migraine experience in the context of perimenopause. In addition to understanding the meaning of the individual experience, the purpose was also to understand common meaning and shared practices across the narratives.	
Population	53 women with migraine aged 40-55 enrolled in 2 consecutive studies in the USA. Study 1 recruited from a health maintenance organisation, study 2 recruited from a university setting, local community and the internet.	
Methods	Study 1: Qualitative interviews, focus groups, paper-and-pencil questionnaires and 6 month daily, primarily quantitative, diaries. Study 2: internet based, with both in-person and phone interviews, similar quantitative questionnaires and online discussion boards that were virtual focus groups. Interviews: open ended questions started with "Tell me the story of your headaches" followed by the use of other probes and clarifying questions as needed. Audio taped 30 to 60 minute interviews. Interviewer also posted open ended questions on discussion boards similar to those used in individual interviews. 8 consecutive 3 to 5 week discussion boards were posted. Interviews transcribed verbatim; discussion board data were cut and pasted into word processing software. Interviews were transcribed verbatim, discussion board data cut and pasted from website into word-processing software. Both analysed using a qualitative software analysis package for organising data. Analysis and data collection proceeded concurrently, creating a circular process that influenced subsequent questions and interpretation of data already obtained. Patterns and themes were identified mostly from the quotes.	
Themes with findings	Changing Headache Patterns	Two major themes: headache patterns; and looking for an answer. Some women were seeking a definite diagnosis. Most had tried a variety of prescription medications and all were looking for non-prescription self-care sources of headache control. One of the reasons commonly given for participating in this research was to learn more about headaches and headache management. Many women described worrying about whether their headaches were related to such causes as a brain tumour or aneurysm; whether they could be the result of problems with wisdom teeth, high blood pressure, or perhaps because of a detached retina.
	Predicting, preventing and controlling headaches	Themes that comprised this pattern were: Is this a migraine or something else?; Identifying triggers; Course of the headache: the lurking migraine; Medications; and I might try… self-care interventions.
	Keeping on the move	Four themes: Working through the headache; Desperation; Keeping my arsenal of medicine; and Having a dirty secret. **Having a dirty secret** – paticipants addressed the stigma and guilt of having this problem, which in the past has been perceived as psychosomatic, and which authors reported as still perceived with skepticism by many people. A few women 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 (coworkers, 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

Study	Moloney 2006[566]	
		power, or of a woman who is using her headaches to avoid responsibilities.
	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.	
Limitations	• Not clear how themes were identified or whether more than one person verified the analysis. • Ethical approval not stated explicitly.	

Study	Packard, 1979[601]		
Aim	To explore the questions: • What do headache patients want when they come to the doctor? • What do physicians think headache patients want? • Are they after the same thing?		
Population	100 outpatients with the chief complaint of headache at a neurology clinic in the USA. • Age range 14 to 64 years, 54 females, 46 males. • 23 patients reported this was the first time they had seen a doctor. • Duration of headaches: < 1 month (n=7), 1 month to 1 year (n=20), 1-4 years (n=28), 5-9 years (n=14), 10-19 years (n=13), >20 years (n=18) • No. of doctors seen: 0-1 doctors (n=23), 2-3 doctors (n=41), 4-5 doctors (n=19), 6-9 doctors (n=9), 10-19 doctors (n=4), >20 doctors (n=5)		
Methods	Questionnaires in two parts were handed out at outpatient clinic until 100 patients had completed the form. In the first part specific information obtained including age, sex, whether this was the first time they had seen a doctor for their headache, how they were referred, how many doctors they had seen previously, duration of headache, whether they had more than one type of headache, did they understand the cause of their headache, how much they believed "nerves" or "tension" were contributing to the headache, did they feel more than one visit would be necessary or helpful, were they worried about a brain tumour, and what they were expexcting: total, some or no relief. In the second part patients were asked to rank 12 factors in order of importance on a scale of 0 (was not important at all) to 10 (was most important). At then end, if they had ranked more than one factor as "10" they were asked to put this in order of importance. Also, 50 physicians from various specialities completed a survey as to what they thought patients wanted when they came to see the doctor.		
Themes with findings		**Most often selected in top 3**	**Most often selected first**
	Ranked factor	Patients (n=91)	Patients (n=100)
	Explanation of cause of pain	77%	46%
	Medication	20%	0
	Explain about medication (how it works, side effects)	32%	3%
	Treatment other than medication (please indicate)	18%	1%
	Time to ask doctor questions	20%	3%
	A psychiatric evaluation	3%	0
	Doctor willing to follow them for their headache	26%	4%
	Complete neurological examination	31%	7%
	Skull x-rays	8%	1%
	Talking to other headache patients in a group	0	0

Study	Packard, 1979[601]		
	Pain relief	69%	31%
	Complete eye examination	11%	4%
	• Expectations of relief: 31 patients total relief, 67 patients some relief, 2 patients no relief • 43 patients reported having more than 1 type of headache. “Although most patients complained of only one type of headache, some combined them into a confusing blend that they tried to present as a single headache”. • 29 patients felt they understood their headache, 71 did not • 26 patients expressed concern about having a brain tumour		
Limitations	• Unclear whether this is just primary headache though study states “chief complaint of headache”. • Leading questions with the factors for ranking being predefined. There was no possiblity for participants to add their own factors of what they want.		

Study	Peters et al, 2003[620] *	
Aim	To investigate patient perceptions and experiences of headache. 1 - Factors involved in the patients' decision making.	
Population	13 migraine sufferers (according to IHS criteria) aged 18-65 in the UK. Recruited from university setting, adverts in supermarkets and members of Migraine Action Association.	
Methods	Semi-structured, individual and tape recorded interviews. 11 open ended initial interview questions. Interviews arranged at the participants convenience in terms of location transcribed verbatim and prepared for analysis in a qualitative software package. All authors, as well as an independent research, were involved in stages of the analysis. No notable differences were found.	
Themes with findings	Headaches, Consultations & Management identified as three main themes for the base data.	
	Management strategies	All described a range of management strategies and self-help measures they had used in the past or were still using. All used several strategies at one time and the combination was individual to every patient.
	The four stages of decision-making	Headache severity, evaluation, decision and behaviour. A complex and dynamic and continuous process that developed over time and operated on a justification and consequence system. Every decision, behaviour and change in migraine severity added to the experience and perceptions of the patient.
	- Headache severity	The diagnosis of the headache types (symptoms, pain severity, frequency duration); the progressive nature of migraine during attacks and over the years and; impact of the headaches (work, family life, social life/leisure activities).
	- Evaluation	Awareness (how to deal with the problem); Assessment (headache severity, experiences of management, outcome and limitations of management); Balancing options with perceptions (Management available – knowledge, Information gathering – from health professionals, family and friends, media, headache societies); Perceptions (Attitudes, beliefs, expectations, satisfaction, preferences).
	- Decision	Specific (related to a specified management strategy); Non-specific (general decisions to headache management).
	- Behaviour	Active and Passive Management strategies (Consultations – doctor or other health professional, Pharmacological – Acute or prophylactic, Non-pharmacological – self-help or alternative therapies).
Limitations	• Not clear who conducted the interviews.	

Study	Peters et al, 2004[621] *	
Aim	To investigate patient perceptions and experiences of headache. 2 - Patients perceptions of the management of their headache.	
Population	13 migraine sufferers (according to IHS criteria) aged 18-65 in the UK. Recruited from university setting, adverts in supermarkets and members of Migraine Action Association.	
Methods	Semi-structured, individual and tape recorded interviews. 11 open ended initial interview questions. Interviews arranged at the participants convenience in terms of location transcribed verbatim and prepared for analysis in a qualitative software package. All authors, as well as an independent research, were involved in stages of the analysis. No notable differences were found.	
Themes with findings	The patients use of management strategies fitted into five areas:	
	Healthcare use	Focused mainly on consultations with doctors and mainly the GP (although other healthcare professionals also described). For GP's some 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. 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 like 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.
	Medication use	The participants' perceptions ranged as widely as the number and types of medications used. All expressed preferences for not taking medication, but all had relied on medication for their headaches in the past. Generally the participants found using acute medication more acceptable than using prophylactic drugs. One participant concluded that there was no effective treatment. Patients had low expectations and worry of side effects, some preferred to cope without medication or restricted their medication use. Others found an effective drug and preferred taking that to having a migraine. The reasons to take medication included pain control, restoring the ability to function or the prevention of headaches. Different medications served different purposes.
	Alternative therapies	Although not all had consulted an alternative therapist, the generally expressed an interest in what they had to offer. Frequently it was the cost that prevented them from trying. Those who had consulted gave little description on how effective they were but expressed satisfaction with the time and advice offered by alternative therapists. The participants also used homeopathic and herbal remedies, compared to pharmacological agents they were

Study	Peters et al, 2004[621] *	
		rated as 'natural', 'safer' and as 'not leading to side effects'.
	Social support	Used to complement or further improve the participants' headache management. Received from families, friends, work colleagues and other headache patients. Having people to talk to about headaches, and particularly other headache patients, 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 learn to better deal with them was considered important. New information was sought through various sources of social support, such as family, friends, work colleagues and other headache patients and the media. Particularly charities such as the Migraine Action Association were thought to be useful since they gave access t the latest developments. Not all participants benefited from social support, for example one was not aware of an association that can provide information on migraine.
	Lifestyle and self-help	Analysis revealed patient as having a central role in their management, and the patients perceived themselves as an essential resource to the management. The participants often thought it was their responsibility to deal with their headaches through self-help and lifestyle changes. Self-help involved taking initiatives and contributing to their own headache management, by gaining information about treatments, selecting their own prescription drugs, and convincing their GPs to prescribe the drugs. Self-help often revolved around triggers and analysis of their own headaches to help find a cause and possibly a cure. Lifestyle management strategies revolved around stress control, getting enough sleep and dietary changes.
Limitations	• Not clear who conducted the interviews.	

** Same study with different sections of the analysis reported.*

Study	Raieli et al, 2010[645]		
Aim	• To assess simultaneously children's and mothers' expectations from medical consultation concerning headache, and paediatricians' opinions about said expectations. • To investigate mothers', children's and paediatricians' opinions about symptomatic and prophylactic treatment of headache.		
Population	100 patients aged 10 to 16 years and their mothers presenting at an outpatient service in Italy for diagnosis and treatment of headache (inside the Child and Adolescent Neuropsychiatry Department) between February 2002 and May 2003. **Exclusion criteria**: patients with headaches transferred from emergency department; **patients with secondary headaches**; patients with cognitive deficits who were not able to answer the questions of the questionnaires; patients with serious neurological or medical conditions. Other than patients transferred from emergency department 18 patients excluded: 6 with probable secondary headache, 7 with cognitive deficits, 5 with epileptic seizures.		
Methods	Questionnaires were given to each patient and their mother at the first consultation before clinical evaluation. Questions were selected in 2 ways: some were from previously published studies on similar topics. Studies cited include previous surveys; and others were designed by the authors. The mother and children questions were multiple choice; for every question they had a choice of 1 to 3 prearranged answers. If they desired, they could also signal an order of preference among the answers. Very few subjects chose to do this. Questionnaire also sent to 50 local family paediatricians recruited while attending a continuing medication education programme unrelated to headache. This assessed their beliefs about the reasons why mothers ask for their consultation and wht the expectations of children and their mothers are about headache treatment options. The physicians were not referring physicians for the sample of 100 children surveyed so their responses were considered generic.		
Themes with findings	**Expectations of children and mothers from the paediatric consultation**		
	Children's and mothers' expectations	Children % (n=100)	Mothers % (n=100)
	To be reassured that it is not a serious illness	60	47
	To find out the causes of headache	45	62
	To receive medication for the treatment of pain after its beginning (symptomatic treatment)	21	5
	To benefit from diagnostic investigations (i.e. blood tests, EEG, etc)	0	28
	To be referred to a headache specialist	8	39
	To have a careful medical examination	28	22
	To receive medication to prevent and reduce the number of the attacks (prophylactic treatment)	20	5
	To know the progression of headache in the future	26	3
	Other	0	2
	Expectations of children and mothers from the headache specialist consultation		
	Children's and mothers' expectations	Children % (n=100)	Mothers % (n=100)

Study	Raieli et al, 2010[645]		
	To be reassured that it is not a serious illness	54	56
	To find out the causes of headache	54	82
	To receive medication for the treatment of pain after its beginning (symptomatic treatment)	26	7
	To profit from diagnostic investigations (i.e. blood tests, EEG, etc)	2	10
	To benefit from neuroradiological investigations (i.e. CT, MRI, etc)	8	5
	To have a careful medical examination	28	41
	To receive medication to prevent and reduce the number of the attacks (prophylactic treatment)	28	11
	To know the progression of headache in the future	32	17
	To get well	33	3
	Other	3	2
	Mothers', children's and paediatricians' opinions about symptomatic treatment		
	What do you think about drugs given for the treatment of the pain after its beginning (symptomatic treatment)?	Children % (n=100)	Mothers % (n=100)
	It is necessary in the presence of severe pain	68	49
	I'm afraid of them, I prefer not to use drugs	12	12
	Drugs are often useful, but sometimes also dangerous	18	18
	Drugs are never advisable for a young patient	2	2
	If the pain is not too intense, it is better to contrast it only by sleeping	23	23
	Other	0	0
	I don't know	8	8
	Mothers', children's and paediatricians' opinions about prophylactic treatment		
	What do you think about drugs given over a long period to prevent and reduce the number of headache attacks (prophpylactic treatment)?	Children % (n=100)	Mothers % (n=100)
	It is necessary in the presence of dangerous pain	35	12
	It can prevent the progression of disease in the future	18	7
	I'm afraid of of side effects	8	24
	A long lasting treatment could be dangerous and induce addition in young patients	14	21
	It is necessary in the presence of severe and long lasting pain	61	37

Study	Raieli et al, 2010[645]		
	I don't know if drugs will induce side effects in the future, so I don't want to use them	6	7
	Other	0	0
	I don't know	2	1
Limitations	Leading questions that may raise concerns that children or mothers did not previously have. Study states it represents a very small and highly selected sample. Study also states that the organisational peculiarity of the Italian paediatric health care network may limit a generalisation to other countries		

Study	Rozen et al, 2006[675]	
Aim	To better understand what patients want from their preventive migraine medication.	
Population	150 migraine patients presenting at the Michigan Head Pain & Neurological Institute (MHNI). Mean age 49, range 13 to 71 years. All patients had been seen at least 1 previous time to be included in the survey, most had been patients for >1 year. All had prior exposure to migraine preventive therapy.	
Methods	10 question survey carried out over a 1 month period as a consecutive series. Patients asked to rank in order of importance characteristics of migraine preventive therapy.	
Themes with findings	Survey question	Mean ranking scale of 1 (little importance) to 10 (extremely important)
	Your physician involves you in the decision of choosing a headache preventive medication	8.7
	Your physician takes time to tell you the possible side effects of the preventive medication beinig prescribed	8.5
	A preventive medication that has been reported in the medical literature as highly effective	8.3
	Taking more than 1 preventive drug at the same time if you had a greater chance of reducing your headaches	8.2
	A preventive medication that may increase or decrease your weight	7.3
	A preventive medication that may cause sedation	6.8
	Once daily dosing of preventive medication	6.6
	A preventive medication that has a high risk of side effects but is very effective at preventing migraine	6.2
	The use of natural therapy (non medicine like vitamins and herbs)	6.1
	A preventive medication that has a low risk of side effects but many not be very effective in preventing headache	3.9
Limitations	• Study reports that patients were attending a migraine speciality clinic therefore most likely had more difficult to treat migraine compared with the general migraine population. Conversely, this patient population had a significant exposure to preventive medication therefore their insight may be more meaningful than those not exposed to prophylaxis.	

E.2.2 Acute pharmacological treatment of tension type headache

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Dahlof et al, 1996[183] **Study design:** RCT (crossover trial) **Setting:** Gothenburg Migraine Clinic, Sweden **Duration of follow-up:** Evaluated 2 hours post dosing	**Patient group:** Adults with episodic tension type headache. **Inclusion criteria:** Aged between 18-70 years; Experienced episodic tension type headache (diagnosed according to IHS criteria) headache in association with or without migraine; Headache history of at least one year; 2-8 headache episodes per month. **Exclusion criteria:** Presence of gastric or duodenal ulcer, inflammatory bowel disease, nasal polyposis, utricaria, coagulation or platelet disorder; Cardiac, renal or hepatic failure; History of asthma; Hypersensitivity to paracetamol, aspirin or other analgesics; Ergotamine and/or analgesic dependence; Concomitant NSAID therapy or treatment with antiepileptics, chloramphenicol or probenecid; Pregnancy, lactation or insufficient contraception; Treatment with other investigational drugs within the previous three months. **All patients** **N:** 40(enrolled); 30 (completed	**Group 1 - Single oral dose of ketoprofen 25mg** **Group 2 - Single oral dose of ketoprofen 50mg** **Group 3 - Single oral dose of paracetamol 500 mg** **Group 4 - Single oral dose of paracetamol 1000 mg** **Group 5 - Placebo** Each patient was provided with the 5 study drugs, one to treat each of the five attacks of episodic tension type headache. A minimum interval of 72 hours between 2 attacks was considered sufficient to ensure the absence of carry over effect between successive attacks. No concomitant medication was allowed for 2 hours after intake of the study medication.	**Pain free at 2 hours** 100mm VAS and verbal scale % (number of patients/total number)	**Group 1:** 28% (8/29) **Group 2:** 32% (9/29) **Group 3:** 17% (5/29) **Group 4:** 17% (5/29) **Group 5:** 17% (5/29)	**Funding:** NR **Limitations:** Unclear randomisation and allocation concealment. Unclear blinding of participants, care administrators and investigators. No mention of duration of study and follow up, unclear as to whether enough time had been allowed for each of the drugs to take effect. Loss to follow up was 25%. No reasons for loss to follow up discussed. Order of dropout not mentioned, not clear what groups they were from. **Additional outcomes:** Change in nervousness/tension, muscle stiffness in the neck and shoulders. Treatment giving best relief as reported by patient. Proportion of patients requiring rescue medication. Adverse events in each group (abdominal pain, asthenia, chills, malaise, pain, dizziness etc) not
			Pain intensity difference Baseline to 2 hours after medication intake, 100 mm VAS	**Group 1:** intermediate between ketoprofen 50 mg and placebo‡ **Group 2:** -31.8±24.6 **Group 3:** no detectable difference from placebo‡ **Group 4:** no detectable difference from placebo‡ **Group 5:** -17.1±25.4 2vs5 (at 2 hours) 0.025	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	study, treated 5 attacks) **N:** 29 (included in analysis) **M:** 13 (32.5%); F: 27(67.5%) **Age (mean ± SD):** M 48±6 (37-56), **F:** 42±8 (19-56) **Drop outs:** 11 [10 (discontinued prematurely); 1(major protocol violation)]				classified as serious. **Notes:** ITT analysis ‡ Data only presented in graphs Last study medication of 10 patients who dropped out reported: 6 Placebo, 2 Paracetamol 100 mg, 1 Paracetamol 500 mg and 1 Ketoprofen 50 mg.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diamond et al, 2000[202] **Study design:** RCT **Comparison:** NSAID vs placebo **Setting:** Multicenter study at 19 different sites in USA **Duration of follow-up: 6 hours**	**Patient group:** Adults with tension type headache. **Inclusion criteria:** 18 years or older; History of acute tension-type headaches as defined by IHS criteria; 3-15 tension type headaches every month for at least the previous year; Headaches had to be responsive 75% of the time at least to non-prescription-strength analgesics. **Exclusion criteria:** Known or suspected to be allergic to any of the study medications; Had a significant coexisting illness or medical condition that would compromise their ability to swallow, absorb, metabolize or excrete the study medication. **All patients** **N:** 385 (for all three arms); 331(treated attack) **Age (mean, range):** 37 (18-73) **Drop outs:** 30 before treatment (9 inappropriate enrolment, 14 protocol violation, 2 treatment of non-qualifying headaches, 5 concurrent caffeine consumption). **Group 1** **N:** 99 **Age (mean, range):** 37 (19-72) **Drop outs:** 0 (after attack treated) **Group 2** **N:** 48 **Age (mean, range):** 36 (19-61) **Drop outs:** 0 (after attack treated)	**Group 1 - Ibuprofen 400mg** **Group 2 - Placebo** Participants were given a single dose of study medication to take home and instructed to use it for the treatment of a moderate intensity tension-type headache within a two month period. Participants rated baseline pain intensity before dosing. They were advised to wait 2 hours before taking any rescue medication. Seen within 1 week at the clinic, assessments were reviewed for completeness and consistency by a staff member and study co-ordinator.	**Time to freedom from pain** Median time to onset of meaningful improvement, minutes	**Group1:** 161 **Group2:** 279	**Funding:** Procter and Gamble Company, Cincinnati, Ohio, USA. **Limitations:** Unclear randomisation and allocation concealment. No details provided regarding blinding of participants and investigators. No data provided on use of concomitant medication **Additional outcomes:** Participants overall evaluation of the medication. Pain relief scores. Percentage of participants who experienced complete relief with each medication. **Notes:** Participants with occasional migraine (less than two per month) included as long as they could differentiate between migraine and tension-type headaches. 4 arm trial with participants randomised in ratio of 2:2:1:1 to [Ibuprofen 400mg +Caffeine 200mg]: Ibuprofen 400mg: Caffeine200 mg: Placebo.
			Median time to onset of perceptible improvement, minutes	**Group1:** 69 **Group2:** 88	
			Incidence of serious adverse events	None	

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener et al, 2005[224] **Study design:** RCT **Setting:** Outpatient clinics, Germany **Duration of follow-up:** Unclear	**Patient group:** Adults with episodic tension type headache and/or migraine with or without aura **Inclusion criteria:** 18-65 years old; Headaches had to meet IHS criteria for episodic tension-type headache and/or migraine with or without aura; Headaches should have been experienced for at least 12 months with a minimum of two headache episodes in the previous 3 months. **Exclusion criteria:** Patients treating their headache with prescription analgesics or migraine drugs, requiring higher single doses of non-prescription analgesics to treat their headache than indicated in the patient information leaflet, normally treated with non-prescription analgesic in effervescent tablet form, headaches occurred on more than 10 days per month or lasted untreated normally less than 4 hours; Close association between the occurrence of headache and menstruation (menstrual migraine); Concomitant treatment with prescription-only and/or non-prescription analgesics, antidepressants or antipsychotic medication (within the previous 4 weeks before study enrolment), anti-rheumatic or anti-inflammatory drugs that may influence the headache symptoms (within the previous 4 days), drugs containing acetyl salicylic acid (above a daily dose of 100mg/day), paracetamol or caffeine; Migraine prophylaxis or administration of drugs that influence headache symptoms; Drug overuse connected with headache; Pregnancy and lactation; Gastrointestinal ulcers, pathologically increased bleeding tendency, glucose-6-phospahate dehydrogenase deficiency, hypersensitivity to paracetamol, caffeine, ASA, salicylates and other antiinflamatory drugs, bronchial asthma, concomitant treatment with anticoagulants, chronic or recurrent gastrointestinal symptoms, Gilbert's syndrome and hyperthyroidism.	**Group 1 - Acetylsalicylic acid (ASA) 2 tablets of 500mg** **Group 2 -** Paracetamol 2 tablets of 500 mg **Group 3 – Placebo 2 tablets** Patients took trial medication as a single dose when headache occurred and when they would normally have taken their usual analgesic. Patients were allowed to use rescue medication 4 hours after the administration of the trial medication if their pain remained and had document details of time, dose and type of drug used.	**Pain intensity difference at 2 hours** Least square mean, mean difference (95% CI)	**Group1:** 40.7, -4.0, (-7.5, -0.6) **Group 2:** 39.5, -5.2 (-8.7, -1.7) **Group 3:** 24.6, -20.1 (-24.6, -15.7)	**Funding:** Boehringer Ingelheim Pharma GmbH & Co. KG, Vertriebslinie Thomae, Germany **Limitations:** Includes patients suffering both from migraine and tension type headaches. No mention of any other therapies used. **Additional outcomes:** Time to 50% pain relief. Time until reduction of pain intensity to 10mm on VAS. Percentage of patients with 50% pain relief at least after 30min, 1, 2, 3 and 4 hours evaluated on VAS. Weighted sum of pain intensity difference (SPID). Global assessment of efficacy and
			Functional health status and health related quality of life Percentage of patients with no impairment of daily activities at 2 hours post medication intake	**Group1:** 48.4% **Group 2:** 48.65 **Group 3:** 30.5%	
			Incidence of serious adverse events (n)	**Group1:** 0 **Group 2:** 1 **Group 3:** 0	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients **N:** 1983 (for six arms of the trial) **Group 1 Acetylsalicylic acid (ASA)** **N:** 296 (randomised); 276(treated), 252(ITT) **Age (median, range):** 38, 18-69 **Drop outs:** 57 [20(not treated), 13(discontinued), 24(excluded for no VAS/not reliable)] **Group 2 Paracetamol** **N:** 284(randomised), 275(treated), 251(ITT) **Age (median, range):** 39, 18-70 **Drop outs:** 60[9(not treated), 27 (discontinued), 24 (excluded for no VAS/not reliable)] **Group 3 Placebo** **N:** 146(randomised), 138 (treated), 128 (ITT) **Age (median, range):** 37, 18-67 **Drop outs:** 24[8 (not treated), 6(discontinued), 10 (excluded)]				tolerability by the patient. **Notes:** Trial was a six arm trial with the other three groups being Acetylsalicylic acid + Paracetamol + Caffeine, Acetylsalicylic acid + Paracetamol and Caffeine

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Friedman et al, 1987[295] **Study design:** RCT **Setting:** Multicentre study **Duration of follow-up: 4 hours**	**Patient group:** Adults with tension type headache. **Inclusion criteria:** Specific diagnosis of tension headache (as defined in Monograph 6 of the National institute of Neurological Diseases and Blindness), characterised by an average of six attacks per month for the three months preceding the study; History of previous episodes for at least 1 year; Age between 18-65 years; Motivation to participate in the study and demonstrated willingness to cooperate. **Exclusion criteria:** If participants' use of drugs, health status or lifestyle interfered with their treatment responses or increased their risk of adverse drug reactions (e.g. drug hypersensitivity, history of organic or structural head/neck disease, hypertension/hypotension, serious medical disorder, pregnancy, routine performance of potentially hazardous tasks). **All patients** **N:** 212 (enrolled for all 3 arms of the trial) **Age (range):** 19-64 years **Drop outs:** 14 (failure to comply with study requirements) **Group 1 – Acetaminophen + Codeine** **N:** 65 (randomised); 1(required additional analgesic medication) **Age (mean):** NR **Drop outs:** Unclear **Group 2 - Placebo** **N:** 67(randomised); 5(required additional analgesic medication) **Age (mean):** NR **Drop outs:** Unclear	**Group 1 -** Acetaminophen with codeine **Group 2 -** Placebo Participants were given two identical capsules to be taken at the onset of their next tension headache, if it seemed typical of previous attacks. They were to evaluate at five designated times over the next four hours the level of pain, tension, and muscle stiffness and the amount of pain relief.	**Pain free at 2 hours** Percentage of patients reporting complete relief of pain at 2 hours **Incidence of serious adverse events**	**Group1:** 24.6% (16/65) **Group 2:** 11.9% (8/67) **P value:** 1vs 2, p<0.05 None	**Funding:** Sandoz Inc., East Hanover, NJ, USA **Limitations:** Unclear randomisation and allocation concealment. Blinding of participants and investigators unclear. Number and reasons for loss to follow up not reported per group. **Additional outcomes:** Mean patient self rating scores for tense/uptight, muscle stiffness, pain relief and pain severity. Physicians' global evaluations. **Notes:** 3 arm trial also comparing Fioricet (acetaminophen + caffeine + butalbital) vs (acetaminophen +codeine) vs placebo. Multicentre (10 centres).

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Kubitzek et al, 2003[458] **Study design:** RCT **Setting:** 22 primary care centres in Germany **Duration of follow-up:** 6 hours post dosing; 1 month for taking medication.	**Patient group:** Adults with episodic tension type headache who regularly used over the counter medication. **Inclusion criteria:** History of episodic tension type headache (as defined by the IHS criteria) with onset before the age of 50; Had at least 10 previous episodes lasting between 30 min and 7 days, but averaging less than 180 days per year and less than 15 days of headache per month; Headache lasts at least 1 hour if left untreated. **Exclusion criteria:** Patients who typically experienced nausea or vomiting, photophobia, phonophobia; history of chronic tension type headache, migraines, cluster headaches, headaches secondary to extra-or intracranial pathologies or associated with drug withdrawal; hypersensitivity to NSAIDs or related drugs; asthma, urticaria, acute rhinitis following treatment with acetylsalicylic acid; history of peptic ulcer, gastrointestinal bleeding/gastrointestinal disease; Patients reporting lack of efficacy with for OTC headache remedies; chronic drug use or abuse habit; continuous treatment with prescription doses of analgesics, NSAIDs, tranquilisers, muscle relaxants or anticoagulants; concomitant medication which might confound pharmacological effects of study drugs. **All patients** **N:** 684 (randomised); 620(used study drug); 504 (completed study) **Drop outs:** 116 (prematurely discontinued, 109 due to use of rescue medication) **Group 1**	**Group 1 Diclofenac 12.5mg tablets** **Group 2 Diclofenac 25mg (2 x 12.5mg tablets)** **Group 3 Ibuprofen 400mg (2x200 mg tablets)** **Group 4 Placebo** Single dose study. Patients experiencing headache within a month took the study drug at least 30 min after onset of pain, when pain was at least moderate. Rescue medication (paracetamol 500mg) could be taken 2 hours after taking study drugs.	**Pain free at 2 hours** Percentage of patients reporting complete relief at 2 hours; n (%)	**Group1:** 29 (18.1%) **Group 2:** 35 (22.6%) **Group 3:** 33 (21.9%) **Group 4:** 12 (7.8%) **P values:** 1vs4, 2vs4, 3vs4= p<0.01	**Funding:** Novartis Consumer Health SA, Nyon, Switzerland. **Limitations:** Unclear randomisation and allocation concealment. Blinding of investigators not reported. No details of concomitant medication or other therapies. **Additional outcomes:** Time to rescue medication. Overall evaluation of efficacy by patient. Time weighted sum of pain intensity differences from baseline (SPID). Time interval weighted sum of the pain relief score (TOTPAR).
			Pain intensity difference	**P values:** 1vs4, 2vs4, 3vs4=p<0.01 at all time pints 1 hour post dosing.	
			Incidence of serious adverse events	None	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 171 (randomised), 160 (treated) **Age (mean, SD):** 42.3(14.9) **Drop outs:** NR **Group 2** **N:** 171 (randomised), 156 (treated) **Age (mean, SD):** 42.1 (14.5) **Drop outs:** NR **Group 3** **N:** 172(randomised), 151(treated) **Age (mean, SD):** 44.7 (15.0) **Drop outs:** NR **Group 4** **N:** 170(randomised), 153(treated) **Age (mean, SD):** 39.9 (13.7) **Drop outs:** NR				**Notes:** Trial also compared diclofenac to ibuprofen

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Mehlisch et al, 1998 [549] **Study design:** RCT **Setting:** Outpatient clinics, USA **Duration of follow-up:** Evaluated 4 hours post dose; Study lasted two weeks to 1 month	**Patient group:** Adults with a history of tension type headache. **Inclusion criteria:** 18 years or older; Reported at least 1 year history of tension headache episodes (according to IHS criteria); Average frequency of ≥1 but not more than 10 episodes per month. **Exclusion criteria:** Pregnancy and lactation; Women enrolled had to be naturally or surgically sterile or using a medically acceptable means of birth control; Experienced migraine, post-concussion or cluster headaches in the past year; Had significant medical conditions; Had abnormal laboratory findings with potential to jeopardise their health or interfere with the results of the study; History of chronic use of analgesics, NSAIDS, tranquilisers or muscle relaxants, drug or alcohol dependence; Known hypersensitivity to NSAIDS or acetaminophen; Treated with an investigational new drug within the previous 30 days. **All patients** **N:** 737 (enrolled), 703 (given study medication), 631 (included in efficacy analysis). **Drop outs:** 72 (5 protocol violation, 67 did	**Group 1:Ketoprofen 25 mg** Tablet/gelcap formulation taken orally with 4 ounces of water. **Group 2: Ketoprofen 12.5 mg** Tablet/gelcap formulation taken orally with 4 ounces of water. **Group 3: Acetaminophen 1000 mg** Tablet/gelcap formulation taken orally with 4 ounces of water. **Group 4: Placebo** Tablet/gelcap formulation taken orally with 4 ounces of water. All medications were to be taken when experiencing a sustained tension headache that was at least moderate in intensity. Time to meaningful pain relief was scored by starting a stopwatch at the time of dosing and stopping it when he individual perceived	**Time to meaningful pain relief** hours:mins (median) Log-Rank with letter codes indicating no statistically significant difference between groups sharing the same letter code; A indicates most effective treatment, B the next most effective treatment, etc.	**Group1:** 0:56 **95% CI:** 0:49,1:02 **Log-Rank:** A **Group2:** 1:07 **95% CI:** 0:59,1.18 **Log-Rank:** AB **Group3:** 1:05 **95% CI:** 1:00,1:21 **Log-rank:** BC **Group4:** 1:25 **95% CI:** 1:07,1:44 **Log-Rank:** C	**Funding:** Pharmaceutical company (SCIREX Corporation, Austin, USA and Bayer AG, Consumer Care, Germany) **Limitations:** Unclear randomisation and allocation concealment. 10.8% loss to follow up; unclear which groups the drop outs were from. Protocol violation not defined. Unclear whether study investigators were blinded to participants exposure to intervention and confounding factors. **Additional outcomes:** SPRID (4-hour sum of pain relief intensity differences). TOTPAR (Total pain relief at 2 and 4 hours). SPID (2 and 4 hour sum of pain intensity difference). **Notes:**
			Pain intensity difference (mean± SD) Baseline to 2 hours after medication intake measured on a scale rating pain intensity as 0=none, 1=mild, 2=moderate, 3=severe.	**Group1:** 4.87±2.07 **Group2:** 4.73±1.98 **Group3:** 4.58±2.11 **Group4:** 4.45±2.11	
			Functional health status and health related quality of life (Change in functional ability impairment across treatment groups from baseline)	No demonstrable difference among groups	

	not record data properly). **Group 1 Ketoprofen 25 mg** **N:** 156 **Age (mean ± SE):** 30.6 ± 0.8 **M/F:** 34/66% **Drop outs:** NR **Group 2 Ketoprofen 12.5 mg** **N:** 158 **Age (mean ± SE):** 31.1 ± 0.8 **M/F (%):** 30/7% **Drop outs:** NR **Group 3 Acetaminophen 1000 mg** **N:** 166 **Age (mean ± SE):** 32.2 ± 0.7 **M/F (%):** 29/71% **Drop outs:** NR **Group 4 Placebo** **N:** 151 **M/F (%):** 35/65% **Age (mean ± SE):** 32.2 ± 0.8 **Drop outs:** NR	meaningful pain relief. Functional ability impairment ratings were recorded at baseline and at 1 hour post dosing on a 4 point scale ranging from 0=none to 3=severe. If study medication was not taken within 30 days of dispensing medication, subjects were asked to return to the clinic and their participation was terminated.	**Incidence of serious adverse events**	**Group1:** 2/156 **Group2:** 4/158 **Group3:** 2/166 **Group4:** 1/151	Concomitant use of medications which could confound the assessment of study drug efficacy and safety was prohibited beginning 4 hours prior to intake of study medication to end of assessment period.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Packman et al, 2000 [602] **Study design:** RCT **Setting:** Headache clinic **Duration of follow-up:** Three hours	**Patient group:** Inpatients aged >12 with moderately severe TTH. **Inclusion criteria:** Age over 12 years; History of episodic TTH defined by IHS criteria; Onset of headaches before 50 years; reporting at headache clinic within 1 hour of onset of moderately severe headache. **Exclusion criteria**: Habituated to analgesics; History of migraine (on average >1 migraine per month over the past 6 months); Menstrual headaches; Allergic hypersensitivity or contraindications to aspirin, NSAIDs or acetaminophen. **All patients** **N:** 154 M/F: 37/117 **Age (mean ± SD):** 39.6± 11.8 **Drop outs:** 0 **Group 1 Ibuprofen** **N:** 60 M/F:14/46 **Age (mean± SD):** 38.5± 10.4 **Group 2 Acetaminophen** **N:** 62 M/F: 15/47 **Age (mean± SD):** 41.2± 12.6 **Group 3 Placebo** **N:** 32 M/F: 8/24 **Age (mean± SD):** 38.3± 12.4	**Group 1Ibuprofen 400mg (2x200 mg liquigels)** Liquigel formulation: encapsulating solubilised ibuprofen in a soft gelatin shell formed by spreading a molten gelatin mass into two lubricated ribbons that shape the liquigel. Ibuprofen is then injected through a wedge in the gelatine mould. **Group 2 Acetaminophen 1000mg (2x500mg caplets)** **Group 3 Placebo** **All patients:** Single dose study. Participants had to rate headache pain as at least moderately severe on a 4 point categorical pain rating scale confirmed by a score of at least 66mm on a 100 mm visual analogue pain scale. Time of perceptible first pain relief and meaningful relief was recorded by patients using two stopwatches started at the time of dosing.	**Time to meaningful pain relief** minutes (median time) Percentage who experienced first perceptible pain relief as well as meaningful pain relief by 30 min	**Group1:** 39 **Group2:** 53 **Group3:** >180 **Group1:** 20% (12/60) **Group2:** 2% 1/62) **Group3:** 0%	**Funding:** Whitehall-Robins Healthcare, Madison, NJ. **Limitations:** Unclear randomisation and allocation concealment. Small sample size for placebo group. Study conducted in specialised headache clinic: may not be generalisable to population. Blinding of participants and investigators unclear. **Additional outcomes:** Sum of pain relief intensity difference scores for 3 hours (SPRID3). Pain relief intensity difference (PRID) at 2 and 3 hours. Time to first perceptible relief. **Notes:** Qualifying subjects stratified by sex before randomisation.

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Pini et al, 2008[631] **Study design:** RCT (Crossover trial) **Setting:** 8 outpatient headache centres in Italy **Duration of follow-up:** 4 hours for each headache attack, to treat a total of three attacks	**Patient group:** Adults with history of tension-type headache (TTH) **Inclusion criteria:** Diagnosis of episodic TTH according to ICHD-II criteria, modified in the single following criterion: absence of nausea, vomiting, photophobia and phonophobia (to exclude subjects with migraine headaches); Mean frequency of 4-14 days with TTH per month; History of response to treatment of TTH with over the counter pain killers; Daily consumption of at least two cups of coffee; Adequate contraception in women of fertile age; Medical history and physical examination inconsistent with organic disorders associated with headaches. **Exclusion criteria:** Known hypersensitivity or allergy to paracetamol or naproxen; Chronic headache, either recurrent or continuous; Concomitant use/overuse of NSAIDS or other analgesics; treatment with antiplatelet or anticoagulant drugs; History of migraine or post-traumatic headache; History of alcohol abuse, drug dependency,	**Group 1 - Paracetamol 1000mg+Caffeine 130mg (in sachets)** **Group 2 - Naproxen sodium 550 mg (in soft gel capsule)** **Group 3 - Placebo (sachets and soft gel capsules)** Each patient was randomly allocated to one of the study treatment sequences to treat the next three consecutive TTH attacks: PCF-NAP-PLA NAP-PLA-PCF PLA-PCF-NAP PCF-PLA-NAP NAP-PCF-PLA PLA-NAP-PCF [PCF paracetamol 1000mg+caffeine 130mg, NAP naproxen sodium 550mg, PLA placebo]. TTH attacks treated with the trial medication had to be separated from each other by at least 48 hours. Patients also received rescue medication (ibuprofen 600mg) to be taken 2 hours after administration of the trial medication if the pain persisted.	**Incidence of serious adverse events** (reported as severe adverse events by patients)	**Group 1:** 3 (1.3%) **Group 2:** 5 (2.3%) **Group 3:**13 (5.8%)	**Funding:** Angelini Farmaceutici, ACRAF SpA (Rome, Italy) **Limitations:** Details of blinding of investigators not provided. Number lost to follow up in each group not detailed. **Additional outcomes:** Total pain relief at 2 and 4 hours (TOTPAR) Sum of pain intensity difference (SPID) at 2 and 4 hours. **Notes:** No serious adverse events were recorded by the study investigators.

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	or psychiatric disease; History of coagulation disorders, peptic ulcer disease, pancreatic disease, clinically significant renal or hepatic disease, blood hypertension, mild/moderate kidney or liver disease, Gilbert's syndrome. **All patients** **N:** 111(enrolled); 99 (took at least one treatment); 12 [excluded 2(did not fulfil inclusion criteria), 10 (did not take study medication; 93(Per protocol population and ITT population). **Age (mean ± SD):** 35.1±10.19 years **M/F (%):** 40.4/59.6% **Headache duration in years (mean± SD):** 22.2±9.09 **Drop outs:** 18				

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, TTH=tension type headache, ICHD=International classification of headache disorders

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Prior et al, 2002[641] **Study design:** RCT **Setting:** Outpatient clinics **Duration of follow-up:** 6 hours	**Patient group:** Adults with history of tension type headache **Inclusion criteria:** 18 years or older; History of acute tension-type headaches of at least moderate intensity that met at least two of the following characteristics (a pressing, tightening, non-pulsating quality, possible inhibition but not prohibition of activity, bilateral or variable location, not aggravated by physical activity) derived from the IHS diagnostic criteria; Headache required treatment with over-the-counter analgesics and occurred between four and ten times per month; Headache was not associated with nausea, vomiting, photophobia, phonophobia or auras; History of response to treatment of acute tension-type headaches with over the counter analgesics; Medical history, physical and neurologic examination inconsistent with organic disorders associated with headaches. **Exclusion criteria:** History of any of the following: Migraine or cluster headaches; Recurrent sinus headaches; Withdrawal headaches from substances such as caffeine or nicotine; Headaches related to food or excess alcohol; Headaches due to other underlying pathology or related to head or neck trauma; Alcohol abuse, drug dependency, or psychiatric disease; Use of daily NSAIDs, other analgesics, low dose aspirin prophylaxis, anti-coagulants or psychotropics; Continuous daily headaches; Headaches unresponsive to treatment with over the counter analgesics; Headaches related to menses; sensitivity or allergy to acetaminophen, aspirin, or NSAIDs; peptic ulcer disease, inflammatory bowel disease, gastrointestinal bleed, unstable clinically significant cardiovascular disease, clinically significant renal or hepatic disease, coagulation disorders, unstable diabetes, pancreatic disease, uncontrolled hypertension, seizures, cerebral vascular ischaemia, infarct, haemorrhage or central nervous system disease, unstable	**Group 1: Naproxen 375mg orally** **Group 2: Acetaminophen 1000mg orally** **Group 3 Placebo** Single dose placebo controlled study Participants were required to be experiencing an acute tension-type headache of at least moderate severity before ingesting the study medication. Participants were to record in a diary the date and time of ingestion, pain intensity before treatment and pain intensity and pain relief after treatment recorded at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 and 6 hours.	**Time to meaningful pain relief** minutes (median)	**Group1:** 138.5 **Group2:** 131.5 **Group3:** 178.5	**Funding:** McNeil consumer & Specialty Pharmaceuticals, Fort Washington, PA. **Limitations:** Unclear allocation concealment. Placebo group had a lower percentage of women at baseline. No information on type of rescue medication or dosing. Pain relief measurement is subjective and could be influenced by the fact that some of the participants were known to the study investigators. **Additional outcomes:** sum of pain intensity difference (SPID) weighted from baseline. Maximum pain intensity difference from baseline (MAXPID) occurring over the observation period. TOTPAR (time interval weighted sum of the
			Pain free at 2 hours Percentage of participants with headaches completely resolved at 2 hours (n)	**Group1:** 31.5% (93) **Group2:** 36.8% (112) **Group3:** 25.9% (78)	
			Headache response at up to 2 hours Percentage of participants with pain reduced to mild or none at 2 hours (n)	**Group1:** 61.7%(182) **Group2:** 65.1% (198) **Group3:** 55.1% (166)	
			Pain intensity difference	Results reported in graph	
			Incidence of serious adverse events	None	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	metabolic disease, current malignancy or active tuberculosis and prior gastrointestinal surgery which could influence absorption, metabolism or excretion of study medication. **All patients** **N:** 963 (enrolled); 915 (took study medication); 900 (completed the study) **Drop outs:** 63 **Group 1** **N**: 321 (randomised); 295(completed trial) **Age (mean):** 34.6 years **Drop outs:** 26 **Group 2** **N:** 321 (randomised); 304 (completed trial) **Age (mean):** 33.2 years **Drop outs:** 17 **Group 3** **N:** 321(randomised); 301(completed trial) **Age (mean):** 33.8 years **Drop outs:** 20				pain relief scores). Maximum pain relief (MAXPAR) that occurred during the observation period. **Notes:** Participants were allowed to use rescue medication after one hour if their pain remained at or returned to the level before treatment.

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Sargent et al, 1988[696] **Study design:** RCT **Setting:** Four study centres (Headache clinics/research centres) across USA **Duration of follow-up: 6 hours**	**Patient group:** Adults with tension type headache **Inclusion criteria:** Confirmed diagnosis of recurrent muscle contraction headaches characterised by a moderate to severe degree of steady or intermittent headache pain and a sensation of increased muscle tension in the posterior neck, occipital, frontal or temporal areas; frequency of recurrent headaches of 4 to 12 per month, average of one to three per week; history of symptoms for at least 3 months. Patient should be able to distinguish between a migraine and a muscle contraction headache, according to the symptoms defined by the National Institute of Neurological Diseases and Blindness. **Exclusion criteria:** Severe daily headaches of any type including those caused by structural intracranial or extra cranial disease; serious medical illness or illness with pain as a prominent symptom; history of bleeding problems or anticoagulant therapy within 4 weeks of the start of the study. **All patients** **N:** 161 (enrolled); 137 (received trial medication) **Group 1** **N:** 64 (randomised) ; 63 (included in efficacy analysis) **Age (mean, range):** 40 (21-73) **Drop outs:** 1(insufficient headache data) **Group 2** **N:** 73 (randomised); 71 (included in efficacy analysis) **Age (mean, range):** 39 (20-62) **Drop outs:** 2 (1 insufficient headache data, 1 protocol violation)	**Group 1- Naproxen sodium 275 mg capsules orally** **Group 2 Placebo** Sufficient trial medication was dispensed for four headache episodes at the first visit; Patients were to take two capsules (either naproxen or placebo) for each headache episode. Rescue medications could be taken if pain was not adequately controlled. Concomitant use of antidepressants was allowed but not corticosteroids, analgesics, anti-inflammatory agents or muscle relaxants.	**Pain intensity difference** (mean)	**Group1:** 7.2 (1 hour post dose), 14.1 (2 hours post dose) **Group2:** 4.0(1 hour post dose), 5.8 (2 hours post dose) **P values:** 1vs 2 at 1 hour post dose = 0.013 1vs2 at 2 hours post dose =<0.001	**Funding:** Syntex Laboratories, Inc. **Limitations:** Randomisation and allocation concealment unclear. Blinding of participants and investigators not detailed. No mention of other therapies used to alleviate pain. **Additional outcomes:** Sum of pain intensity differences (SPID). Use of rescue medication.
			Incidence of serious adverse events [Complaints reported as severe by patients]	**Group1:** 3 (one GI, two CNS complaints) **Group 2**: 16 (7 GI, 5 CNS and 4 other)	

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Schachtel et al, 1988[700] **Study design:** RCT **Setting: NR** **Duration of follow-up: 2 hours**	**Patient group:** Adults with history of tension type headache and previous response to non-prescription analgesic **Inclusion criteria:** Adult subjects with a diagnosis of muscle contraction headache who reported history of satisfactory relief of headaches from a non-prescription analgesic (aspirin, acetaminophen, ibuprofen); Not receiving treatment from a physician; history of at least moderately severe muscle contraction headaches occurring at least twice a month during the past year. **Exclusion criteria:** History of migrainous headache or hypersensitivity to ibuprofen or aspirin; use of any drugs including analgesics, tranquilisers and mood-altering agents within 4 hours preceding the headache evaluation. **All patients** **N:** 70 (randomised) **Group 1** **N:** 35 **Age (mean, range):** 20.1 (18-23) **Drop outs:** NR **Group 2** **N:** 35 **Age (mean, range):** 21.2 (19-38) **Drop outs:** NR	**Group 1 - Ibuprofen 400 mg orally** **Group 2 - Placebo orally** Both groups completed a headache diary when they experienced a muscle contraction headache and had to swallow single dose of study medication, complete efficacy evaluations at 15, 30, 45, 60, 90, 120 minutes after dosing and note the occurrence of side effects.	**Pain intensity difference** (at various times post dose)	**Group1:** 12.6±11.1 (30 mins) 21.1±14.0 (45mins) 28.9±18.1 (60mins) 37.6±19.6 (90 mins) 43.7±20.5 (120 mins) **Group 2:** 1.8±4.1 (30 mins) 2.7±6.0 (45 mins) 3.5±6.9(60 mins) 3.7±8.4 (90mins) 3.5±8.2 (120 mins) **P values:** 1vs 2 at all time points was statistically significant. P<0.001	**Funding:** Whitehall laboratories Inc. **Limitations:** Unclear randomisation and allocation concealment. Blinding of participants and investigators not described. Details of follow up and assessment not provided. No mention of other therapies used to alleviate pain. No mention of comorbidities. **Additional outcomes:** Headache pain relief scores.
			Incidence of serious adverse events	None	

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Steiner et al, 1998[760] **Study design:** RCT **Setting:** Outpatient clinic s **Duration of follow-up:** 72 hours after headache attack	**Patient group:** Adults with episodic tension type headache (ETTH) **Inclusion criteria:** 18-65 years; Healthy except ETTH (with or without peri-cranial muscle disorder) diagnosed by the IHS criteria. **Exclusion criteria:** Suffering from other headaches including migraine; Pregnant, at risk of pregnancy or breastfeeding; Presently or previously had evidence of peptic ulceration or gastrointestinal haemorrhage; History of alcohol or medication misuse; Otherwise ill, physically or mentally; Taking regular medication. **All patients** **N:** 453 (randomised); 348 (treated at least one attack of ETTH); 9(excluded for taking treatment <1 hr or >12hr after onset); 339 (intention to treat population ITT) **Drop outs:** 39 (protocol violation) **Group 1 Ketoprofen (25mg)** **N:** 109(treated at least one attack of ETTH); 107 (included in ITT analysis) **Age (median, range):** 42(18-74) **Drop outs:** Unclear **Group 2 (Acetaminophen 1000 mg)** **N:** 123(treated at least one attack of ETTH);119 (included in ITT analysis) **Age (median, range):** 39(18-64)	**Group 1 Ketoprofen 25mg orally** **Group 2 Acetaminophen 1000 mg orally** **Group 3 Placebo** After baseline assessment, patients were issued with a medication pack for one attack. Pack had 2 bottles, 1 containing ketoprofen or matching placebo and the other acetaminophen or matching placebo with instructions on the correct use of the trial medication and in completion of diary cards. Trial medication from both bottles was taken at home between 1 and 12 hours of onset of an otherwise untreated attack; headache intensity had to be at least moderate subjectively. Allowed three months in which to treat an attack; were considered dropouts if they did not.	**Pain free at 2 hours** Percentage of patients experiencing total relief at 2 hours	**Group 1:** 27% (28/102) **Group 2:** 22% (25/116) **Group 3:** 16% (18/ 112)	**Funding:** NR **Limitations:** Unclear randomisation and allocation concealment. Unclear if double blinded or not; details not reported Numbers and reasons for dropout according to groups not provided. Unclear how patients were monitored at home; no details of rescue medication/ concomitant therapy provided. Unclear if randomisation was done prior to screening patients for inclusion as exclude patients for not fulfilling inclusion criteria after randomisation. **Additional outcomes:** Patients' global assessment at 2 hours. Pain relief at 4 hours.
			Functional health status and health related quality of life	**Group 1:** 75% normal at 2 hrs 88% at 4 hrs **Group 2:** 68% normal at 2 hrs 78% at 4 hrs **Group 3:** 53% normal at 2 hrs 68% at 4 hrs	
			Incidence of serious adverse events	No serious adverse events were reported	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: Unclear **Group 3 Placebo** **N:** 116 (treated at least one attack of ETTH);113 (included in ITT analysis) **Age (median, range): 42 (20-67)** **Drop outs:** Unclear				

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Steiner et al, 2003[761] **Study design:** RCT **Setting:** GP surgeries **Duration of follow-up:** 4 hours	**Patient group:** Aged over 16 with episodic tension type headache **Inclusion criteria:** 16-65 years; Met IHS diagnostic criteria for episodic tension-type headache but not for migraine; Had no other serious physical or mental illness or contraindications to study treatment. **Exclusion criteria:** Women who were pregnant or who might become pregnant; Concomitant use of antidepressants or drugs known to interact with study medication. **All patients** **N:** 638 (randomised); 542 (took study medication) **Drop outs:** 96 (did not take study medication) **Group 1** **N:** 126 (randomised);111 (took study medication, included in ITT) **Age in years, mean (SD):** 39.9 (11.8) **Drop outs:** 15 **Group 2** **N:** 128(randomised); 103 (took study medication, included in ITT) **Age in years, mean (SD):** 41.0(12.3) **Drop outs:**25	**Group 1:Aspirin 500mg** **Group 2: Aspirin 1000mg** **Group 3: Paracetamol 500mg** **Group 4: Paracetamol 1000mg** **Group 5: Placebo** Each participant received a diary card and one dose of trial medication with instructions to treat an attack of episodic tension-type headache occurring within 8 weeks of enrolment. Headache had to be moderate in intensity and the study medication could not be used for a headache associated with a cold, influenza, other viral infection or hangover. Rescue medication was	**Pain free at 2 hours**: Percentage of participants recording 'total relief' or 'some worth while effect' at 2 hrs post dose	**Group 1:** 70.3% (78/111) **Group 2:** 75.7% (78/103) **Group 3:** 63.8% (67/105) **Group 4:** 71.2% (79/111) **Group 5:** 54.5% (49/112) **p values:** 1vs5: 0.011; 2vs5: 0.00009 3vs5: 0.014; 4vs5: 0.007 2vs4: 0.275; 1vs3: 0.19	**Funding:** Bayer AG, BG Consumer Care, Germany **Limitations:** Unclear randomisation and allocation concealment. Patients were not monitored at home. Unclear how groups were followed up. Blinding of investigators unclear. Reasons for loss to follow up unclear. **Additional outcomes:** Use of rescue medication at 2 hours. Global evaluation analysis. Sum of pain intensity difference scores (SPID). Notes:
			Pain intensity difference	**P values:** 2vs5: 0.0001 (2 hrs); significant at each time point from 30 min to 2 hours 4vs5: 0.0058 and 3vs5: 0.0018;(at 2 hrs); not significant at any time point prior to 2 hrs	
			Functional health status Return to normal function by 1 hr	**Group1:** NR **Group 2:** 41.7% **Group 3:** NR **Group 4:** 26.1% **Group 5:** 19.6%	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 3 **N:** 128 (randomised); 105 (took study medication, included in ITT) **Age in years, mean (SD):** 39.7 (11.4) **Drop outs:** 23 **Group 4** **N:** 128 (randomised); 111 (took study medication, included in ITT) **Age in years, mean (SD):** 38.4 (11.8) **Drop outs:** 17 **Group 5** **N:** 128(randomised); 112 (took study medication, included in ITT) **Age in years, mean (SD):** 40.6 (11.4) **Drop outs:** 16	permitted after two hours of medication intake.		**p-values:** 2vs5: 0.0003 2vs4: 0.012 4vs5:0.16	5 arm trial with 2 different doses of aspirin and paracetamol. Participants were recruited from the UK general population by advertisement in GP surgeries and local newspapers.
			Incidence of serious adverse events	None	

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

E.2.3 Acute pharmacological treatment of migraine

Oral, nasal & subcutaneous treatments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Intravenous, intramuscular and subcutaneous treatments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Bell et al, 1990[70] **Study design:** RCT – single blind **Comparison:** 3 arms: Antiemetic (chlorpromazine) vs lidocaine vs ergot (dihydroergotamine) **Setting:** 2 university affiliated emergency departments **Duration of follow-up:** 24 hours	**Patient group:** Adults (18-60yrs) presenting to emergency department with migraine. **Inclusion criteria:** Migraine diagnosed by emergency physician defined as either: 'common' characterised by recurrent attacks of headache lasting hours or days, associated with gastrointestinal disturbance, and having some features of pulsatile character, photophobia, sonophobia, unilaterality, and positive family history; or 'classic' exhibiting recurrent attacks of headache as in common migraine but preceded by a motor, sensory or visual aura. **Exclusion criteria:** Non-migraine headache, aged under 18 or over 60, substance abuse, neurologic or seizure disorder, alcohol abuse, allergy or sensitivity, pregnancy or breast feeding, peripheral vascular disease, coronary vascular disease, hypertension, or hepatic or renal failure. **All patients** **N:** 90 (76 completed) **Age (mean):** NR	**Group 1:** 12.5mg chlorpromazine IV **Group 2:** 1mg dihydroergotamine (DHE) IV **Group 3:** 50mg lidocaine IV All patients had an IV line started and received a 500ml bolus of normal saline, followed by the study drug. The initial dosage could be repeated once at 30 minutes for a total max dose of 2mg DHE, twice at 20min intervals for total max dose of 37.5mg chlorpromazine and twice at 20min intervals for total max dose of 150mg lidocaine. IV drip of normal saline maintained during therapy at 75ml/hr. If patient didn't respond or deteriorated, physician could terminate study and use alternative therapy.	**Pain free up to 2 hours** * reported as complete relief at 1 hour (n (%)) **Remaining pain free at 24hrs** N (%) NB. N values too low	**Group1:** 8/24 (33.3) **Group 2:** 6/26 (23.1) **Group 3:** 2/26 (7.7) **95% CI:** NR **p value:** NS **Group1**: 16/18 (88.9) **Group 2:** 10/19 (52.6) **Group 3:** 5/17 (29.4) **95% CI:** NR **p value:** NR	**Funding:** Not stated **Limitations:** N values very low. Single blind (patients only). Groups not comparable at baseline. 14 patients dropped out after randomisation but the numbers are not given by group. Not clear how many patients had additional study drug doses. Analysis not clear. High risk of bias. **Additional outcomes:** Headache severity on a 10cm VAS. Additional medication taken in following 24 hours (narcotics or chlorpromazine). Patients opinion on medication received. **Notes:** States that analysis showed the three groups were

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 16/60 44% history of migraine 43% family history (42% both) **Drop outs:** 19 (either due to incomplete records, early self-discharge or request for withdrawal from the trial) **Group 1 – Chlorpromazine** **N:** 24 **Age (mean):** NR for any group **Drop outs:** NR for any group **Headache intensity (0-10 mean):** 8.5 **Group 2 - Dihydroergotamine** **N: 26** **Headache intensity (0-10 mean):** 7.5 **Group 3 - Lidocaine** **N: 26** **Headache intensity (0-10 mean):** 8.0				statistically different, assumed this was at baseline). Groups 2 and 3 were subsequently found not to differ (except for side effects) and therefore were grouped for comparisons to group 1. Dosage could be repeated after 30 mins, therefore cannot be sure pain free was at 1 hour, but it would still be within a 2 hour window.

Abbreviations: NR=not reported, NS=not significant, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IV=intravenous, DHE=dihydroergotamine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Brousseau et al, 2004[110] **Study design:** RCT **Comparison:** Antiemetic (Prochlorperazine) vs NSAID (Ketorolac) **Setting:** 2 Paediatric emergency departments (ED) **Duration of follow-up:** 48 hours	**Patient group:** Children aged 5-18 (avg 13) presenting to emergency department with migraine. **Inclusion criteria:** Aged 5-18 meeting Prensky and Sommer criteria for migraine: Recurrent headaches with pain-free intervals and at least 3 of the following: 1) an aura; 2) unilateral location; 3) throbbing pulsatile pain; 4) nausea, vomiting or abdominal pain; 5) relief after sleep; and 6) a family history of migraines. **Exclusion criteria:** Any contraindications to the use of either Prochlorperazine or ketorolac and those unable to complete a Nine Faces Pain Scale. **All patients** **N:** 62 (36 F) **Age (mean):** 13.7 (7.25-18) **Group 1 – Prochlorperazine** **N:** 33 (18 F, 15 M) **Age (mean (SD)):** 13.8 (3.0) **Initial pain score (SD) max 1:** 0.82 (0.11)	**Group 1** - IV Prochlorperazine (0.15mg/kg; max 10mg) **Group 2** – IV ketorolac (0.5mg/kg; max 30mg) Both administered over a 10 min period. Each child, concurrent with study medication, received a 10mL/kg bolus of normal saline solution over a 30-minute period to standardize treatment protocol. If initial treatment not successful, the child received the other medication (again blinded). Pain scoring repeated. All children discharged with a prescription for naproxen sodium (5mg/kg) 3 times per day for 48 hours as needed for pain.	**Pain free up to 2hrs** Lowest possible pain score after 60mins (% (n))	**Group1:** 33.3% (11/33) **Group 2:** 6.9% (2/29) **95% CI:** 8-45%	**Funding:** No outside funding or support **Limitations:** Age range might make population inappropriate. Pain scale doesn't meet our criteria for 'headache response' **Additional outcomes:** Treatment success defined as a ≥50% reduction in pain score (30 or 60 min after drug) Taken from Nine Faces Pain Scale Headache recurrence at 48 hours Adverse events if reported **Notes:** Block randomised by hospital pharmacist who held code for blinding until study completion. Only randomised once decision had been made to treat with IV medication.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Previous clinical diagnosis of migraine %: 61 **Current migraine duration (hr, median):** 25 **Use of migraine specific medication pre ED visit %:** 32 **Any pain medication pre visit:** 84.8 **Drop outs:** 1 (after 60 minutes) **Group 2 - Ketorolac** **N:** 29 (18 F, 11 M) **Age (mean (SD)):** 13.7 (2.6) **Initial pain score (mean (SD)) max 1:** 0.82 (0.08) **Previous clinical diagnosis of migraine %:** 55 **Current migraine duration (hr, median):** 24 **Use of migraine specific medication pre ED visit %:** 35 **Any pain medication pre visit:** 82.8 **Drop outs:** 1 (after 60 minutes)				

Abbreviations: NR=not reported, NS=not significant, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, ED=emergency department, IV=intravenous

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener, 1999[210] **Study design:** Multicentre RCT **Comparison:** Triptan v aspirin **Setting:** 17 centres in Germany **Duration of follow-up:** NR	**Patient group:** Adults with migraine **Inclusion criteria:** Age 18-65 years. Met IHS criteria for migraine with or without aura. History of migraine of at least 1 year's duration. Experiencing 2-6 migraine attacks per month during the last 12 months. **Exclusion criteria:** Participation in a study during the 30 days immediately prior to the start of the study, including the treatment of a second migraine attack, intake of analgesics or migraine drugs 24 hours before the administration of the study medication. Intake of compound analgesics, sumatriptan. Ergotamine tartrate or DHE, codeine or barbiturates on > 10 days per month. Hypertension with diastolic BP >160mmHg. Coronary heart disease and/ or history of myocardial infarction, asthma of any origin, hypersensitivity to salicylates, urticaria or other allergic diatheses, hypersensitivity to sumatriptan and drug intake according to DSMIIIR (alcohol, drug abuse, or dependence, also in medical history). **All patients** **N:** 279 randomised 278 received study medication (ITT) **Drop outs:** 4 (1 patient unaccounted for in the randomised groups below **Group 1 (sumatriptan)**	**Group 1** Sumatriptan 6 mg (subcutaneous) **Group 2** L-ASA 1.8g (corresponding to 1g acetylsalicylic acid) (intravenous) **Group 3** Placebo injections (results not reported in this table) **All patients** Patients who experienced a qualifying migraine attack were asked to come to the study centre within a period of no more than 6hours after the onset of the attack. Change in pain intensity was measured at 30 min intervals on a VRS and at 15 min intervals on a VAS over 120 min.	**Headache response up to 2 hours**	**Group1 (sumatriptan):** 104/114 (91.2%) **Group 2 (L-ASA):** 88/119 (73.9%) **p value:** 0.001	**Funding:** Bayer Vital. GmbH % Co, KG, Germany **Limitations:** Randomisation unclear: patients were given their random numbers consecutively and in ascending order. Allocation concealment: unclear. **Additional outcomes:** Change in pain intensity measured by VAS over time (2hours). VAS response responder. Recurrence of headache within 24 hours. Time until ability to work. Need of rescue medication. Relief of accompanying symptoms. Adverse events. **Notes:** Headache severity 3= severe 2= moderate 1= mild 0= no pain
			Pain free at 2 hours	**Group1:** 87/114 (76.3%) **Group 2:** 52/119 (43.7%) **p value:** <0.0001	
			Sustained headache response at 24 hours (derived from those with recurrence of headache at 24 hours)*	**Group1**: 80/114 * **Group 2:** 72/119 * Not significant	
			Serious adverse events	**Group1:** 6 **Group 2:** 4 **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 116,114 received treatment dose **Age (mean):** 40.9 (SD 11.0) **Male sex:** 21 (18.4%) **Days with headache per month:** 4.0 (SD 3.5) **Migraine since (years): 19**.1 (SD 11.8) **Rate of aura (%):** 30.5 (SD 39.3) **Mean duration of attacks (h):** 30.8 (SD 22.6) **Drop outs:** NR **Group 2 (L-ASA)** **N:** 119, 119 received treatment dose **Age (mean):** 41.5 (SD 11.8) **Male sex :**24 (20.2%) **Days with headache per month:** 4.1 (SD 2.6) **Migraine since (years):** 20.4 (SD 11.5) **Rate of aura (%):** 24.2 (SD 34.9) **Mean duration of attacks (h):** 32.5 (SD 24.2) **Drop outs:** NR **Group 3 (placebo)** **N:** 43, 42 received treatment dose **Age (mean):** 39.8 (SD 11.7) **Male sex:** 10 (23.8%) **Days with headache per month:** 4.1 (SD 2.2) **Migraine since (years):** 18.3 (SD 16.0) **Rate of aura (%):** 20.0 (SD 29.9) **Mean duration of attacks (h):** 31.9 (SD 25.5) **Drop outs:** NR				Ratio Placebo to active treatments 1:6. Blinding: double-blind, double-dummy

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Duarte et al, 1992[240] **Study design:** RCT **Comparison:** NSAID (ketorolac) vs opioid + antiemetic (meperidin + hydroxyzine) **Setting:** Emergency department (ED) **Duration of follow-up:** 1 hour / discharge from ED	**Patient group:** Adults presenting to ED with migraine with or without aura **Inclusion criteria:** Migraine with or without aura diagnosed according to ICHD criteria. **Exclusion criteria:** First migraine, allergy or sensitivity to study drugs, known intracranial masses, traumatic etiology, gastritis, peptic ulcer disease, bleeding dyscrasias, **pregnancy** and nursing mothers. **<u>All patients</u>** **N:** 49 patients enrolled, representing 52 visits. **Drop outs:** 2 withdrew before receiving medication leaving 50 cases from 47 patients for analysis) **<u>Group 1 –</u>** <u>Ketorolac</u> **N:** 25 **Age (mean±SD):** 34.9 ±10.1 **M/F (%):** 20/80 **Headache duration, hours (mean±SD):** 41.4±38.1 **Initial pain score, cm (mean±SD):** 7.74±1.84 **<u>Group 2</u>** - <u>Meperidine/Hydroxyzine</u> **N:** 25 **Age (mean):** 34.4± 12.3 **M/F (%):** 20/80 **Headache duration, hours (mean±SD):** 16.5±20.5 **Initial pain score, cm (mean±SD):** 8.28±1.65	**Group 1** Ketorolac 60mg IM injection **Group 2** Meperidin (100mg) and hydroxyzine (50mg) IM injection Patients received a single IM injection in left deltoid(arrived pre-mixed at ED by pharmacy)	**Headache response up to 2 hours** Recorded at 30 and 60 mins. 60 mins reported here. Based on verbal descriptor scale.	**Group1:** 15/25* (60%) **Group 2:** 14/25* (56%) **p value:** 0.77	**Funding:** NR **Limitations:** Patients consecutively randomised as presented in ED – 3 patients enrolled twice. No details on random number tables. N values very low. Groups different in headache duration at time of enrolment (group 1 longer). **Additional outcomes:** Pain intensity on a 10cm VAS scale at 30 and 60 minutes. Adverse events reported (but not classified for severity). Need for additional analgesia after study. **Subgroups:** Pregnant women excluded. Under 18s excluded. **Notes:** * Calculated by NCGC All patients in ketorolac group and 4 of 5 patients in meperidine/hydroxyzxine group who reported a small amount of pain relief required additional analgesia, as did all five patients from both groups who obtained no pain relief (no differences between groups).

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, ED=emergency department, IM=intramuscular, ICHD=International classification of headache disorders

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Friedman et al, 2005[296] **Study design:** RCT **Comparison:** Triptan vs antiemetic **Setting:** 2 emergency departments in USA **Duration of follow-up:** 24 hours	**Patient group:** Adults with migraine with or without aura **Inclusion criteria:** ≥18 years old. Migraine with or without aura as defined by the IHS **Exclusion criteria:** High likelihood that patient had secondary headache or if patient was to receive a lumbar puncture in the ED. Temperature >100.3 degrees, pregnancy, lactation, allergy to a study medication or use of a study medication within 2 days. Known or suspected atherosclerotic disease or hypertension. New objective neurologic abnormality at the time of physical exam Use of sumatriptan during the planning phase of the trial, during the current migraine attack. **All patients** **N:** 78 **Drop outs:** NR **Group 1 (sumatriptan)** **N:** 38 **Age (mean):** 34 **Gender F (%):** 84 **Migraine with aura (%):** 8	**Group 1 (sumatriptan)** 6 mg SC administration by clinical nurse. Bag also contained 4 vials of placebo which were injected into the 50mL bags of normal saline and administered IV at 30 minute intervals by the clinical nurse. Each arm B bag also contained 2 vials of placebo which were inserted into saline bags 1 and 3. **Group 2 (metoclopramide+ diphenhydramine)** IV administration. Each bag contained 4 vials, each containing 20mg of metoclopramide. The contents of each vial were inserted into a 50mL bag of normal saline by a clinical nurse. These normal saline bags containing metoclopramide were then administered IV at 30 minute intervals. In addition, each Arm A bag had 2 vials, each containing 25mg of diphenhydramine. The diphenhydramine was inserted into saline bags 1 and 3 along	**Pain-free at 2 hours**	**Group1:** 13/37* (35%) **Group 2:** 24/40* (59%) **Difference:** 24% **95% CI:** 2 to 46% **p value:** 0.04	**Funding:** NR **Limitations:** Patients with chronic migraine headache were not excluded. Patients with a past history of triptan use (14%) were not excluded. Subjects in the sumatriptan group could have had a placebo response as they received up to 4 doses of IV placebo. Substantially more patients in the metoclopramide arm had pre-medicated prior to presenting to the ED. **Additional outcomes:** Use of rescue medication. Adverse events. Early discharge due to sufficient pain relief. Comparison of the change in NRS (numerical rating scale) scores between time 0 and 2 hours. Relief of nausea. **Notes:**
			Pain free at 24 hours	**Group1:** 10/37* (27%) **Group 2:** 16/40* (40%) **Difference:**13% **95% CI:** -9 to 35% **p value:** 0.23	
			Functional health status at 2 hours	**Group1:** 26/37* (69%) **Group 2:** 34/40* (85%) **Difference:**16% **95% CI:** -3 to 35% **p value:** 0.10	
			Functional health status at 24 hours	**Group1:** 18/37* (49%) **Group 2:** 19/40* 68%) **Difference:**19% **95% CI:** -3 to 41% **p value:** 0.09	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Prophylactic medication (%): 0 **Duration of headache (95% CI), h:** 29 (22-37) **Self-medicated prior to ED visit, %:** 60 **Drop outs:** 1 **Group 2 (metoclopramide)** **N:** 40 **Age (mean):** 34 **Gender F (%):** 88 **Migraine with aura (%):** 8 **Prophylactic medication, (%):**3 **Duration of headache (95% CI) h**: 32 (26-39) **Self-medicated prior to ED visit %:** 83 **Drop outs**: 0	with the metoclopramide by the clinical nurse. Finally, each arm A bag had a vial of 'sumatriptan' placebo which was administered SC by the clinical nurse. All Patients At time 0, subjects received one SC injection (containing either placebo or sumatriptan) as well as one 50mL bag of IV normal saline (containing either metoclopramide and diphenhydramine or placebo). Every 30 minutes the research assistant would ask if the subject required more medication for headache. If so, the subject received an additional IV infusion containing either metoclopramide or placebo. The protocol lasted for 2 hours.			* numbers calculated by NCGC using percentages reported. These have been rounded to whole numbers. Pharmacist inserted medication into vials and placed the vials into sequentially numbered brown paper research bags in an order determined by random number tables. Randomisation in blocks of 6 using computer-generated random number tables. Allocation concealment: sealed opaque manila envelope. Blinding: double-dummy. Study population largely Latino.

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, ED=emergency department, AE=Adverse events, IV=intravenous, SC=subcutaneous, IHS=International headache society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Karabetsos et al, 1997[418] **Study design:** RCT **Comparison:** NSAID (ketoprofen) vs paracetamol **Setting:** Not stated – but all patients treated as outpatients **Duration of follow-up:** 4 hours	**Patient group:** Adults with classical or common migraine **Inclusion criteria:** Suspected acute migraine attack, Paroxysmal headache accompanied by at least two of the following: (a) unilateral pain, (b) nausea, (c) visual and/or limb symptoms and (d) positive family history. Average of at least 2 or more attacks each month, Not receiving recognized migraine prophylactic drugs or oral contraceptives. **Exclusion criteria:** History of allergy to NSAIDs, under 18 yrs of age, pregnant or lactating. **All patients** **N:** 64 **Age (mean):** 42.2 (20 – 64yrs) **Drop outs:** None **M/F:** 28/36 **Group 1 – Ketoprofen** **N:** 34 **Age (mean):** 42.2 **Migraine type:** 15 classical, 19 common **Attack frequency/month:** 1-3 **Severity of symptoms**: 1 slight, 8 moderate, 25 severe	**Group 1 Ketoprofen** IM injection 100mg If pain persisted up to 30 minutes, or if relapse occurred during first or second hour after first dose, a second dose of ketoprofen was administered. No further doses were allowed – NB results reported after the 1st dose time. **Group 2 Paracetamol** IM injection 500mg	**Time to freedom from pain** Mean, hrs (SD) **Pain free up to 2 hours** (reported at 30-40 mins) **% reporting serious AEs**	**Group1:** 4.9 (5.15) (n=24) **Group 2:** 3.6 (2.4) (n=28) **P value:** 0.909 **Group 1:** 28/34 **Group 2:** 5/30 **P value:** <0.001 **Group1:** 0 **Group 2**: 0 **p value:** Not significant	**Funding:** NR **Limitations:** Study says it was a crossover, but methods stated don't reflect this – assumed to be a parallel design. Randomisation and blinding methods not clear. Setting not stated, but possibly ED. **Additional outcomes:** Severity of headache. Severity of associated symptoms. Overall rating of the effect of drug on migraine attack. Adverse events. **Notes:** Not clear at what point results are reported, or if sample size reported for time to freedom from pain is the n that achieved freedom from pain, or n the sample was taken from.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 - Paracetamol **N:** 30 **Age (mean):** 42.4 **Migraine type:** 14 classical, 16 common **Attack frequency/month:** 1.3-3.3 **Severity of symptoms:** 1 slight, 9 moderate, 20 severe				

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, AE=adverse events, ED=emergency department, IM=intramuscular

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Karachalios et al, 1992[419] **Study design:** RCT **Comparison:** NSAID (Diclofenac sodium) vs paracetamol **Setting:** NR **Duration of follow-up:** 180mins	**Patient group:** People over 18 with acute migraine **Inclusion criteria:** Fulfill Vahlquist's criteria for migraine: paroxysmal headaches accompanied by at least two of the following: 1) unilateral pain, 2) nausea, 3) visual and limb symptoms & 4) positive family history. Average of at least 2 attacks each month. Not receiving recognised migraine prophylactic drug or oral contraceptives. **Exclusion criteria:** History of allergy to NSAID, aged under 18 or pregnant or lactating women. **All patients** **N:** 86 **Drop outs:** 2 (developed severe headache and refused second injection) **Group 1 – Diclofenac** sodium **N:** 46 **Age (mean):** 47.5 18 M, 21 F **Migraine type:** 19 Classical, 26 Common **Attacks/month (mean):** 2±1 **Symptom severity:** 1 slight, 10 moderate, 35 severe **Group 2 - Paracetamol**	**Group 1 –** Diclofenac sodium 75mg injection (Intramuscular) **Group 2 -** Paracetamol 500mg injection (Intramuscular) If pain persisted up to 30mins after injection, or if headache relapsed during first or second hour after first dose, a second dose of diclofenac was administered.	**Pain free up to 2hrs** n (%) at 30-35 minutes) **Percentage reporting serious adverse events**	**Group1:** 40/45 (88%) **Group 2:** 7/40 (17.5%) Relative risk: 95% CI: **p value:** <0.001 **Group1:** 0 **Group 2:** 0	**Funding:** NR **Limitations:** States groups were comparable at baseline except for length of migraine history, but data not reported. Two subjects withdrew, but don't know which group they were in. Setting not stated, but possibly ED. **Notes:** Five patients in diclofenac group needed another injection for complete relief of pain during 2-4 hour follow-up period. 33 paracetamol patients did not respond to drug and were treated with IM diclofenac after 30 minutes of follow-up observation (complete relief of pain observed after 30-45 minutes in 32 of these patients. Second dose of treatment allowed, but pain free still would have fallen within 2hours.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 40 **Age (mean):** 48.3 **Migraine type:** 20 Classical, 21 Common **Attacks/month (mean):** 2.5±1.1 **Symptom severity:** 1 slight, 10 moderate, 30 severe				

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Touchon et al, 1996[798] **Study design:** Randomised crossover study **Comparison:** Triptan vs dihydro-ergotamine **Setting:** Outpatient **Duration of follow-up:** Not reported	**Patient group:** Migraine **Inclusion criteria:** Men and women aged 18-65, at least 1 year history of 1 to 6 migraine attacks per month, able to differentiate migraine attacks from other types of headache, IHS criteria for migraine with or without aura, usually experienced frequent and disabling migraine attacks with severe/moderate headache. **Exclusion criteria:** Lactation, pregnancy or inadequate contraception, history suggestive of ischemic heart disease, uncontrolled hypertension or other systemic disease, drug or alcohol abuse, contraindications to the use of dihydroergotamine, hypersensitivity to or intolerance of sumatriptan or dihydroergotamine. **All patients** **N:** 317, 289 treated 1st	**Group 1** 1st attack Sumatriptan & placebo DHE 2nd attack Dihydroergotamine (DHE) & placebo Sumatriptan **Group 2** 1st attack DHE & placebo Sumatriptan 2nd attack Sumatriptan & placebo DHE 2 attacks treated in each group (1 per treatment) Drugs Sumatriptan 6mg subcutaneous injection into thigh from prefilled syringe with auto injector device Dihydroergotamine (DHE) nasal spray (1 spray of 0.5mg in each nostril) Patients taking DHE had the option to take a 2nd dose after 30 minutes of 1st dose if headache not	**Headache reseponse at 2 hours** reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none) or 1 (mild)	Data not reported. States Sumatriptan significantly better than DHE **p value:** ≤ 0.001	**Funding:** Glaxo Wellcome **Limitations:** Details on randomisation and allocation concealment not provided. No mention of a washout period. Actual event rates not provided, calculated from percentages. Patients on DHE permitted to take a 2nd dose if inadequate headache relief, patients on Sumatriptan not permitted to take 2nd dose. **Additional outcomes:** Nausea, vomiting, photophobia & phonophobia relief at 2 hours; 'meaningful' (undefined) relief of attack, rating of treatment efficacy by patients (5 point scale); number of adverse events; patients withdrawing from study due to adverse events.
			Freedom from pain at 2 hours reduction of headache severity from grade 2 (moderate) or 3 (severe) at baseline to 0 (none)	Data not reported. States Sumatriptan significantly better than DHE **p value:** ≤ 0.001	
			Sustained headache response at 24 hours – patients with headache response at 2 hours and neither recurrence nor use of rescue medications in 24 hours.	**Sumatriptan:** 144*/266 (54%) **DHE:** 104*/266 (39%) **p values:** <0.001 * number calculated by NCGC	
			Use of rescue medication	**Sumatriptan:** 74*/266 (28%) **DHE:** 112*/266 (42%) **p values:** <0.001 * number calculated by NCGC	
			Use of 2nd dose of DHE (or placebo if using active Sumatriptan)	**Sumatriptan:** 146*/266 (55%) **DHE:** 226*/266 (85%) **p values:** <0.001	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	attack, 266 treated 2nd attack as well **Drop outs:** 51 **Group 1** **N:** No. randomised NR, 145 treated 1st attack, 133 treated 2nd attack as well **Age (mean):** 42±10 (n=133)* **Gender F/M:** 119/14 (n=133)* **Drop outs:** NR **Usual severity of headache:** moderate 37, severe 96 (n=133)* **Group 2** **N:** No. randomised NR, 144 treated 1st attack, 133 treated 2nd attack as well **Age (mean):** 42±10(n=133)* **Gender F/M:** 111/22 (n=133)* **Drop outs:** NR **Usual severity of headache:** moderate 32, severe 101 (n=133)* * relates to patients who treated 2 attacks only	completely relieved. To maintain blinding patients in Sumatriptan group took a second dose of placebo DHE. Patients instructed to prepare both treatments (active & placebo) then to administer within 1 minute of each other. Rescue medication permitted if migraine symptoms not relieved after two hours. Ergotamine containing medications, DHE or Sumatriptan not permitted as rescue medications. Prophylactic medication excluding oral DHE permitted provided dosage remained unchanged during study.		* number calculated by NCGC	**Notes:** Outcome data relates to all patients who completed treatment for 2 attacks.
			Relief of clinical disability – reduction of functional ability from 2 (functional/working ability severely impaired) or 3 (bed rest required) to 0 (able to function normally) or 1 (functional/working ability impaired to some degree)	Actual numbers unclear. Reports 63% of patients in both groups were severely disabled or required bedrest pre-treatment. Reduction in disability significantly less in DHE group at all time points. **p values:** <0.001	

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

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

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

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

E.2.4 Acute pharmacological treatment of cluster headache

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Cittadini et al, 2006[151] **Study design:** RCT, 3 armed crossover **Comparison:** Triptan vs Placebo **Setting:** Germany, Italy, UK **Duration of follow-up:** 3 attacks (30 min for assessment)	**Patient group:** Cluster headache patients between 18 – 65 years **Inclusion criteria:** Established diagnosis of CH according to IHS. Required to have CH attacks lasting at least 45 minutes when untreated. Patients should have used Zolmitriptan in the past, zolmitriptan naive patient were included if in the investigators opinion it was safe to do so. **Exclusion criteria:** Patients unsuitable for zolmitriptan tablet or nasal spray use in the country that the study was being conducted according to regulatory use in that country. Patients with 2 or more of the following risk factors were also excluded: cardiovascular disease, patients using regular ergotamine derivatives or analgesics, and patients with ENT disorders that would preclude use of intranasal zolmitriptan **All patients** **N:** 92 **Age (mean):** 40+/-10 **Drop outs:** 34 **Sex M/F:** 80/12 **Headache type:** Episodic 59, Chronic 33	**Group 1 Zolmitriptan 5 mg** (nasal spray) **Group 2 Zolmitriptan 10 mg** (nasal spray) **Group 3 Placebo** Patients asked to treat 3 attacks at least 24 hours apart with study medicine. Patient to apply one dose of study drug to contralateral nostril when the headache had reached at least a moderate severity. Escape medication allowed at 30 minutes using oxygen or an analgesic, not a ergotamine or triptan derivative	**Headache response** (up to 2 hours) At 30 minutes Reduction from moderate, severe or very severe to mild or no pain.	**Group1:** 27/65 (42%) **Group 2:** 38/63 (60%) **Group 3:** 14/61 (23%) **p value:** 0.002	**Funding:** AstraZeneca supported the work. They provided the study medication, matching placebo and randomisation schedule. They did not initiate, design or analyse the study; interpret the data or have any role in writing the manuscript. **Limitations:** Method of randomisation and allocation concealment not stated **Additional outcomes:** Headache response at 5, 10, 15, and 30 minutes. Pain free at 30 minutes Percentage of patients reporting improvement in associated symptoms. **Notes:** Frequency of escape medication use: Group 1: 23/65 (35.4%) Group 2: 17/63 (27%) Group 3: 30/61 (49.2%)
			Reduction in pain at 30 minutes Assessments made at 5, 10, 15, and 30 minutes.	**Group1:** 27/65 (42%) **Group 2:** 38/63(60%) **Group 3:**12/61(20%) **p value:** NR	
			Adverse events	No serious adverse events were reported. One important adverse effect that led to withdrawal occurred in one patient (shortness of breath, vomiting and rheumatic pain)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Duration of bout, week (mean): 8+/-6 **Headache history, yrs (mean):** 12+/-7 **Previous use of**: Sumatriptan injection 67, Sumatriptan nasal spray 40, Zolmitriptan oral 18, Oxygen: 72 **Group 1** **N:** 65 **Age (mean):** NR for any group **Drop outs:** NR for any group **Group 2** **N:** 63 **Group 3** **N:** 61				

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Cohen et al, 2009[157] **Study design:** Randomised, placebo controlled double blind crossover. **Comparison:** 100% Oxygen Vs Placebo (Air) **Setting:** Clinics from the national hospital for neurology, London and patients identified through support groups (OUCH-UK) **Duration of**	**Patient group:** 18-70 years, with either episodic or chronic cluster headache **Inclusion criteria:** Episodic or chronic cluster headache classified using 1st edition of ICHD; experienced between 1 attack every other day to 5 a day (duration of attacks between 45 minutes and 3 hours), between the ages of 18-70 years **Exclusion criteria:** Chronic migraine or other episodic headaches (if they could be distinguished from cluster headaches); were pregnant and lactating; had moderate to severe chronic obstructive pulmonary disease; could not tolerate the oxygen mask in the correct fitting; had previously tried oxygen at doses of 4 L/min and higher. **All patients** Unless stated values are mean(SD) **N:** 109 **Age:** 39 (9) **Drop outs:** 33 **Sex n(%):** M 89 (82) F 20 (18) **Type of cluster headache (n):** Episodic: 81(74) Chronic: 28(26) **Attack duration, min:** 83 (31) (n=81) **Average bout duration, episodic cluster headache per week:** 11 (16) **Cluster headache history, years:** 12.3 (9.1) **Previous use, No.:** Sumatriptan injection: 30,	**Group 1- 100% Oxygen** 100% oxygen delivered at 12 mL/min. For 15 minutes from the early part of an attack **Group 2- Air** Air delivered at 12 mL/min. For 15 minutes from the early part of an attack Patient received 2 cylinders: one labelled “treatment 1” and one labelled “treatment 2” Patients instructed to administer a single treatment for any attack using “treatment 1” at 12 mL/min for 15 minutes through a firm plastic non-re breathing facial mask and use the treatment 2 cylinder at the same rate and duration for the next attack, then switching again for the next 2 attacks (alternating cylinders in crossover fashion) If after 15 minutes of treatment there was no relief the patient could take rescue medication. All patients taught how to use compressed air cylinder and received diary cards to record treatment effect at 5, 10, 15, 30 and 60 minutes.	**Headache response up to 2 hours** Reduction in pain at 60 minutes **Reduction in pain scale** at 30 min **Adverse events**	**Group1:** 95/103 (92%) **Group 2**: 38/64 (59%) **p value:** NR **Group1:** 93/109 (85%) **Group 2:** 28/74 (38%) **p value:** NR 9 (no data for separate groups) 4 not related to trial 2 possibly related to trial, 1 probably not and 2 were related to the trial.	**Funding:** University college London and BOC Limited (supplied cylinders and masks) **Limitations:** Rescue medication allowed after 15 minutes – could affect outcomes. Use differed between groups (see notes) **Additional outcomes:** Overall response to the treatment and overall functional disability. Effect on associated symptoms. **Notes:** Need for rescue medication from 15 mins (No. Of attacks): Group1: 30/249 (28%) Group 2: 76/ 249 (53%) Pain scale: 0= pain free, 1=mild, 2= moderate, 3=severe, 4= very severe. Randomisation: opaque sealed envelopes containing

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
follow-up: 4 attacks (Maximum of 5 years)	Sumatriptan intranasal or oral: 16, Other triptans: 12, Other analgesics: 23, Low-flow oxygen (<4 L/min): 4, No documented previous cluster headache medications: 31 (n=28) **Patients taking preventative medcations:**4 **Group 1: 100% Oxygen** **N:** 40 **Age (mean):** NR **Drop outs:** 2 **Group 2: Air** **N:** 36 **Age (mean):** NR **Drop outs:** 1				cards labelled “A” or “B” ITT analysis of 57 patients with episodic cluster headache and 19 with chronic cluster headache Multilevel multivariate analysis used to account for the fact that attacks not strictly independent.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Ekbom et al, 1991[253] **Study design:** RCT crossover **Comparison:** Sumatriptan 6mg vs placebo **Setting:** 12 hospital neurology departments in Denmark, France, Poland and Sweden **Duration of follow-up:** 2 subsequent attacks	**Patient group:** Cluster headache patients 18-65 years **Inclusion criteria:** History of episodic or chronic cluster headache according to IHS. And if untreated attacks typically lasted 45 minutes or more. **Exclusion criteria:** Regular use of narcotic analgesic drugs, currently taking ergotamine or had taken it within the previous year, pregnant or nursing women. Women not using adequate contraception and patients with any of the following: history suggestive of ischaemic heart disease, peripheral vascular disease, severe hypertension, mild to moderate hypertension being treated with a calcium antagonist or b-adrenergic antagonist drug, epilepsy, renal, hepatic or heart disease or serious psychiatric illness. **All patients** **N:** 49 **Age (mean):** 42+/-10 **Drop outs:** 10 **Sex M/F:** 31/8 **Headache type:** Chronic 17, Episodic 22 **Frequency of attacks during cluster**	**Group 1 - Sumatriptan 6mg (s.c)** **Group 2 - Placebo** All patients hospitalised once they entered a cluster period. First injection usually given after 1 or 2 days of hospitalisation. One group received sumatriptan for first attack and placebo for second, the other group received placebo for first attack and sumatriptan for second. Each injection administered s.c. by a physician or nurse and had to be given within 10 minutes of the onset of an attack. Minimal interval between study injections was 24 hours, the longest interval was 9 days. If a patient had an attack in this 24 hour period they were permitted to use medication that did not contain ergotamine. If medication was administered then patients had to wait another 6 hours after simple analgesic, or 24 hours after taking opiates before second study injection could be administered.	**Headache response:** Relief of pain from moderate, severe or very severe to mild or no pain (15 minutes) For group 2 only % stated in paper. **Adverse Events** Denominator= number of attacks. Figures given in % in paper.	**Group1:** 29/39 (74%) **Group 2:** 10/39 (26%) **95% CI:** NR **p value:** <0.001 **Group1:** 17/49 (35%) **Group 2:** 12/47 (26%) **p value:** NR	**Funding:** NR **Limitations:** Denominator used in headache response- number of patients (after dropouts) or number of attacks?) **Additional outcomes:** Efficacy of pain relief 5 and 10 minutes after injection. Need for rescue medication. Pain free at 30 minutes. Decrease in functional disability. Patients response at 5, 10, 15, 20, 25, 30, 60, 90 and 120 minutes. **Notes:** Assessed and randomly assigned to one of two groups. Rescue medication allowed: 100% oxygen (7L/min) allowed at 5 minutes, simple analgesics allowed after 120 minutes. Using oxygen at 15 minutes:

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	period: 1 every other day: 4-1 per day: 8, 2-8 per day: 27 **Usual duration of headache without medication**: 45-60 mins: 18, 60-90 min: 11, 90-180 min: 9 **Usual response of headache to oxygen:** response: 10, no response: 6, no experience: 23 **Group 1** **N:** 49 **Age (mean):** NR **Drop outs:** NR **Group 2** **N:** 49 **Age (mean):** NR **Drop outs:** NR				Group 1: 13% Group 2: 49%

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Ekbom et al, 1993[252] **Study design:** RCT crossover **Comparison:** Triptan vs Placebo **Setting:** Multicentre **Duration of follow-up:** 2 attacks	**Patient group:** Cluster headache patients 18-65 years. **Inclusion criteria**: History of episodic or chronic cluster headache meeting criteria of IHS, typical duration of 45 minutes or more when untreated. Patients who had not previously received sumatriptan. **Exclusion criteria:** Abused or regularly used narcotic analgesic drugs, currently or within the last year abusing ergotamine, pregnant or nursing. Women not using adequate contraception. Any of the following: history suggestive of ischaemic heart disease, peripheral vascular disease, severe hypertension, mild to moderate hypertension being treated with a calcium antagonist or b-adrenergic antagonist, epilepsy, renal, hepatic or heart disease or serious psychiatric illness. **All patients*** **N:** 157, **M/F**: 116/ 18 **Age (mean):** 41 **Drop outs:** 23 **Headache type:** Episodic 97,	**Group 1 Sumatriptan 6mg (s.c)** **Group 2 Sumatriptan 12mg** **Group 3 Placebo** All patients hospitalised for the study. Following clinical assessment the patients were assigned to one of 6 treatment sequence groups. Each patient received two of the three possible study treatments. Patients received s.c. injection of one of the study drugs within 10 minutes of onset of attack of at least moderate severity. Interval of at least 18 hours between treatment of attacks with study drugs. Second attack treated with second assigned study drug in sequence.	**Headache response** (headache relief at 15 minutes) From moderate, sever or very sever to mild or no pain Values are number of attacks (figures calculated from %)	**Group1:** 69/92 (75%) **Group 2:** 70/88 (80%) **Group 3:** 30/88 (35%)	**Funding:** Not stated **Limitations:** 21 patients received only 1 treatment. *patient demographics based on 134 included in efficacy analysis (all patients who treated 2 headaches). **Additional outcomes:** Global response to medication. Functional disability. **Notes:** Rescue medications: 100% oxygen (7L/min for 15 min) administered if no relief after 15 minutes, simple analgesic drugs allowed after 120 minutes for patients who required further medication. Randomisation generated by computer in blocks of 6; each block contained each of the 6 treatment sequences in random order. Patients were enrolled and assigned sequence, in ascending sequential order of patient number at each centre.
			Adverse events Safety data based on different number of attacks than efficacy data (figures calculated from %)	**Group1:** 34/101 (33.6%) **Group 2:** 42/94 (44.7%) **Group 3:** 15/96 (15.6%)	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Chronic 37 **Frequency of attacks during cluster period:** 1 every other day 15, 1 per day 39, 2-8 per day 77, >8 per day 3 **Usual response of headache to oxygen:** response 32, no response 20, no experience 82				

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Fogan, 1985[275] **Study design:** RCT, crossover **Comparison:** Compressed room air vs 100% oxygen **Setting:** Department of neurology, UCLA, USA **Duration of follow-up:** 12 attacks (6 attacks to be treated with each intervention)	**Patient group:** Male cluster headache patients. **Inclusion criteria:** Males suffering from cluster headaches, aged between 20 and 50. **Exclusion criteria:** NR **All patients** **N:** 19 **Age (mean):** NR **Drop outs:** 8 **Group 1** **N:** 16 **Age (mean):** NR **Drop outs:** 4 **Group 2** **N:** 14 **Age (mean):** NR **Drop outs:** 2	**Group 1 100% oxygen** **Group 2 compressed room air** All patients instructed to breathe at a normal respiratory rate via a non rebreathing mask at a flow of 6 L/min, for up to 15 minutes. If the headache continued beyond that time he was to switch off the cylinder, and was allowed to take a short acting analgesic. Treatments crossed over after 6 individual cluster headaches were treated. Patients instructed to complete a questionnaire for each headache treated concerning: date, time, time first breathed from the cylinder, time first noted any effect on the intensity of the pain, and time the gas flow stopped, quality of headache relief, evaluation of pain relief.	**Reduction in pain at 30 minutes** (Pain relief scores at 15 minutes (mean+/-SE)) 0= no relief 1= slight relief 2=substantial relief 3= complete relief	**Group1:** 1.93 +/-0.22 **Group 2**: 0.77+/-0.23 **p value:** NR Maximum likelihood F ratio calculated for this study. Statistically significant difference between relief scores of the air and oxygen treatments ($p<0.01$, $F=11.50$, $df=1$) SE paired= 0.91 Ln RR paired= 1.79	**Funding:** NR **Limitations:** Validation of diary: used a different pain relief scale. Patients all male 11/19 patients evaluated both gases **Additional outcomes:** n/a **Notes:** Physician and patient blinded. Adequate allocation concealment. Contents of cylinder only known to the inhalation department.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Kudrow, 1981[459] **Study design:** RCT crossover **Comparison:** Ergotamine tartrate (sublingual) Vs Oxygen **Setting:** California medical clinic for headache **Duration of follow-up:** NR	**Patient group:** NR "50 patients" **Inclusion criteria:** Not stated explicitly. Chronic or episodic cluster headache **Exclusion criteria:** NR **All patients** **N:** 50 **Age (mean):** 44 **Drop outs:** NR **Group 1** **N:** 25 **Age (mean):** 42 **Drop outs:** NR **Sex M/F**:22/3 **Cluster headache type**: Episodic: 16, Chronic: 9 **Group 2** **N:** 25 **Age (mean):** 46 **Drop outs**: NR **Sex M/F:** 20/5 **Cluster headache type:** Episodic: 20, Chronic: 5	**Group 1 100% Oxygen.** At onset of attack instructed to breathe oxygen at a rate of 7L/ min for 15 minutes whilst sitting upright in a chair. To treat a total of 10 attacks, noted the time of onset of oxygen inhalation, and the time of complete or almost complete relief of headache **Group 2 Sublingual ergotamine tartrate.** Allowed every 15 minutes for a maximum of 3 tablets if necessary. Record keeping similar to group 1. At the end of the 10 attack period patients from both groups reported to the clinic where they crossed over to the other treatment Prophylactic medication withheld from both groups.	Complete or almost complete cessation of head pain within 15 minutes for at least 7/10* attacks. *table heading states 8/10 attacks-inconsistency.	**Group1:** 41/50 (85%) **Group 2:** 35/50 (70%) **p value:** NR	**Funding:** NR **Limitations:** Doesn't state length of crossover period (first period was 10 attacks) Patients could use prophylactic medication throughout trial. Randomisation, allocation concealment and blinding NR **Additional outcomes:** Comparative success of oxygen and ergotamine treatment in chronic and episodic subgroups: Significant difference between episodic oxygen treated and chronic ergotamine treated p<0.01

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Rapoport et al, 2007[654] **Study design:** RCT crossover **Comparison:** Triptan vs Placebo **Setting:** 4 headache centres in the US **Duration of follow-up:** 3 attacks	**Patient group:** Patients with cluster headache aged 18-65 years. **Inclusion criteria:** Diagnosis of episodic or chronic cluster headache meeting criteria of IHS. Cluster attacks with minimum duration of 45 minutes untreated. Patients using ergotamine compounds or triptans for the acute treatment of cluster headachewere allowed into the trial if they agreed to discontinue these before randomisation. **Exclusion criteria:** Contraindications to the use of triptans, patients using ergotamine derivatives as a preventative therapy, patients in use of methysergide, and patients with major depression or other serious condition that would preclude entry to study. **All patients** **N:** 78 (52 treated) **Age (mean):** 45.2+/-11.2 **Drop outs:** 17 **M/F:** 31/14 **Headache type:** Episodic 37, Chronic 15	**Group 1 Zolmitriptan 5mg (nasal)** **Group 2 Zolmitriptan 10mg** **Group 3 Placebo** Each of the three treated attacks had to be separated from each other by at least 24 hours. Immediately after assessing the pain of an attack (using a questionnaire with a 5 point scale), subjects were instructed to apply one spray of the study medication in each nostril when the headache reached at least moderate severity. Assessments made at at 5, 10, 20, 15, 30, 60 minutes post-dose. 3 attack crossover (each treatment used once).	**Headache response** at 30 minutes number of attacks (ITT- number who treated at least 1 attack) (reduction from moderate, severe or very severe to mild or no pain) Events calculated from % given in paper	**Group1:** 26/52 (50%) **Group 2:** 33/52 (63.3%) **Group 3:** 16/52 (30%)	**Funding:** Study medication and placebo were supplied by AstraZeneca. **Limitations:** Allocation concealment unclear. **Additional outcomes:** Pain free at 15 minutes. **Notes:** Escape medication was allowed at 60 minutes post-dose and included oxygen, lidocaine, or an analgesic (not a triptan or ergotamine derivative). Use of rescue medication: (based on number of attacks treated) Group 1: 16/52 (30%) Group 2: 15/52 (28%) Group 3: 20/52(38%) Randomly assigned to treatment sequence in balanced blocks with equally probability for each treatment sequence. Randomisation generated by person blinded to all other procedures using random number generator program.
			Adverse events Number of patients with adverse events calculated from % given in paper (based on ITT population of 52)	**Group1:** 21 events, (13/52 patients, 25%) **Group 2:** 30 events (17/52 patients, 33%) **Group 3:** 12 events (8/52 patients, 16%)	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Sicuteri et al, 1984[722] **Study design:** RCT crossover **Comparison:** Ergot vs Placebo **Setting:** Inpatient **Duration of follow-up:** 3 headache attacks	**Patient group:** Hospitalised males with cluster headache **Inclusion criteria:** Established diagnosis of cluster headache. **Exclusion criteria: NR** **<u>All patients</u>** **N:** 8 **Age (mean):** 36.2 **Drop outs:** 0	**Group 1**Somatostatin (infusion):(Treatment B) 1 mL saline i.m; 25 ug somatostatin in 2.5 mL saline/ min for 20 mins **Group 2** Ergotamine (i.m): Treatment C) 250 ug ergotamine tartrate i.m; 2.5 mL saline/min for 20 min **Group 3** Placebo: (Treatment A) 1mL saline i.m; 2.5 mL saline/ min for 20 min) Each patient treated 3 times with each treatment. The order of treatment was random. Patients administered treatment 10 minutes after the onset of the painful attack an i.m. injection was administered and a 20 minute infusion was started.	**Time to freedom from pain** (Minutes, mean). Mean of 3 administrations of each drug to each patient	**Group1:** 65.6 **Group 2:** 55.8 **Group 3:** 93.3	**Funding:** Pain research commission of the Austrian academy of sciences, Austrian scientific research fund, Italian National research council. **Limitations:** Randomisation and allocation concealment NR **Additional outcomes:** Maximal pain intensity (VAS). Pain area. **Notes:** Double blind. Double dummy technique used.

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: van Vliet et al, 2003[818] **Study design:** RCT crossover **Comparison:** Triptan vs Placebo **Setting:** US, UK, Netherlands **Duration of follow-up:** 2 attacks	**Patient group**: Cluster headache sufferers aged 18 to 65 years **Inclusion criteria:** Established diagnosis of cluster headache according to IHS criteria. Cluster attacks with minimum duration of 45 minutes untreated. **Exclusion criteria:** Patients with 2 or more of the risk factors for cardiovascular disease, patients using ergotamine or analgesics regularly, or patients who were on prophylaxis with lithium or methysergide. Women who were pregnant or breastfeeding. ENT disorder that would preclude use of intranasal sumatriptan. Serious adverse event when using triptans in the past. **All patients** **N:** 118 **Age (mean):** 43+/-11 **Drop outs:** 33 **M/F:** 97/21 **Headache type:** Episodic 89, Chronic 29 **History of cluster headache (yrs):** 13+/-9 **Average duration of bout, wk:** 8+/-5 **Previous use of sumatriptan:** oral 33, injection 53, nasal 6	**Group 1 Sumatriptan 20mg (nasal spray)** **Group 2 Placebo** Patients instructed to treat 2 attacks, at least 24 hours apart with either sumatriptan or placebo in a randomised order. Grade attacks on 5 point scale, apply study drug in contralateral nostril when headache graded as at least moderate in severity. Subsequent assessments at 5, 10, 15, 30 minutes.	**Headache response** (at 30 minutes) Reduction in headache from moderate, severe, or very severe to mild or nil	**Group1:** 44/77 (57%) **Group 2:** 20/77 (26) p value: 0.002 *see limitations	**Funding:** Glaxosmithkline **Limitations:** Randomisation and allocation concealment NR Confusion between number of attacks and no of patients in paper. Values given as no. of patients with headache response/ no. of attacks. **Additional outcomes:** Associated symptoms. Meaningful relief. **Notes:** Escape medication was allowed at 30 minutes post dose, usually oxygen or an analgesic, but not a triptan or ergotamine derivative.
			Time to freedom from pain (stated as time to initial relief in paper) (Minutes)	**Group1:** 12.4+/-6 **Group 2:** 17.6+/-12 **p value:** 0.01	
			Adverse events:	No serious adverse events. Two patients using sumatriptan reported chest pressure after using the spray. Most frequently reported adverse event was bitter taste (21 % sumatriptan and 1% of placebo)	

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

E.2.5 Prophylactic pharmacological treatment of tension type headache

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Pfaffenrath et al, 1994[626] **Study design:** RCT **Comparison:** Antidepressant vs Placebo **Setting:** NR (7 study centres in 3 countries (4 in Germany, 1 in Austria and 2 in Switzerland) **Duration of follow-up:** 24 weeks	**Patient group:** Adults meeting IHS criteria for chronic tension type headache. **Inclusion criteria:** Female and male patients aged 18–65 years; IHS criteria for tension type headache; headache present on more than 15 days/month for at least 6 months. **Exclusion criteria:** Accompanying migraine; Participation in a study in previous three months; Suspected poor compliance; Pregnant/breastfeeding women; Drug abuse and psychiatric illness; Patients taking simple analgesics, mixed analgesics, ergotamine tartrate or dihydroergotamine tartrate, acetylsalicylic acid and/or paracetamol or codeine on more than 10 days/month, other antidepressants, neuroleptics, tranquilisers, established headache prophylactics (β blockers or calcium channel blockers) less than 3 months before baseline phase, drugs for treatment of bipolar affective disorders (lithium and carbamazepine); Use of medications leading to headache as side effect; Contraindications for tricyclic antidepressants; Impaired renal function; Hepatic failure and haematological disorders. MAO inhibitors had to be discontinued within 4 weeks prior to the beginning of study. All patients on prophylactic treatment for TTH required a wash-out phase of 2 weeks before the beginning of baseline phase. **All patients** **N:** 211 (available for evaluation); 197 (received study treatments 110 F, 87 M) **Age (mean):** NR **Drop outs:** 14 (in baseline period due to non-attendance,	**Group 1 Amitriptyline** 25 mg tablets **Group 2 Placebo** **Both groups**: 4 week baseline period (no treatment medication given), 12 week treatment period and follow up period of 8 weeks. 1 tablet in weeks 5-8 2 tablets in weeks 9-12 2 or 3 tablets in weeks 13-16. Doses were increased only if the previous lower dose had been well tolerated. Patients kept a daily headache diary throughout the study to record the frequency and duration of headache.	**Change in patient-reported headache days** (Final values mean ± SD in last 4 weeks of therapy)	**Group1:** Baseline 16±8 Final 15±10 **Group 2:** Baseline 15±8 Final 16±9	**Funding:** NR **Limitations:** Unclear randomisation, allocation concealment and blinding. Patients with suspected poor compliance excluded but no reason given. **Additional outcomes:** Change in mean duration of headache per day. Response rate defined as at least 50% reduction of the product of duration x frequency of headache and at least 50% reduction in headache intensity after 16 weeks as compared to baseline. **Previous medication tried:** NR **Notes:**
			Change in patient-reported headache intensity VAS 0=no pain to 8=unbearable pain (Final values mean ± SD in last 4 weeks of therapy)	**Group1:** Baseline 3.7±1.9 Final 2.8±2.0 **Group 2:** Baseline 3.4±1.5 Final 1.7±2.0	
			Incidence of adverse events % reporting moderate to severe adverse events	**Group1:** 73.1% (48/67) **Group 2:** 57.8% (37/64)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	language difficulties or accompanying migraine) **Group 1 Amitryptiline** **N:** 67 (ITT) **Age (mean):** NR **Drop outs:** 18/67 (26.9%)[19.4% poor compliance, 7.5% lack of efficacy, 17.9% side effects] **Group 2 Placebo** **N:** 64 (ITT) **Age (mean):** NR **Drop outs:** 13/64 (20.3%) [17.2% poor compliance, 12.5% lack of efficacy, 10.9% side effects]				Three armed study looking at amitriptylinoxide, amitriptyline and placebo. Amitriptylinoxide data not reported here.

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

E.2.6 Migraine

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

E.2.7 Prophylactic pharmacological treatment of menstrual migraine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Brandes et al, 2009[104] **Study design:** RCT **Comparison:** Triptan vs Placebo **Setting:** NR (55 sites in Europe and North America) **Duration of follow-up:** 4 months	**Patient group:** Women ≥ 15 years of age with difficult to treat menstrual migraine (MM)*. **Inclusion criteria:** Women aged ≥ 15 years (in USA, France, Sweden and Finland) or ≥ 18 years (in Canada, Norway, Germany , Italy and the UK); had menses occurring at regular and predictable intervals; women using oral contraceptive pills were required to be on a stable regimen maintained for 2 months before screening; documented history of MM for ≥ 12 months and had MM in at least two of their previous three cycles; presence of difficult to treat MM defined as having previous exposure to non-triptan (acute and/or prophylactic) therapy for the treatment of MM and an inadequate response to triptan therapy (determined using Migraine Medication History Questionnaire) for the acute treatment of MM over a minimum of two menstrual cycles. *MM defined as migraine experienced with menstruation as well as at other times of the cycle (menstrually-related migraine), or pure MM in which migraine occurred only in association with menstruation on or between day -2 to day +3 of cycle, with day 1 counting as first day of menses. **Exclusion criteria:** Pregnant or breastfeeding women; had more than three migraines per month that were not MM attacks or ≥ 15 headache days per month; a history of myocardial infarction, heart disease, coronary vasospasm, peripheral vascular disease, uncontrolled hypertension or cerebrovascular disease (including basilar or hemiplegic migraine); severe renal or hepatic dysfunction or any serious illness that would interfere	**Group 1** - Frovatriptan 2.5 mg tablets once daily **Group 2 -** Frovatriptan 2.5 mg tablets twice daily **Group 3 -** Placebo (tablets) Patients randomised to treat three perimenstrual periods (PMP) over a 4 month period if they experienced MM in one of two single-blind run-in phases of two consecutive PMPs of 6 days which were treated with placebo. Medication commenced 2 days before anticipated onset of an MM and continued for 6 days. Both frovatriptan groups received loading dose of 5mg frovatriptan on day 1 of treatment; Group 2 received 5mg both in morning and evening and Group 1 received 5mg in the morning and placebo in the evening.	**Change in headache days** Total number of days with headache pain over a standardized 28-day cycle	**Group 1:** -0.4; n=149 **Group 2**: -0.5; n=101 **Group 3:** +0.5; n=160 **P value:** 2vs3, p=0.05	**Funding:** Vernalis Development Ltd, and Endo Pharmaceuticals Inc. **Limitations:** Frovatriptan also used as a rescue medication (may limit sensitivity of the study). Some patients inaccurately anticipated MM onset. 35% of patients in placebo group, 30% in the frovatriptan once daily group and 24% in the twice daily group were using oestrogen containing contraceptives. **Additional outcomes:** Time to first migraine. Incidence of intercurrent migraine. Ratio of severe to mild attacks. Ratio of severe vs mild functional impairment. Previous medication tried: Non triptan therapy (medications not
			Use of acute pharmacological treatment % of patients using rescue medication	**Group 1:** 67% (99/149) **Group 2:** 68% (68/101) **Group 3:** 86% (137/160)	
			Incidence of serious adverse events: Reported as severe adverse events	**Group 1:** NR **Group 2:** NR **Group 3:** 2 (inguinal hernia, prolonged chest discomfort for 8 days - Patient had taken frovatriptan as rescue medication 1 day before chest pain occurred)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	with study participation; or received any investigational medications (within 30 days or 5 half-lives);had a history of allergy to triptans; had participated in a previous trial of frovatriptan for the prevention of MM. **All patients** **N:** 587 (screened); 427 (randomised) **Average MM attacks over previous three cycles:** 2.9±0.4 **Group 1 Frovatriptan 2.5 mg once daily** **N:** 155 (randomised); 149 (mITT) **Age (mean, SD):** 37.8±7.9 **Drop outs:** 31(20%) **Group 2 Frovatriptan 2.5 mg twice daily** **N:** 104 (randomised); 101 (mITT) **Age (mean, SD):** 38.9±7.6 **Drop outs:** 24 (23%) **Group 3 Placebo** **N:** 168 (randomised); 160 (mITT) **Age (mean, SD):** 37.9±7.2 **Drop outs:** 23 (14%)	Additional open label frovatriptan 2.5mg tablets were provided (nine per cycle in a separate non-blinded container) for treatment of breakthrough MM and for non-menstrual (intercurrent) migraine.			specified). Triptans previously used: Almotriptan (19%), Eletriptan (24%), Frovatriptan (11%), Naratriptan(19%), Rizatriptan (36%), Sumatriptan (52%), Zolmitriptan (35%). **Notes:** Study was conducted among refractory patients and may not be generalisable to all. Includes pure menstrual and menstrually related migraine. The modified ITT population included all patients who received at least one dose of study medication and provided data for the primary efficacy end-point (number of headache free PMPs out of three treated PMPs).

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, mITT= modified Intention to treat analysis, PMP=Perimenstrual period, MM=Menstrual migraine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Newman et al, 2001[587] **Study design:** RCT **Comparison:** Triptan vs Placebo **Setting:** Outpatient clinics (18 study sites in USA) **Duration of follow-up:** 4 months	**Patient group:** Adult females with history of migraine with/without aura. **Inclusion criteria:** Women > 18 years of age; at least 6 month history of migraine with/without aura as defined by IHS criteria; had regular menstrual cycles and could predict within 1 to 2 days the onset of menstrual flow; had at least 1 migraine attack during the last peri-menstrual period (PMP)* at a predictable time relative to the onset of menstrual flow. *PMP defines as beginning 2 days before the onset of menses and ending 4 days after the onset of menstrual flow (6 days in total). **Exclusion criteria:** 15 days or more of tension type headache or more than 6 migraines per month during either of the two months before screening; uncontrolled hypertension (diastolic blood pressure ≥95mmHg or systolic blood pressure≥160 mmHg); confirmed or suspected ischaemic heart disease, Prinzmetal angina, Raynaud syndrome; peripheral vascular, cardiovascular, or cerebrovascular disease, cardiac arrhythmias requiring medication; Basilar or hemiplegic migraine or evidence or history of abuse of alcohol or other drugs including ergotamine in the past year; history of epilepsy; contraindication to naratriptan; pregnant or breastfeeding, sexually active but not using contraception. **All patients** **N:** 372 (screened), 220 (enrolled), 206 (ITT), 171	**Group 1 - Naratriptan 2.5 mg twice daily orally** **Group 2 - Naratriptan 1 mg twice daily orally** **Group 3 - Placebo tablets twice daily orally** Baseline phase: Patients documented their headaches daily through the end of their next PMP in a diary. 2nd visit: Patients who documented a menstrually associated migraine (MAM) in baseline phase were randomised and given study medication for one PMP. Instructed to begin treatment 2 days prior to expected onset of MAM and continue for a total of 5 days. MAM was defined as migraine occurring within the perimenstrual period. Instructed not to use serotonin agonists or medications containing	**Change in patient reported headache intensity** Peak headache severity; on a 4-point scale :0=no pain to 3=severe pain; Reported for breakthrough MAMs in treated PMPs (Baseline and final values, mean) **Headache specific QOL** Migraine Specific Questionnaire **Incidence of serious adverse events**	**Group 1**: n=70 Baseline PMP: 2.3 Mean over 4 treated PMPs†: 2.3 **Group 2:** n=70 Baseline PMP: 2.3 Mean over 4 treated PMPs†: 2.1 **Group 3:** n=66 Baseline PMP: 2.2 Mean over 4 treated PMPs†: 2.2 No significant difference between groups **Group 1:** 0 n=71 **Group 2:** 0 n=71 **Group 3:** 0 n=68	**Funding:** Glaxo Wellcome Inc. **Limitations:** Unclear randomisation and allocation concealment. Difference in baseline characteristics. Difference in proportion of patients using concomitant long term prophylactic medication. Concomitant use of oral contraceptives 39% in Group 3, 35.7% in Group 2 and 38.5% in Group 1. Unclear if attacks of migraine occurred with aura. **Additional outcomes:** Number of MAMs that occurred over 4 PMPs. Number of MAM days over four PMPs. Total hours of migraine pain/symptoms per attack. **Previous medication tried:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	(completed study) **Drop outs**: 39 **Group 1Naratriptan 2.5 mg** **N:** 70 **Age (mean):** 36.3 **Drop outs:** 16 **Group 2 Naratriptan 1 mg** **N:** 70 **Age (mean):** 38.0 **Drop outs:** 10 **Group 3 Placebo** **N:** 66 **Age (mean):** 36.4 **Drop outs:** 13	ergotamine or ergot type medications 24 hours before or after using study medication 3rd visit: 1 to 7 days after treatment of first PMP; study medication given for next three PMPs; instructed to come to clinic after treatment of fourth PMP.			Chronic prophylactic medications (not specified) remained unchanged throughout study **Notes:** †Adjusted by the number of peri-menstrual days at risk 96 days per pmp) and standardised to four PMPs . Nb. Patients not diagnosed with menstrual or menstrually related migraine.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, MAM= Menstrually associated migraine, PMP= Peri-menstrual period, IHS=International Headache Society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Tuchman et al, 2008[807] **Study design:** RCT **Comparison:** Triptan vs Placebo **Setting:** NR (27 sites in the US) **Duration of follow-up:** 3 months	**Patient group:** Adult females with menstrual migraine (MM)* **Inclusion criteria:** Women aged ≥18 years who had regular menstrual periods; established diagnosis of menstrual migraine headache according to the IHS criteria; migraine attacks occurring during the defined time window in at least 75% of previous menstrual cycles; at least three menstrual migraine headaches of moderate or severe intensity within the previous three months; a history of 15 or fewer days of non-migraine headache per month; any preventative treatment of migraine was to be discontinued prior to study inclusion and randomisation, with a washout interval of at least five half lives of the longest acting agent. *MM defined as occurring exclusively within 2 days before the expected onset of menses through to the end of menses, but not at other times of the menstrual cycle. **Exclusion criteria:** Any medical or psychiatric condition that any interfere with data collection; a history of symptoms or of significant risk factors for cardiovascular disease; uncontrolled hypertension; a history of basilar, ophthalmoplegic or hemiplegic migraine; any serious neurological condition associated with headache; use of monoamine oxidase A inhibitors or treatment with SSRIs; pregnancy and lactation; history of poor compliance with treatment regimens. **All patients** **N:** 253 (randomised); 217 (completed study); 244 (ITT population, provided post treatment efficacy data) **Drop outs:** 36 **Group 1 Zolmitriptan 2.5 mg 3x/day** **N:** 85(randomised); 83 (ITT)	**Group 1 Zolmitriptan 2.5 mg 3x/day** **Group 2 Zolmitriptan 2.5 mg 2x/day and placebo tablet once daily** **Group 3 Placebo 3x/day** Patients were instructed to treat three consecutive menstrual cycles, starting treatment 2 days prior to expected onset of menses and continuing through to 5 days after the onset of menses (i.e. 7 days treatment in total) Use of escape medication was to be recorded in diary cards. It could be taken any time after the onset of breakthrough migraine	**Responder rate** % of patients achieving ≥50% reduction in frequency of MM attacks over three consecutive cycles	**Group 1:** 58.6% (49/83) **Group 2:** 54.7% (44/80) **Group 3:** 37.8% (31/81) **P values:** 1vs 3, p=0.0007 2vs 3, p=0.002	**Funding:** AstraZeneca, **Limitations:** Unclear allocation concealment and blinding of investigators. Study assumes that patients would not experience migraine attacks between menses and overlooks the fact that preventative therapy could delay attacks until after the treatment period. Some patients experienced aura with attacks (which does not fit IHS description of pure menstrual migraine). **Previous medication tried**: No patient was receiving preventative treatment for migraine prior to study inclusion and randomisation. **Notes:** Study was conducted in two phases; first phase evaluated the efficacy of
			Use of acute pharmacological treatment % of breakthrough attacks requiring use of escape medication	**Group 1:** 61.6% (77/125) **Group 2:** 60.7% (102/168) **Group 3:** 74.4% (154/207) **P values:** 1vs 3, p=0.0004 2vs 3, p=0.0055	
			Incidence of serious adverse events	**Group 1:** 2 **Group 2:** 2 **Group 3:** 1	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean, SD): 39.4 , 7.0 **Drop outs:** 13 **Group 2 Zolmitriptan 2.5 mg 2x/day** **N:** 83 (randomised); 80 (ITT) **Age (mean):** 38.1, 6.3 **Drop outs:** 10 **Group 3 Placebo 3x/day** **N:** 85 (randomised); 81 (ITT) **Age (mean):** 39.2, 6.3 **Drop outs:** 14				zolmitriptan in the treatment of acute menstrual migraine. Findings reported here are of the second phase. None of the serious adverse events were considered treatment related. NB. Pure menstrual migraine only

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

E.2.8 Prophylactic pharmacological treatment of cluster headache

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

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

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

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

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

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

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

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

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

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

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

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

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

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

E.3 Non-pharmacological treatment of primary headaches

E.3.1 Prophylactic non-pharmacological management of primary headaches with acupuncture

Tension type headache

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Ebneshahidi et al, 2005[244] **Study design:** RCT **Comparison:** Laser acupuncture vs sham laser **Setting:** 3 outpatient departments **Duration of follow-up:** 3 months	**Patient group:** Adults with chronic tension type headache **Inclusion criteria:** Chronic tension type headache for which the subject had not received any treatment in the previous two weeks. **Exclusion criteria:** Other causes of chronic headache. Patients with papilloedema, pulsating headaches, asymmetrical papillary reflexes, neurological deficits, systemic disorders (hypertension or metabolic disorders) or contraindications to treatment (anticoagulation therapy, other simultaneous treatment, localised skin infection, fear of acupuncture). **All patients:** **N:** 50 **M/F:** 40/10 **Drop outs**: 0 **Group 1 – Laser acupuncture** **N:** 25 **Age (mean):** 33 (25-52)	**Group 1 Laser acupuncture** Low energy laser radiation treatment from Endolaser 476. Gallium-Arsenide-Aluminium (Ga-As-Al). Output wave length of 830nm, max output intensity of 39mW/cm2 For each point: intensity 1.3J (~13 J/cm^2), output 100%, continuous mode, using vertical contact with pressure and a duration of 43 seconds. The points for exposure to laser radiation were selected by reference to authoritative sources on acupuncture. These included four points, two local and two distal: GB14, GB20, L14 and LU7. Treated bilaterally. **Group 2 Placebo laser acupuncture** Same intervention as above except that the power output was set to zero during the treatment. Both received three times per week for 10 sessions	**Change in patient-reported headache days** (Change from baseline – Median (IQR) at 3 months) **Change in patient-reported headache intensity** (VAS 0-10 Change from baseline – Median (IQR) at 3 months) **Incidence of serious adverse events (%)**	**Group1:** -8 (21.5) **Group 2:** 0 (0.0) **p value**: <0.001 **Group1:** -2 (6.3) **Group 2:** 0 (0.0) **p value:** <0.001 No AEs reported	**Funding:** NR **Limitations:** Patients selected consecutively by neurologists according to inclusion/exclusion criteria. States randomised, but no more details. Observer not blinded. Different methods of data collection used for baseline data vs follow-up (investigator assessment vs diaries) – possible measurement bias. **Additional outcomes:** Duration of attack (hours) All reported at 1,2 and 3 months **Notes:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Migraine intensity (VAS): 10 (3.0) **Headache days (per month, median (IQR)):** 20 (15.0) **Group 2 – Placebo acupuncture** **N:** 25 **Age (mean):** 38.6 (26-54) P=0.04 cf Gp1 **Migraine intensity (VAS):** 10 (1.0) **Headache days (per month, median (IQR)):** **18** (15.0)	No concomitant analgesics allowed			Patients were naive to acupuncture Outcomes recorded in daily diaries. Powered for detecting 6 point difference in VAS.

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IQR=inter-quartile range

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Endres et al, 2007[259] **Study design:** RCT **Comparison:** Acupuncture vs sham **Setting:** 122 family physician practices **Duration of follow-up:** 6 months	**Patient group**: Adults with IHS defined episodic or chronic tension type headache **Inclusion criteria:** Aged 18-65 with diagnosis of episodic or chronic tension type headache according to IHS criteria (in particular minimum frequency of 10 headache days per four weeks defined as a day on which headache lasts at least 4hr or when analgesics are taken for headache pain, in which case the headache pain could persist for less than four hours). **Exclusion criteria:** Duration of symptoms less than six months; >1 migraine headache day per four weeks; medication overuse headache or other secondary headache; other severe pain disorders; use of analgesics other than aspirin, paracetamol and NSAIDS; any change in pain medication during the previous 8 weeks; TTH prophylaxis during the previous 12 months; any acupuncture treatment during the previous 12 months; and prior use of acupuncture for headache.	**Group 1 Acupuncture** Consisted of fixed points used in all patients with additional points chosen individually by the physicians on the basis of traditional Chinese medicine diagnosis, including tongue diagnosis. Needles were inserted 2-30mm and manually stimulated to achieve De Qi. Neither electrical stimulation nor moxibustion were allowed. Patients were reassessed at each visit and chosen acupuncture points were modified if clinically indicated. **Group 2 Sham** Avoided all known verum points or meridians for needling; no points on the head could be used. Needles were inserted superficially (1-3mm) and were not stimulated, so as to avoid De Qi. **Both groups:** The number (10-25) and type of needles (sterile, single use needles, coated, 0.25-0.30mm thick, 25-40,, long) and number (10-15), length (30 min) and frequency (2/week) of treatment	**Patient-reported headache days** (baseline and final values per 4 weeks) N: Gp1 199, Gp2 192	**At 3 months** **Group1:** Baseline 15.6 (5.3) Final 6.8 (6.3) Group 2: Baseline 16.4 (6.1) Final 9.1 (8.0) **Between group difference**: 1.80 **95% CI:** 0.58;3.02 **p value**: 0.004	**Funding:** German public health insurance companies: AK, BKK, IKK, Bundesknappschaft, Bumdesverband de Landwirtschaftlichen Krankenkassen and Seekasse **Limitations:** Single blind (assessor and patient) A small number of patients in each group reported being unblinded by their physician, but only half of these correctly identified their allocation. Baseline differences between medication use. Study notes their different definition of responder rate may have affected results, therefore does a post-hoc analysis to calculate normal responder rate. **Additional outcomes:** Patient global assessment of therapy effectiveness (1-6 scale). Quality of acupuncture
			Patient-reported headache days (baseline and final values per 4 weeks) N: Gp1 204, Gp2 194	**At 6 months** **Group1:** Final 6 (6.2) **Group 2:** Final 8.4 (7.9) **Between group difference:** 1.94 **95% CI**: 0.69;3.18 **p value:** 0.002	
			Patient-reported headache intensity (Von Korff chronic pain grade scale (modified 3 month version) Mean (SD)/4 wks) N: Gp1 198, Gp2 191	**At 3 months** **Group1: Baseline 68.3 (12.1) Final 57.6 (17.2)** **Group 2:** Baseline 67.5 (12.5) Final 60.0 (16.3) **Between group difference:** 2.58 **95% CI:** -0.75;5.91 **p value:** 0.13	
			Patient-reported headache intensity (Von Korff chronic pain grade scale (modified 3 month version) Mean (SD)/4	**At 6 months** **Group1:** Final 53.5 (18.4) **Group 2:** Final 56.7 (19.6) **Between group difference: 3**.24 **95% CI**: -0.51;6.99	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients **N:** 413 randomised (4 to amitriptyline group) **Group 1 – Acupuncture** **N:** 209 (randomised) 208 (received treatment) **Age (mean):** 39.2 (11.4) 30-47 **M/F:** 46/163 (22 vs 78%) **Duration of TTH (yrs):** 11.2 (10.3) 4.1-15.4 **TTH days/4wks (median):** 14 (12-18) **TTH type:** 56% episodic 44% chronic **Drop outs:** 1 (refused) **Missing data:** 5 **Group 2 - Sham** **N:** 200 (randomised) 195 (received treatment)	sessions were the same. Investigators were instructed to treat patients in each group identically other than the placement of needles. Rules for point selection and Chinese diagnosis were established on the basis of international literature and a consensus process. All patients could receive an additional 5 sessions if they experienced a reduction in headache days per 28 days of at least 20% but no more than 50%. This was assessed in a telephone interview after 10 sessions. During the study patients were allowed to take only one of their pre-baseline oral headache analgesics. They were not allowed to change this analgesic.	wks) N: Gp1 204, Gp2 194	**p value:** 0.09	treatment. Patient blinding. Medication use as: none, 1, >1, >15days. **Notes:** Trial initially included an arm receiving treatment with amitriptyline, however poor early accrual was ascribed to patient unwillingness to receive antidepressant medication and independent data and safety monitoring committee recommended that this arm be dropped after one year (only 4 patients included). Most patients recruited through adverts in local newspapers and reports on radio and television. A minority spontaneously sought out a trial physician. Daily diaries kept to record outcomes as well as blinded telephone interviews.
	Age (mean): 38.9 (12.2) 29-48 **M/F:** 42/158 (21 vs 79%) **Duration of TTH (yrs):** 11.7 10.7) 3.1-18.3 **TTH days/4wks (median):** 14 (12-19) **TTH type:** 53% episodic 47% chronic **Drop outs**: (2 refused, 3 did not return)		**Responder rate** (50% reduction in headache days ICH criteria)	**At 3 months** **Group1:** 119/199 (60%) **Group 2:** 91/192 (47%) **Absolute risk difference: 12**% **95% CI** 3-22% **p value:** 0.014	
			Responder rate (50% reduction in headache days ICH criteria)	**At 6 months** **Group1: 135/204 (66%)** **Group 2:** 106/194 (55%) **Absolute risk difference:** 12% **95% CI:** 2-21% **p value:** 0.024	
			Responder rate (50% reduction in headache days † see notes)	**At 6 months** **Group1:** 68/209 (33%) **Group 2:** 53/200 (27%) **Absolute risk difference:** 6% **95% CI** -3-15% **p value:** 0.18	
			Quality of life **SF-12 physical component** (Baseline and Final values, mean(SD)) Gp1 n=199, Gp2=188	**At 3 months** **Group1: Baseline 39.6 (8.1) Final 46.8 (8.1)** **Group 2:** Baseline 41.8 (8.1) Final 46.5 (8.3) **Between group difference:** 1.06 **95% CI:** -0.45;2.57 **p value**: 0.17	
			Quality of life	**At 3 months**	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Missing data: 9		**SF-12 mental component** (Baseline and Final values mean (SD))	**Group 1:** Baseline 45.9 (10.3) Final 50 (9.1) **Group 2:** Baseline 46.1 (10.1) Final 50.2 (9) **Between group difference:** -0.10 **95% CI:** -1.65;1.46 **p value:** 0.90	† Responder was defined as >50% reduction in number of headache days/ 4 weeks, however if one of the following criteria applied the patients were characterised as non-response regardless of whether a reduction of >50% had been achieved: patient unblinding, excluded concomitant treatments, injections (except vaccinations insulin, heparin), wrong acupuncture treatment (, median number of needles more or fewer than the permitted 10-25 per session, treatment cessation or any change of analgesics.
			Quality of life **SF-12 physical component** (Baseline and Final values (mean (SD))	**At 6 months** **Group1:** Final 47.1 (8.1) **Group 2:** Final 46.5 (8.6) **Between group difference:** 1.38 **95% CI:** -0.17;2.92 **p value:** 0.08	
			Quality of life **SF-12 mental component** (Baseline and Final values, mean (SD))	**At 6 months** **Group 1:** Final 50.6 (8.4) **Group 2:** Final 50.8 (9.2) **Between group difference: 0**.05 **95% CI**: -1.48;1.58 **p value:** 0.95	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Karst et al, 2001[422] **Study design:** RCT **Comparison:** Acupuncture vs sham **Setting:** NR, assumed outpatients **Duration of follow-up:** 5 months post treatment (~6 months total)	**Patient group:** Adults with episodic or chronic tension type headache **Inclusion criteria:** Episodic or chronic tension type headache according to IHS classification. **Exclusion criteria:** Anticoagulation, predominantly operating factors (e.g. secondary gain, compensation, disability and psychosocial factors), rebound analgesic headache syndrome, symptomatic or other concomitant headache. Patients with past or present episodes of migraine. **All patients** N: 69 **Group 1 – Acupuncture** **N:** 34 **Age (mean):** 47.9 (13.8) **M/F:** 17/17 **Episodic / chronic:** 9/25 **Mean headache days/month:** 21.1 (10.2) **Analgesics/month:** 9.0 (11.1) **Drop outs:** NR **Group 2 - Sham** **N:** 35	**Group 1 Acupuncture** Seirin B-type needles no.8 (0.3x0.3mm) and no.3 (0.2x0.15mm) used **Group 2 Sham** The tip of the needle is blunt in order to cause a pricking sensation without actually puncturing the skin. The needle was inserted through a cube-shaped elastic foam to obscure the patients' vision on the insertion point. Both groups had two treatments per week for a total of 10 treatments. Needles inserted at acupoints GB20, LI4 and LR3 and depending on the symptoms at acupoints GB8, GB14, GB21, GB41, UB2, UB10, UB60, LU7, TW5, ST8, ST36, ST44, DU20 and Extra1. A maximum of 15 needles were inserted but treatment was usually carried out with not more than 6-10	**Patient-reported headache frequency** (Days per month, mean (SD)) **Patient-reported headache intensity** (Pain intensity, 0-10 VAS, mean of 4 weeks, mean (SD)) **Functional health status and health-related quality of life** (Nottingham Health Profile mean (SD)) **Functional health status and health-related quality of life** (Everyday Life Questionnaire, mean (SD)) **Functional health status and health-related quality of life**	**At 5months post** **Group1:** Baseline 21.1 (10.2) Final 16.7 (12.0) **Group 2:** Baseline 20.5 (10.3) Final 17.2 (12.0) **p value:** NS **6 weeks post (almost 3mo)** **Group1:** Baseline 4.6 (1.8) Final 4.0 (1.9) **Group 2:** Baseline 4.4 (1.3) Final 4.6 (1.7) **p value:** NS **6 weeks post (almost 3mo)** **Group1**: Baseline 29.9 (7.2) Final 34.1 (4.5) **Group 2:** Baseline 28.6 (5.7) Final 31.4 (5.4) **p value:** NS **6 weeks post (almost 3mo)** **Group1:** Baseline 114.7 (25) Final 132.1 (20.6) **Group 2:** Baseline 116.1 (23.8) Final 127.8 (23.7) **p value:** NS **6 weeks post (almost 3mo)** **Group1:** Baseline 5.6	**Funding:** NR **Limitations:** Randomisation unclear. Single blind (patients and assessors) Incomplete outcome reporting (QoL measures not reported at 5 months) **Additional outcomes:** Pain intensity (VAS) Site and duration of headache attack CGI (VAS) Freiburg Questionnaire of coping with illness Von Zerssen Depression Scale

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 48.2 (14.6) **M/F:** 14/21 **Episodic / chronic:** 12/22 **Mean headache days/month:** 20.5 (10.2) **Analgesics/month:** 15.6 (32.4) **Drop outs:** NR	needles. The needles were left in place for 30 min after insertion. Concomitant medication (including analgesics and rescue medications) allowed but had to be reported.	(Life Quality Scale (0-10) mean (SD))	(2.2) Final 6.6 (2.0) **Group 2:** Baseline 5.2 (2.6) Final 6.5 (2.2) **p value:** NS	
			Use of acute pharmacological treatment (no. analgesics per month, mean (SD))	**6 weeks post (almost 3mo)** **Group1:** Baseline 9.0 (11.1) Final 5.3 (9.0) **Group 2:** Baseline 15.6 (32.4) Final 26.0 (74.0) **p value:** NS	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, QoL=quality of life, NS=Not significant, IHS=International headache society, CGI=clinician global impression, VAS=visual analogue scale

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Melchart et al, 2005[553] **Study design:** RCT **Comparison:** Acupuncture vs sham **Setting:** 28 outpatient centres **Duration of follow-up:** 24 weeks	**Patient group:** Adults with episodic or chronic tension type headache **Inclusion criteria:** Diagnosis of episodic or chronic tension-type headache according to IHS criteria, at least 8 days with headache a month in the previous three months and in the baseline period, age 18-65 years, duration of symptoms at least 12 months, completed baseline headache diary and written informed consent. **Exclusion criteria:** Additional migraine headache, secondary headaches, start of headaches after age 50, use of analgesics on more than 10 days a month, prophylactic headache treatment with drugs during the previous four weeks, and any acupuncture treatment during the previous 12 months or at any time if done by the participating trial physician. **All patients** **N:** 296 randomised (26 excluded in 1 trial centre) **Drop outs:** 26 – one trial centre	**Group 1 - Acupuncture** Semi standardised – all treated at 'basic' points bilaterally unless explicit reasons for not doing so were given; additional points could be chosen individually. Physicians instructed to achieve 'de qi' if possible and to stimulate needles manually at least once during each session. Total number of needles was limited to 25 per session. **Group 2 - Minimal acupuncture (sham)** Physicians needled at least five out of 10 predefined distant non-acupuncture points bilaterally (at least 10 needles) and superficially using fine needles. Physicians avoided 'de qi' and manual stimulation of the needles. **Group 3 - Waiting list (not reported here)** Both groups: Consisted of 12 sessions of	**Patient-reported headache days** (baseline and final values, Mean (SD)) **N** Gp1=118, Gp2=57 at week 12 **N** Gp1=112, Gp2=55 at week 24	**Wk 9-12** **Group1: Baseline 17.5 (6.9)** Final 9.9 (8.7) **Group 2:** Baseline 17.7 (6.7), Final 10.8 (8.3) **Change difference between groups**=0.6 days, 95% CI: -1.5, 7.2 **P**<0.001 **Wk 21-24** **Group1:** Final 10.4 (8.6) **Group 2:** Final 11.2 (8.6)	**Funding:** Various social health insurance funds **Limitations:** Groups were not comparable at baseline for all outcomes – especially in previous use of acupuncture. Trial physicians couldn't be blinded, but assessors were. **Additional outcomes:** Hours with headache, headache score, days with more than mild headache, disability (PDI), Pain affective and sensoric (SES standard scores), average pain on 1-10 scale. Details of mild side effects. **Notes:** Most participants recruited through reports in local newspapers; a minority were patients who spontaneously contacted trial centres. 1 study centre excluded from analysis (before analysis started) n=26. Due to repeated severe protocol violations and suspicion of
			Patient-reported headache intensity (Average pain scale 0-10, baseline and final values, mean (SD)) **N Gp1=118, Gp2=57 at week 12** **N** Gp1=112, Gp2=55 at week 12	**Wk 9-12** **Group1:** Baseline 30.0 (13.5) Final 15.8 (15.3) **Group 2:** Baseline 29.9 (14.1), Final 17.2 (14.4) **Change difference between groups =-**0.8 days, 95% CI: -4.4;2.7 P=0.64 **Wk 21-24** Group1: Final 17.6 (16.7) Group 2: Final 18.6 (16.2)	
			Change in patient-reported headache intensity (Headache score, sum of intensity ratings (1-3) of days with headache, baseline and final	**Wk 9-12** **Group1: Baseline 4.5 (1.5)** Final 2.9 (1.6) **Group 2:** Baseline 4.9 (1.5), Final 3.1 (1.7) **Change difference between groups** =-0.1 days, 95% CI: -	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	excluded, 25 for various reasons **Group 1 – Acupuncture** **N:** 132 randomised, 124 with week 12 data, 114 week 24 **Age (mean(SD)):** 42.3 (13.5) **Drop outs:** Wk 12: 6 (1 didn't tolerate needles, 1 private reasons, 4 other) 2 lost to follow up. Wk 24 10 lost to follow up **TTH type:** 57% episodic, 43% chronic **Previous acupuncture:** 46 (35%) **Duration of disease (yrs):** 13.7 (11.1) **Days with headache*:** 17.5 (6.9) **Days with medication*:** 4 (3.7) **SF-36:** Physical; 42.9 (7.2) Mental; 45.6 (10.5) **Group 2 – Minimal acupuncture** **N:** 63 randomised, 59 with week 12 data, 56 for week 24 **Age (mean(SD)):** 43.4 (12.9) **Drop outs:** Wk 12: 1 (intercurrent disease) 3 lost to follow up, Wk 24: 3 lost to follow up **TTH type:** 49% episodic, 51% chronic **Previous acupuncture:** 34 (54%) **Duration of disease:** 16.8 (13.8)	30 minutes given over 8 weeks (preferably 2 sessions in each of the first four weeks, followed by one session a week in the remaining four weeks). 4 weeks baseline phase. All patients were allowed to treat acute headaches as needed. Treatment had to be documented in the headache diary.	values, mean (SD)) **N** Gp1=119, Gp2=58 at week 12 **N** Gp1=113, Gp2=54 at week 12	0.6;0.4 P=0.77 Wk 21-24 **Group1:** Final 2.8 (1.8) **Group 2:** Final 3.1 (1.8)	data-manipulation by some patients. Most commonly reported side effects were triggering of headache or other pain, haematoma and dizziness. Study states there were differences in guesses about treatment allocation at the end of trial which might indicate some degree of unblinding – 63/127 guessed in the acupuncture group and 20/63 in the minimal acupuncture group. * Calculated by NCGC
			Functional health status and health-related quality of life (SF-36)	**Wk 9-12** **Group1:** Physical baseline; 42.9 (7.2) Final 48.2 (7.5) Mental baseline; 45.6 (10.5) Final 47.4 (9.8) **Group 2:** Physical baseline; 44.3 (6.8) Final 49 (6.1) Mental baseline; 44.1 (12.1) Final 46.1 (11.8) **Wk 21-24** **Group1: Physical Final 48.1 (6.9)** Mental Final 47.2 (10.3) **Group 2:** Physical Final 49.1 (5.4) Mental Final: 47.6 (10.1)	
			Responder rate (50% reduction in headache days) Those with no data counted as non-responders	**Wk 9-12** **Group1: 46% (61/132*)** **Group 2:** 35% (22/63*) **p value:** 0.163	
			Use of acute pharmacological	**Wk 9-12** **Group1: baseline 4 (3.7)**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Days with headache*: 17.7 (6.7) **Days with medication*:** 4.2 (4.2) **SF-36:** Physical; 44.3 (6.8) Mental; 44.1 (12.1)		**treatment** (days with analgesic use)	Final 1.9 (2.9) **Group 2:** Baseline: 4.2 (4.2) Final 2.6 (2.6) Wk21-24 **Group1 Final:** 2.3 (4.0) **Group 2 Final:** 2.9 (3.5)	
			Incidence of serious adverse events (%)	**Group1:** 2 **Group 2:** 1 (All hospital stays considered unrelated to the study)	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, TTH=tension type headache

Migraine

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener et al, 2006[221] **Study design:** RCT **Comparison:** Acupuncture vs sham **Setting:** 149 Outpatient departments **Duration of follow-up:** 6 months	**Patient group**: Adults with migraine **Inclusion criteria:** Aged 18—65. Between two and six migraine attacks in 4 weeks; first migraine attack before the age of 50; migraine diagnosis at least 26 weeks before study entry; duration of migraine attacks 4-72 hr without acute medication or at least 2hr with acute medication. Two migraine characteristics were to be met and at least one of the following: nausea, vomiting, photophobia or phonophobia. **Exclusion criteria:** Severe migraine attacks with inability to go to work on more than 4 days a month; other neurological disease; secondary headache; neuralgia of the face or head; more than 6 days of non-migrainous headache per month; experience with acupuncture for migraine; any body needle acupuncture in the past 12 months; previous unsuccessful treatments with beta blockers; drug abuse; pregnancy; lactation; insufficient contraception; intake of antipsychotic or antidepressant drugs. Patients were also excluded if they had participated in another clinical trial, taken analgesics on more than 3 days a month for other chronic pain, used prophylactic	**Group 1 Acupuncture** Chinese acupuncture points consisted of obligatory points and additional points individually chosen by the physicians on the basis of traditional Chinese medicine diagnosis for syndromes (including tongue diagnosis), acupuncture channels related to the headache area, and Ah Shi points (locus dolendi points). Needles were inserted 2-20mm in depth and manual stimulation of the needle was applied to achieve 'De Qi' based on subjective reporting of the patient. **Group 2 Sham** Acupuncture done on areas of the skin in which no traditional Chinese medicine acupuncture points are known. Up to 6 needles were applied superficially on either side of the upper arm, on both thighs and below both scapulae (depth of needle insertion max 3mm), and no manual stimulation was done. The head has a high density of acupuncture points and was excluded from sham acupuncture sessions. **Both groups:** Consisted of 10 sessions of 30 minutes	**Change in patient-reported migraine days** (change from baseline, mean (SD))	**At 13 weeks** **Group1:** -2.2 (3.1) **Group 2:** -1.9 (3.6)	**Funding:** Various public health insuring bodies **Limitations:** Single blind (patients and assessors blind). Acupuncture group treated with significantly more needless than sham (15.4 (4.6) vs 13.8 (4.3) p<0.0001) **Additional outcomes:** Pain-related impairment and pain days according to von Korff; patient global assessment of therapy effectiveness; quality of acupuncture therapy; maintenance of blinding. **Notes:** ITT analysis used last observation carried forward for missing data. Outcomes recorded in diaries. 44% of patients
			Change in patient-reported migraine days (change from baseline, mean (SD))	**At 26 weeks** **Group1:** -2.3 (3.6) **Group 2:** -1.5 (3.8) **95% CI:** Group1: 1.9;2.7, Group2 1.1;2.0 **p value:** 0.031	
			Patient-reported migraine intensity (Pain intensity on Von Korff scale (0-10), baseline and final values, mean (SD))	**At 13 weeks** **Group1: Baseline 73.7 (13.3), Final 63.5 (19.1)** **Group 2:** Baseline73.8 (13.3), Final 62.6 (18.9) **p value**: 0.393	
			Patient-reported migraine intensity (Pain intensity on Von Korff scale (0-10), change from baseline, mean (SD)). Scale NR.	**At 26 weeks** **Group1: Final 57.7 (20.4)** **Group 2:** 60.9 (20.4) **95% CI:** Group1: 1.9;2.7, Group2 1.1;2.0 **p value:** 0.045	
			Responder rate (50% reduction in	**At 13 weeks** **Group1: 128/290**	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	medication for migraine in past 6 months, were receiving cortisone treatment, had epilepsy or had a psychiatric disease. **All patients** N: 960 randomised, 835 treated **Group 1 – Acupuncture** **N:** 313 randomised, 305 received treatment, 290 analysed **Age (mean):** 37.1 (10.5) **Drop outs:** 8 pre-treatment, 15 after **Migraine attacks/month:** 3.8 (3.0) **Migraine days:** 6.0 (3.2) **With/without aura:** 52/48% **Disease duration, months:** 201.6 (150.9) **Days with other headache:** 1.5 (2.9) **Using medication for other pain:** 21 (22%)	duration, administered over 6 weeks preferably at a rate of two sessions per week. Only body needle acupuncture without electrical stimulation or moxibustion was allowed. The same number and type of needles (sterile, single-use acupuncture needles, coated 0.25-0.30mm thick, 25-40mm long) were used in both treatment groups. The investigators were instructed to provide the same level of care and attention to both groups. Total number of needles was restricted to a maximum of 25 and a minimum of ten per treatment. Both verum and sham points had to be selected from a prescribed list and needling was bilateral. During treatment, communication with the patient was restricted to a minimum of necessary explanations to avoid unblinding of the patient. For the purpose of this study acupuncture points were established on basis of international literature and consultation with experts. To better approximate clinical practice, all patients could receive 15 instead of 10 interventions 9to per week) if their treatment was graded as only partly successful in the telephone interview at the end of the treatment phase. **Group 3 Standard treatment**	migraine days, n (%))	**(46%)** **Group 2:** 128/317 (42%) **At 26 weeks** **Group1:** 133 (47%) **Group 2:** 121 (39%)	correctly guessed whether they were receiving verum or sham acupuncture (119 (42%) verum, 81 (26%) sham). Only 28% guessed wrong.
	Pervious acupuncture >12mo pre screening (not for migraine): 41 (14%) **Group 2 - Sham** **N:** 339 randomised, 328 received treatment, 317 analysed **Age (mean):** 38.3 (10.4) **Migraine attacks/month:** 3.8 (3.0) **Migraine days:** 5.8 (3.2) **With/without aura:** 48/52% **Disease duration, months:** 199.5 (131.7)		**Use of acute pharmacological treatment** (baseline and final n of people using acute medication (%)	At 13 weeks Group1: Baseline 270 (93%) Final 254 (89%) Group 2: Baseline 292 (92%) Final 272 (87%)	
			Use of acute pharmacological treatment (baseline and final n of people using (%)	**At 26 weeks** **Group1:** Final 254 (88%) **Group 2:** Final 272 (86%)	
			Functional health status and health-related quality of life (SF-12 physical health mean (SD) baseline and final values)	At 13 weeks Group1: Baseline 43.2 (8.4) Final 47.6 (7.3) Group 2: Baseline 42.7 (8.8) Final 46.0 (8.2) p value: 0.029	
			Functional health status and health-related quality of life (SF-12 mental health	Group1: Baseline 48.5 (9.5) Final 51.5 (8.4) **Group 2**: Baseline	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Days with other headache: 2.1 (3.9) **Using medication for other pain:** 32 (37%) **Pervious acupuncture >12mo pre screening (not for migraine):** 42 (13%) **Drop outs:** 11 pre-treatment, 11 after **Group3 – Standard care** **N: 308 randomised, 202 received treatment, 187 analysed**	Not reported here including use of beta-blockers, flunarazine or valproic acid).	mean (SD))	48.1 (9.9) Final 50.9 (8.8)	
			Functional health status and health-related quality of life (SF-12 physical health mean (SD) baseline and final values)	**At 26 weeks** **Group1: Final 47.3 (8.2)** **Group 2:** Final 46.3 (8.7)	
			Functional health status and health-related quality of life (SF-12 mental health mean (SD))	**At 26 weeks** **Group1: Final 51.4 (9.0)** **Group 2:** Final 51.0 (9.4)	

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Facco et al, 2008[269] **Study design:** RCT **Comparison:** Acupuncture vs ritualised sham vs standard sham **Setting:** NR **Duration of follow-up:** 6 months	**Patient group:** Adults with migraine without aura (with or without tension-type symptoms) **Inclusion criteria:** Diagnosis of migraine without aura according to ICHD, with or without tension-type symptoms; frequency of migraine attacks 3-8 per month; previously received at least one prophylactic treatment for migraine with no improvement. **Exclusion criteria:** Onset of headache or acupuncture treatment less than 1-year before; headache caused by other diseases **All patients** **N:** 160 enrolled, 127 completed **Drop outs:** 33	**Group 1 – True acupuncture** Patients clinically evaluated according the traditional Chinese medicine (TCM) syndrome definition. Each type of syndrome was treated with a specific acupoint selection according to TCM as suggested by Liu Gongwan (personal communication) the acupoints were defined according to the Whorld Health Orgainisation (WHO) standard acupuncture nomenclature. Twice a week, all patients were submitted to 2 courses of 10 acupuncture applications each, with a 1-week rest between the 2 courses. Acupuncture was performed with single-use stainless steel filiform needles, 25 or 40mm long, diameter 0.30mm. After the needle insertion and arrival of Qi, the required method of treatment was applied to each acupoint (reducing method consisted of 1 minute stimulation of the needle obtained with a large rotation at a rate of about 3 rotations/second. The reinforcing method was performed with a small rotation for 1 minute at a rate of about one every 2 seconds) Stimulation was repeated 3 times at intervals of 5 minutes. The session lasted 30 minutes. **Group 2 – Ritualised mock acupuncture**	**Headache specific QoL** (MIDAS Index, Baseline and final vales, Mean±SD)	**At 3 months** **Group1 (n=32): Baseline 22.2±6.0, Final 2.1±1.5** **p value:** <0.0001 **Group 2** (n=30): Baseline 21.1±6.3, Final 5.0±1.5 **p value:** <0.0001 **Group 3** (n=31): Baseline 22.0±6.3, Final 7.5±3.3 **p value:** <0.0001 **95% CI:** NR	**Funding:** NR **Limitations:** Single blind (patients and assessors) Allocation concealment unclear Population includes those with and without tension headache Rizatriptan use at baseline not reported **Additional outcomes:** None **Notes:** Randomisation done after stratifying for sex (using random number generator in excel) Per protocol analysis
			Headache specific QoL (MIDAS Index, Baseline and final vales, Mean±SD)	**At 6 months** **Group1** (n=32): Final 2.2±1.1 **p value:** <0.0001 **Group 2** (n=30): Final 8.0±1.5 **p value:** <0.0001 **Group 3** (n=31): Final 8.2±3.2 **p value:** <0.0001 **95% CI:** NR	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 – Acupuncture **N:** 32 **Age (mean):** 35.2 ± 6.1 (25-48) **M/F:** 14/18 **Drop outs:** 8 **Group 2 – Ritualised mock acupuncture** **N:** 30 **Age (mean):** 39.4 ± 6.4 (25-50) **M/F:** 14/16 **Drop outs:** 10 **Group 3 – Standard mock acupuncture** **N:** 31 **Age (mean):** 35.4 ± 6.3 (25-48) **M/F:** 15/16 **Drop outs:** 9	Acupuncture apparently the same as in group 1 but the needles were not inserted. A small cylinder of foam (height and diameter=1cm) was applied to the skin by means of a double-adhesive plaster n each acupoint; needles with blunted tips were inserted into the cylinder, touching but not penetrating the skin. This allowed the patient to feel a superficial, light pricking-like sensation, thus stimulating the needle insertion. A slight pressure was applied on the needle handle 3 times at 3 second intervals in order to simulate the arrival of "Qi". The reducing or reinforcing methods were also simulated by rotating the needles within the foam cylinder. **Group 3 – Standard mock acupuncture** The Western approach was used for diagnosis and the standard acupoint selection used (Touwei (ST8), Xuanlu (GB5), Fengchi (GB20), Dahui (GV14), Lieque (LU7)) with the same methods of insertion used in group RMA. All patients allowed to take Rizatriptan to treat attacks during prophylactic treatment with acupuncture / sham. Rizatriptan wafer administered at 10mg, a second dose was allowed after 2 hours if pain persisted.	**Use of acute pharmacological treatment** (Rizatriptan intake during treatment, no. of tablets Mean±SD)	**Group1:** 3 mo:10.0±5.0 6mo 4.2±1.5 **P value:** <0.0001 **Group 2:** 3 mo: 14.4±5.1 6mo: 17±5.0 **P value:** NS **Group 3:** 3 mo: 17.2±5.4 6 mo: 16.0±5.0 **P value:** NS **95% CI:** NR	reported only

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, TCM=traditional Chinese medicine, RMA=ritualised mock acupuncture, ICHD=International classification of headache disorders

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Hesse et al, 1994[374] **Study design:** RCT **Comparison:** Acupuncture vs beta-blocker **Setting:** NR **Duration of follow-up:** 17 weeks	**Patient group:** Adults with migraine with or without aura **Inclusion criteria:** Aged 21-70 with a history of migraine for at least 2 years; 2-6 attacks monthly; fulfilling criteria for migraine with or without aura according to ICHD; not taking prophylactic drugs and capable of distinguishing tension-type headache from migraine pain. **Exclusion criteria:** Patients suffering from other chronic pain syndromes or with contraindication for beta-blocking agents. Previous experience with acupuncture or metoprolol, pregnancy, drug abuse or disablement pension. **All patients** **N:** 85 randomised, 77 ITT **Drop outs:** 8 (1 regretted consent at 1st visit, 4 refused during treatment (2 per group), 1 intercurrent disease, 1 pregnancy, 1 error in allocation) **Group 1 – Acupuncture + placebo** **N:** 38 **Age (mean):** 42.9 (26-66) **M/F:** 5/33 (13/87%)	**Group 1 Acupuncture + placebo** At each visit patients were dry needled for a few seconds using the sharp end of the needle. The number of trigger points per treatment, interval between treatments and total number of treatments were determined individually by the therapist according to patient's clinical response to the needling. **Group 2 Metoprolol + sham acupuncture** At each visit patients were touched superficially with the blunt end of the needle. The number of trigger points per treatment, interval between treatments and total number of treatments were chosen at random, but within the range of group A (i.e. 4-6 needlings per treatment, 1-3 weeks between treatments and 6-8 treatments during the study period). Plus metoprolol 100mg/day. After 17 weeks, it was gradually withdrawn over a period of 10 days. **Both groups:** 17 weeks of treatment preceded by a 4 week run-in period during which only symptomatic medication was allowed. At each visit patients had their most tender trigger points in musculus trapezius, m.rhomboideus and m.semi-spinalis capitis chosen for treatment.	**Change in patient-reported migraine frequency** (median difference in migraine frequency between groups)	**Group1 vs Group 2:** 0.7 **95% CI:** -1.6;2.7 **p value:** >0.20	**Funding:** Danish Health Foundation and Danish Medical Research Council **Limitations:** Single blind (patients and assessors). Randomisation and allocation concealment unclear. Selective reporting of outcomes. Baseline and final values not reported. Drop outs not reported per group. **Additional outcomes:** Duration of migraine attacks. Occurrence of tension type headache and consumption of analgesics both stated as recorded, but results not reported. **Notes:** ITT analysis usually based upon last observation carried forward (not stated when this was not the case). Outcomes recorded in a dairy card. * Global rating scale, 1=mild,
			Change in patient-reported intensity (migraine severity median difference between groups) Based on global rating*	**Group1 vs Group 2:** 0.3 **95% CI:** 0.1;0.5 **p value:** <0.05	
			Incidence of serious adverse events (%)	**Group1:** 0 **Group 2**: 1 (severe abdominal pain, withdrew from trial)	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	With/without aura: 6/32 (16/84%) **Duration of migraine (yrs):** 20.3 (2-40) **Tension type headache:** 36 (95%) **Drop outs:** NR **Group 2 – Metoprolol + sham** **N:** 39 **Age (mean):** 46.5 (25-70) **M/F:** 7/32 (18/82%) **With/without aura:** 8/31 (21/79%) **Duration of migraine (yrs):** 26.5 (2-55) **Tension type headache:** 36 (95%) **Drop outs:** NR	Patients were permitted to continue symptomatic medication, but any form of physical therapy was avoided.			2=moderate, 3=severe

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Li et al, 2012[494] **Study design:** RCT **Comparison:** Acupuncture vs sham **Setting:** Outpatients (multicentre – 9 hospitals, China) **Duration of follow-up:** 16 weeks (acupuncture given for 4 weeks)	**Patient group:** Adults with migraine with or without aura **Inclusion criteria:** ICHD criteria for migraine; experienced acute migraine attacks for more than one year with two or more attacks per month during the previous three months and during the baseline period; aged 18-65 years; onset of migraine before age 50; completed a baseline headache diary' did not take any prophylactic migraine medication during the previous month; willing to complete 20 acupuncture treatments during a four-week period (weeks 1-4); and able to provide written informed consent. **Exclusion criteria:** Had headache due to organic disorders (e.g. Subarachnoid haemorrhage, cerebral haemorrhage, cerebral embolism, cerebral thrombosis, vascular malformation, arthritis, hypertension, arteriosclerosis), psychosis, pregnancy or lactation, allergies, bleeding disorders or serious diseases of the heart, liver, kidney or other organs. **All patients** **N:** 480 **Drop outs:** 4 pre treatment, 37 during treatment period **Age:** 36.9 (12.3)	**Group 1 - Acupuncture** The treatments, which included electro-stimulation, were provided by specialised acupuncturists who had at least five years' training and give years; experience using a standardised protocol. The acupuncture points were selected according to a systematic review of ancient and modern literature, consensus meetings with experts and experience from a previous study. The Shaoyang-specific and sham acupuncture points chosen were used In a previous study of acute migraine Attacks. The three acupuncture groups were: Shaoyang-specific (SS); Shaoyang-nonspecific (SN); and Yangming-specific (Y). **Group 2 sham acupuncture**	**Change in patient-reported migraine days** (baseline and final vales) Mean(95% CI) ±SD unless otherwise stated. Data reported in weeks 13-16 (wks 1-4 acupuncture treatment)	**Acupuncture:** **SS:** Baseline=6.3 (5.4-7.2), Final= 2.2 (1.7-2.7) p=0.003 **SN:** Baseline=5.6 (5-6.2), Final= 2.1 (1.6-2.6) p<0.001 **Y:** Baseline=6.1 (5.3-7) Final= 2.4 (1.9-2.9) p=0.011 **All*** Baseline=6±4.4, Final= 2.23±2.76 **Sham:** Baseline=5.5 (4.8-6.2) Final= 3.3 (2.8-3.8)	**Funding:** National Basic Research Programme of China (no role in design, data collection / analysis or manuscript) **Limitations:** Person administering treatment not blinded to group (however all other participants including outcome assessor were). SDs not given (calculated from 95% CIs by NCGC) **Additional outcomes:** Pain intensity on 0-10 VAS Patients documented pain medication taken and side effects in their diaries, but results not given. **Notes:** * Pooled values for all 3 acupuncture groups calculated by NCGC. 90% power (5% significance, 2 sided) to detect a difference of 1.6
			Change in patient-reported migraine frequency (no. migraines separated by pain free intervals of ≥48 hours) Baseline & final values	**Acupuncture:** **SS:** Baseline= 4 (3.6-4.3) Final= 1.6 (1.3-1.9) p>0.001 **SN:** Baseline=4 (3.7-4.3) Final= 1.7 (1.4-2) P=0.002 **Y:** Baseline= 4 (3.7-4.4) Final= 1.9 (1.6-2.2) P=0.024 **All*** Baseline= 4±1.84 Final= 1.73±1.66 **Sham:** Baseline= 3.9 (3.6-4.2) Final= 2.4 (2.1-2.7)	
			Change in patient-reported migraine	**Acupuncture:** **SS:** Baseline= 2.0 (1.0-2.1)	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 – Acupuncture Original study had 3 acupuncture groups NB these are pooled for our analysis. **N:** 358 **Shaoyang-specific** **N:** 121 randomised, 108 assessed **Dropouts:** 13 (7 reason unclear, 3 unsatisfied, 3 other reason) **Age (mean):** 37.1 (11.7) **M/F:** 21/100 **With/without aura:** 18/103 **Duration of migraine (months):** 119.8 (115.3) **Previous use of acupuncture (n):** 5 **Use of acute pain medication (n):** 35 **Shaoyang-non specific** **N:** 119 randomised, 110 assessed **Dropouts:** 9 (5 reason unclear, 4 unsatisfied) **Age (mean):** 36.2 (12.4) **M/F:** 20/99 **With/without aura:** 14/105 **Duration of migraine (months):** 91.8 (78.6) **Use of acute pain medication (n):** 40 **Previous use of acupuncture (n):** 2 **Yangming-specific**	**Both groups:** Acupuncture was applied unilaterally, alternating between the left and right sides. The goal was to elicit a de qi sensation in the three acupuncture groups but not in the sham-acupuncture group. Two types of Hwato needles (Suzhou Hua Tuo Medical Instruments, Suzhou, China) were used in all groups (length 25-40mm, diameter 0.25 mm; length 13mm, diameter 0.18mm). The patients received 20 treatments (30 min each) over a four week period: once per day for 5 consecutive days followed by a two-day break. Details published elsewhere. Patients were informed that they would receive one of four types of acupuncture treatment, three of which used traditional Chinese acupuncture theories	**intensity** (0-3 scale)	Final= 1.0 (0.9-1.3) p=0.002 **SN:** Baseline= 2.1 (2.0-2.2) Final= 1.4 (1.2-1.6) p=0.31 **Y:** Baseline= 2.0 (1.9-2.1) Final= 1.3 (1.1-1.5) p=0.17 **All*** Baseline= 2.03±0.55 Final= 1.23±1.12 **Sham:** Baseline= 2 (1.9-2.1) Final= 1.5 (1.3-1.8)	migraine days between Shaoyang-specific acupuncture and control groups, 105 patients per group were required. Block randomisation stratified by centre – block length unknown to centres. Patients, outcome assessors and statisticians were blinded to randomisation. All analysis based on ITT population in original study (number randomised who received at least one treatment session) Not able to interpret ACA figures
			MSQL restrictive	**Acupuncture:** **SS:** Baseline= 61.2 (58.7-63.7) Final= 81.9 (79.1-84.7) p<0.001 **SN:** Baseline= 58.5 (55.6-61.4) Final= 77.8 (75.1-80.6) p=0.01 **Y:** Baseline= 60.3 (57.9-62.7) Final= 77.3 (74.5-80.0) p=0.022 **All*** Baseline= 60.01±14.44 Final= 79.02±15.60 **Sham:** Baseline=58.5 (55.8-61.2) Final= 72.7 (70-75.5)	
			MSQL preventive	**Acupuncture:** **SS:** Baseline=70.5 (67.6-73.4) Final=87.2 (84.7-89.7)	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 118 randomised, 111 assessed **Dropouts:** 7 (4 reason unclear, 4 unsatisfied) **Age (mean):** 36.8 (13.0) **M/F:** 26/92 **With/without aura:** 12/106 **Duration of migraine (months):** 104 (100.7) **Use of acute pain medication (n):** 36 **Previous use of acupuncture (n):** 1 **Group 2 –sham** **N:** 118 randomised, 110 assessed	and one which was based on modern acupuncture theory. Patients were instructed not to take any regular medications for the treatment of migraines. In cases of severe pain, ibuprofen (300mg each capsule with sustained release) was allowed as rescue medication.		p<0.001 **SN:** Baseline=66.5 (63.1-69.9) Final=83.7 (81.2-86.1) p=0.019 **Y:** Baseline=69.5 (66.5-72.5) Final=71 (67.9-74.1) p=0.12 **All*** Baseline= 68.84±17.22 Final= 84.42±13.68 **Sham:** Baseline= 66.9 (63.4-70.4) Final= 79.5 (77.1-82)	
	Dropouts: 8(2 reason unclear, 4 unsatisfied, 2 other reason) **Age (mean):** 37.5 (12.1) **M/F:** 15/103 **With/without aura:** 12/106 **Duration of migraine (months):** 102 (93.4) **Use of acute pain medication (n):** 45 **Previous use of acupuncture (n):** 12		**MSQL functional**	**Acupuncture:** **SS:** Baseline=70.3 (66.9-73.7) Final=88 (85.1-90.8) p=0.008 **SN:** Baseline=67 (63.4-70.6) Final=83.7 (81-86.5) P=0.58 **Y:** Baseline=71 (67.9-74.1) Final=82.5 (79.8-85.3) p=0.96 **All*** Baseline= 69.43 ±18.7 Final= 84.76±15.54 **Sham:** Baseline= 69 (65.9-72.1) Final=82.6 (79.9-85.4)	
			Incidence of adverse events (not stated whether considered serious	**Acupuncture:** **SS:** 9 (6 subcutaneous haemorrhage, 1 subcutaneous haematoma, 1 subcutaneous ecchymosis, 1 leg weakness)	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
			or not, but all patients recovered fully)	**SN:** 8 (65subcutaneous haemorrhage, 3 subcutaneous haematoma) **Y:** 12 (10 subcutaneous haemorrhage, 2 subcutaneous haematoma) **All*** 29 **Sham:** 8 (4 subcutaneous haemorrhage, 4 subcutaneous ecchymosis)	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, SS=shaoyang specific, SN=Shaoyang non-specific, Y=yangming specific

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Linde et al, 2005[501] **Study design:** RCT **Comparison:** Acupuncture vs sham **Setting:** 18 outpatient centres **Duration of follow-up:** 24 weeks	**Patient group:** Adults with migraine with or without aura (IHS criteria) **Inclusion criteria:** Diagnosis of migraine, with or without aura, according to IHS criteria; 2-8 migraine attacks per month during the last 3 months and during the baseline period; aged 18-65yrs; had migraines for at least 12 months; completed baseline headache diary. **Exclusion criteria:** Interval headaches or additional tension-type headache on more than 10 days per month; inability to distinguish between migraine attacks and additional tension type headache' secondary headaches; start of headaches after age 50 years; use of analgesics on more than 10 days per month; prophylactic headache treatment with drugs during the last 4 weeks; any acupuncture treatment during the last 12 months or at any time if performed by the participating trial physician.	**Group 1 Acupuncture** Semi standardised developed by consensus of acupuncture experts – all treated at 'basic' points (gallbladder 20, 40 or 41 or 42, Du Mai-governing vessel 20, liver 3, San Jiao 3 or 5, extra point Taiyang) bilaterally unless explicit reasons for not doing so were given; additional points could be chosen individually according to patient symptoms. Sterile disposable 1-time-use needles had to be used but physicians could choose needle length and diameter. Physicians instructed to achieve 'de qi' if possible and to stimulate needles manually at least once during each session. Total number of needles was limited to 25 per session. **Group 2 Minimal acupuncture (sham)** Number, duration and frequency of the sessions were the same as for acupuncture group. In each session, at least five out of 10 predefined distant non-acupuncture points were needled bilaterally (at least 10 needles) and superficially using fine needles. De qi and manual	**Patient-reported migraine days** (mean (SD) baseline and final values)	**Wks 9-12** **Group1:** Baseline 8.3 (3.4)) Final 4.9 (3.4) **Group 2:** Baseline 8.3 (3.6) Final 4.7 (3.4) **Mean difference:** 0.1 **95% CI:** -0.8;1.1 **p value:** 0.76	**Funding:** Various social health insurance funds **Limitations:** Single blind (patients and assessors only) **Additional outcomes:** Days with moderate to severe headache Headache days Accompanying symptoms Days activities impaired Responder rate in terms of days of moderate to severe headache Modified version of German society for the study of pain questionnaire Pain Disability Index Emotional aspects of pain Depression scale Allgemeine Depressionskalla **Notes:** Most patients recruited through reports in local newspapers; some spontaneously contacted the trial centres.
			Patient-reported migraine days (mean (SD), baseline and final values)	**Week 24** **Group1:** Final 5.2 (3.3) **Group 2:** Final 4.8 (3.1) **Mean difference:** 0.4 **95% CI:** -0.6;1.3 **p value:** 0.42	
			Patient-reported migraine intensity (pain rating scale (scale not stated), baseline and final values, mean(SD))	**Week 12** **Group1:** Baseline 5.6 (1.6) Final 3.7 (2.0) **Group 2:** Baseline 5.6 (1.6) Final 3.6 (2.1) **Mean difference:** 0.1 **95% CI:** -0.5;0.6 **p value:** 0.87	
			Patient-reported migraine intensity (pain rating scale, baseline and final values, mean (SD))	**Week 24** **Group1**: Final 3.8 (2.1) **Group 2:** Final 3.4 (2.0) **Mean difference:** 0.4 **95% CI:** -0.2;1.0 **p value:** 0.24	
			Responder rate (50% reduction in	**Wks 9-12** **Group1:** 78/138 (56%*)	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients N: 304 randomised (2 erroneously – did not return after baseline). **Group 1 – Acupuncture** **N:** 145 (randomised) 138 at 12 wks, 131 wk 24 **Age (mean):** 43.3 (11.8) **M/F:** 16/129 (11/89%) **With/without aura:** 40/109 (28/75%) **Disease duration (yr):** 20.9 (12.1) **Previous acupuncture:** 63 (43%) **Days medication needed (mean):** 5.0 (2.8)	stimulation of the needles were avoided. **Group 3 Waiting list** (not reported here) Both consisted of 12 sessions of 30 minutes given over 8 weeks (preferably 2 sessions in each of the first four weeks, followed by one session a week in the remaining four weeks). 4 weeks baseline phase. All patients were allowed to treat acute headaches as needed. Treatment had to be documented in the headache diary.	migraine days)	**Group 2:** 43/78 (55%*) **Mean Difference:** 1.01 **95% CI:** 0.79;1.31 **p value:** >0.99	* Calculated by NCGC
			Responder rate (50% reduction in migraine days)	**Week 24** **Group1:** 64/145 (44%) **Group 2:** 39/81 (48%) **Mean difference:** 0.92 **95% CI:** 0.69;1.23 **p value:** 0.58	
			Use of acute pharmacological treatment (days medication used, mean (SD))	**Wks 9-12** **Group 1:** Baseline 5.0(2.8) Final 3.2(3.0) **Group 2:** Baseline 4.8(2.6) Final 3.4 (2.9) **Mean diff:** -0.2 **95% CI:** -1.0;0.6 **p value:** 0.65	
	Medication use during baseline: triptans 28%, ergot 1%, analgesics 71%, combinations 21% **Drop outs:** wk 12 7 (3 unclear, 1 unsatisfied, 1 personal reasons, 1 moved, 1 lost to follow-up), At week 24, 7 lost to follow-up **Group 2 - Sham** **N:** 81 randomised, 78 at wk 12, 72 at wk 24		**Use of acute pharmacological treatment**	**Week 24** **Group1:** 3.6 (3.7) **Group 2:** 3.4 (2.5) **Mean diff:** 0.1 **95% CI:** -0.8;1.1 **p value:** 0.76	
			Functional health status and health-related quality of life (SF-36 physical health, baseline and	**Wks 9-12** **Group 1:** Baseline 41.6(7.7) Final 46.7(7.5) **Group 2:** Baseline 44.0 (6.6) Final 47.5 (7.0) **Mean diff:** -0.8	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 41.3 (10.2) **M/F:** 8/73 (10/90%) **With/without aura:** 23/62 (28/77%) **Disease duration (mean, yrs):** 19.2 (11.7) **Previous acupuncture:** 30 (37%) **Days medication needed (mean):** 4.8 (2.6) **Medication use during baseline:** triptans 30%, ergot 2%, analgesics 79%, combinations 14% **Drop outs:** wk 12, 3 (2 unclear, 1 lost to follow-up) at wk 24 6 lost to follow-up		final values) Group1n=138, Group2=78	**95% CI:** -2.9;1.3 **p value:** 0.44	
			Functional health status and health-related quality of life (SF-36 mental health, baseline and final values)	**Wks 9-12** **Group1:** Baseline 47.6(10.1) Final 48.6 (8.8) **Group 2:** Baseline 47.2(10.0) Final 47.6 (9.6) **Mean diff:** 0.9 **95% CI:** -1.6;3.5 **p value:** 0.47	
			Functional health status and health-related quality of life (SF-36 physical health, baseline and final values)	**At week 24** **Group1:** Final 46.7 (7.0) **Group 2:** Final 48.8 (7.3) **Mean diff**: -2.1 **95% CI:** -4.2;0.0 **p value**: 0.05	
	Group 3 – Wait list control (not reported here)		**Functional health status and health-related quality of life** (SF-36 mental health, baseline and final values)	**At weeks 21-24** **Group1:** Final 49.4 (9.0) **Group 2:** Final 47.7 (9.8) **Mean diff:** 1.7 **95% CI:** -1.0;4.4 **p value:** 0.22	
			Incidence of serious adverse events (n)	**Group1**: 4 **Group 2:** 1 All hospital stays considered unrelated	

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

E.3.2 Prophylactic non-pharmacological management of primary headaches with manual therapies

Tension type headache

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Bove & Nilsson, 1998[102] **Study design:** RCT **Comparison:** Spinal manipulation vs placebo **Setting:** Outpatient facility of Chiropractic research institution in Denmark **Duration of follow-up:**	**Patient group:** Adult patients (20-60 years) fulfilling IHS criteria for Episodic Tension Type Headache (ETTH). **Inclusion criteria:** Fulfilled IHS criteria for ETTH with more than 5 but fewer than 15 headache episodes per month; age 20-60 years; score for typical headache intensity between 25 and 85 on visual analogue scale from 0 to 100; no relative or absolute contraindications to manipulation. **Exclusion criteria:** After inclusion, participants could be excluded for any adverse reaction to treatment or any event triggering or potentially triggering a change in headache status (e.g. vehicular crash or neck injury). **All patients** **N:** 75 (randomised) **Age (mean):** 38 (range 20-59) **Drop outs:** 5 **Group 1** – Spinal manipulation + soft tissue therapy **N:** 38 (randomised); 36 (completed trial) **Age (mean):** 37 (range 22-59) **Drop outs**: 2 **Pharm treatment:** Usual pattern of medication continued	**Group 1 Spinal manipulation + soft tissue therapy** Manipulation group received joint manipulations of the cervical spine as determined by chiropractor and also deep friction massage. **Group 2 Placebo (Laser+ soft tissue therapy)** Control group received deep friction massage and application of low-power laser light to upper cervical region (effect reported to be equal to placebo). Weeks.1 and 2: Baseline data collected Weeks 3-6: Randomised patients treated 8 times, usually twice a week. Post treatment data was collected from patients' headache diaries completed during weeks 7, 11, 15 and 19.	**Patient-reported headache intensity** [Mean headache intensity, (95%CI)] Intensity calculated on Visual analogue scale 0-100	**Group 1** Baseline: 37 (33-41); SD = 12.17* Week 15:29 (23-35) SD = 18* **Group 2:** Baseline: 37 (33-41) SD = 12* Week 15: 33 (25-41) SD = 23.64* **p values:** 2vs 1 (baseline): 0.89 2vs 1 (week 15): 0.41	**Funding:** Nordisk Institut for Kiropraktik og Klinisk Biomekanik (Odense, Denmark) **Limitations:** Unclear randomisation and allocation concealment. No blinding of care administrators. No information on validation of headache diaries used. **Additional outcomes:** Mean headache hours per day. **Notes:** All patients continued usual pattern of medication. *Calculated at NCGC
			Use of acute pharmacological treatment (Mean number of analgesics per day, 95%CI)	**Group1:** Baseline: 0.66 (0.49-0.83) SD = 0.52* Week 15: 0.48 (0.34-0.62) SD = 0.42* **Group 2:** Baseline: 0.82 (0.50-1.14) SD = 0.96* Week 15: 0.60 (0.26-0.94) SD = 1.00*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
19 weeks	**Group 2** – Placebo (Laser+ soft tissue therapy) **N:** 37 (randomised); 34 (completed trial) **Age (mean):** 38 years (range 20-58) **Drop outs:** 3 (1 did not receive treatment, 2 lost to follow up) **Pharm treatment:** Usual pattern of medication continued.			**p values:** 2vs 1 (baseline):0.38 2vs 1 (week 15): 0.51	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Carlsson et al, 1990[132] **Study design:** RCT **Comparison:** Physiotherapy v Acupuncture **Setting:** Outpatient clinics in Departments of Neurology and Neurosurgery, Sahlgrenska hospital, Sweden **Duration of follow-up:** Unclear	**Patient group:** Female patients with chronic tension headaches **Inclusion criteria:** Female; aged 18-60 years; had chronic tension headache. **Exclusion criteria:** Presence of malignant or other serious diseases; headaches which had started in close temporal relation to an organic disorder; difficulty in understanding and speaking Swedish; patients with generalized myalgia and headache as part of a fibromyalgic syndrome. **All patients** **N:** 62(randomised); 52 (completed study) **Age (mean):** 34 years **Drop outs:** 10 **Group 1** – Physiotherapy **N:** 31 (randomised), 23(completed) **Age (mean):** NR **Drop outs**: 8 **Group 2** - Acupuncture **N:** 31(randomised);	**Group 1 – Physiotherapy** Treatment extended over 2-3 months (10-12 sessions), with 1-2 sessions per week, each with 30-45 min of individual instruction. Treatment involved: teaching the patient to handle any situation with as little physical tension as possible and to avoid causative factors of headache; teaching the patient that pain relief could be obtained without analgesics massage, cryotherapy, and TENS which were used and managed by the patient herself; relaxation of the whole body performed according to a technique presented by Jacobsen including two 10 min sessions of daily training at home. Contracted and tender muscles were contracted heavily for 10 seconds and relaxed for 10 seconds and then passively stretched for 20 seconds. Patient was taught to practice relaxation in everyday life. **Group 2 – Acupuncture** Acupuncture was performed by two physicians using the same technique. Standard 1.5 inch stainless steel electrodes were used and needles were inserted perpendicularly to a depth where the sub cutaneous 'De Chi' phenomenon occurs. In all patients local points [GB20, GB21] and one distal point [LI 4] were treated. In patients with a probable migrainous component, the following additional points were used: GB14, the extra points Tai Yang in the	**Change in patient-reported headache intensity** [reported on a five point scale, mean(SD)]	**Group 1** Baseline: 3.72(0.73) After treatment: 2.52(0.80) Change: -1.21 **Group 2** Baseline: 3.78(0.96) After treatment: 3.24(1.04) Change: -0.54(1.01)	**Funding:** Grants from Renee Eanders Hjalpfond and the Swedish fund for scientific research without animal experiments **Limitations:** Unclear randomization and allocation concealment Unblinded trial-high degree of performance bias likely Different loss to follow up in both groups Treatment administered by study authors/investigators Treatment and follow up duration unclear: Initial assessments at 3-8 weeks before start of treatment, treatment period reported 10-12 weeks in physiotherapy group, 8-10 weeks in acupuncture group; Follow up assessments at 4-9 weeks after treatment termination. **Additional outcomes:** Muscle tenderness Cervical spine mobility **Notes:** 23 patients had a combination of migraine and tension

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	29(completed study) **Age (mean):** NR **Drop outs:** 2	temporal region and Yin Tang between the eyebrows. Needles were inserted and twiddled by hand at the first session and electrical stimulation via the needles was used from the second treatment on. Electrical parameters used were frequency 1-2 Hz, pulse width 0.5 milliseconds and intensity in the range of 4-7 volts. Length of each treatment was at least 20 min. Patients were advised to reduce their intake of analgesics as much as possible. 4-5 treatments were performed over a trial period and further treatments were given only if patients reported clear pain relief.			headache, with a clear predominance of tension headache. (Group not specified). 28 patients had taken analgesics exclusively for headaches before. 20 patients had taken analgesics and some other therapy such as relaxation programmes, TENS, zone therapy, ultrasound or acupuncture. (Group not specified).

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=Confidence interval, TENS= Transcutaneous electrical nerve stimulation

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Castien et al, 2011[137] **Study design:** RCT **Comparison:** Manual therapy vs Usual care **Setting:** Multicentre trial (38 GP practices in the Netherlands) **Duration of follow-up:** 26 weeks	**Patient group:** Adults with chronic tension type headache (CTTH) **Inclusion criteria:** 18-65 years of age; fulfilled IHS criteria for CTTH; headache occurred on at least 15 days on average per month for a period of more than 3 months; headache lasted for hours or was continuous; Headache had at least one of the following characteristics: bilateral location, pressing/tightening(non-pulsating) quality, mild or moderate intensity, not aggravated by normal physical activity; had both the following characteristics; no more than one of photophobia, phonophobia or mild nausea, neither moderate or severe nausea nor vomiting. **Exclusion criteria:** Presence of rheumatoid arthritis, suspected malignancy, pregnancy, intake of either triptans, ergotamines or opioids on ≥10 days/month or simple analgesics on ≥15 days per month on a regular basis for ≥3 months; received manual therapy in the 2 months before enrolment into the study; not able to read and write Dutch. **All patients** **N:** 82 (randomised) **Drop outs:** 7 **Group 1 –** Manual therapy **N:** 41 (randomised); 40 (received treatment); 38 (present at follow up at 26 weeks) **Age (mean):** 40.2 (range 20-59) **Drop outs:**3	**Group 1 Manual therapy** Combination of mobilisations of the cervical and thoracic spine, exercises and postural correction specifically chosen for the management of cervicogenic headache Duration of each treatment session was 30 min; maximum of 9 treatments Type of techniques and exercises decided by manual therapist at each session **Group 2 Usual care** Treatment by GP according to Dutch general practice guideline for management of headache (included information, re-assurance and advice, and if required prescription of analgesics/NSAIDs or changing current medication)	**Change in patient-reported headache days** [mean change(SD)at 26 weeks]	**Group 1:** -9.1(4.2) **Group 2:** -4.1(4.4) **Between group mean difference:** -4.9(0.99) **95% CI:** -6.95 to -2.98 **p value:** <0.001	**Funding:** NR **Limitations:** Unclear randomisation. No blinding of participants and care administrators. **Additional outcomes:** Sick leave taken up to 26 weeks. Headache Disability Inventory. Cervical range of movement. Endurance neck flexor. **Notes:** Amitriptyline was prescribed as a rescue medication to two patients but not reported in which group.
			Change in patient-reported headache intensity [mean change(SD) in average pain intensity on a 0-10 numeric rating scale at 26 weeks]	**Group 1:** -3.1(2.8) **Group 2:** -1.7(2.5) **Between group mean difference:** -1.4(0.63) **95% CI**: -2.69 to -0.16 **p value:** 0.027	
			Headache specific QoL [HIT 6-reported as mean change (SD) at 26 weeks]	**Group 1:** -10.6(8.4) **Group 2:** -5.5(8.6) **Between group mean difference:** -5.0(1.97) **95% CI**: -9.02 to -1.16 **p value:** 0.012	
			Responder rate (50% reduction in headache frequency at 26 weeks)	**Group 1:** 81.6% (31/38) **Group 2:** 40.5% (15/37) **Relative risk:**2.0 **95% CI:** 1.3 to 3.0)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Pharm treatment: 41.5% (analgesics); 70.7%(NSAIDs) **Number of years with headache (mean, SD):** 12.5, 10.7 **Group 2 –** Usual care **N:** 41 (randomised); 40 (received treatment); 37 (present at follow up at 26 weeks) **Age (mean):** 40.6 (range 20-63) **Drop outs:**4 **Pharm treatment:** 41.5%(analgesics); 65.9% (NSAIDs) **Number of years with headache (mean, SD):** 13.1, 12.3		**Resource use** (Use of additional medical specialists at 26 weeks)	**Group1:** 1 (2.6%) **Group 2:** 6(16.2%) **Difference:**13.5% **95% CI:** 0.7-26.5%	
			Resource use (Use of additional health care-other than hospital attendance or medical specialists at 26 weeks)	**Group1:** 3 (7.8%) **Group 2:** 1(2.7%) **Difference:**5.1% **95% CI:** -4.8-15.2%	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, CTTH =Chronic tension type headache, NSAIDs: Non-steroidal anti-inflammatory drugs

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Söderberg et al, 2006[745] **Study design:** RCT **Comparison:** Manual therapy (physical training) v Acupuncture v Psychological therapy (Relaxation training) **Setting:** Physiotherapy primary care units in Sweden **Duration of follow-up:** 2.5 to three months(treatment); follow up till six months after treatment	**Patient group:** Adults with a diagnosis of chronic tension type headache (CTTH) **Inclusion criteria:** Aged 18-65 years, diagnosed with CTTH according to IHS criteria, had tension headaches for at least 15 days for at least 6 months. **Exclusion criteria:** Headache that began after the age of 50 years; migraine more than once a month during the last year; inability to speak or read Swedish; serious somatic or psychiatric disease; drug abuse or use of analgesics and triptans >10 days per month. **All patients** **N:** 90 (randomised) **Age (median, range):** 37.5, 18.0-59.0 **Group 1 –** Manual therapy-Physical training **N:** 30 (randomised), 30 (Completed), 26 (three months after treatment), 19 (six months after) **Age (median, range)**: 35.9, 18.0-56.0 **Drop outs:** 11 **Headache duration in years (median, range):** 5.0, 2.0-30.0	**Group 1 – Manual therapy-Physical training** Training was performed by five registered physiotherapists. Patients performed two 45 minute training sessions a week at the clinic for 5 weeks and then a home training programme three times a week three times a week for 5 weeks (total of 25 sessions). Each training session consisted of 5 exercises repeated 35 times and three sets of each. Exercises focused on neck and shoulder muscles. Patients rested for 1-2 minutes between exercises. **Group 2 – Acupuncture** Acupuncture was done by five registered physiotherapists who had long experience in treating patient with acupuncture. Disposable needles with a dimension of 15x0.25 mm and 30 or 40x0.30 mm were used. Needles were inserted to a depth of 2-5 mm or 10-30 mm depending on location. Needles were twilled by hand until the patient felt the characteristic 'de qi' sensation. Mandatory points to be needled were GB 20, GB 14, LI 4, ST 44; Optional points were PC 6, PC 7, SP 6, GB 34, ST 8, EX 2 and EX 1. Treatment comprised of 10-12 sessions	**Patient-reported headache intensity** (reported on a VAS scale of 0-100)	**Group 1:** N=30 **Baseline Mean:** 22.03, **Median:** 19.26 **Range:** 4.66-48.20 Immediately after last treatment **Mean:** 15.50 **Median:** 14.82 **Range:** 0.30-51.53 3 months after last treatment **Mean**: 16.88 **Median:** 10.75 **Range:** 0.00-56.75 **Group 2:** N=30 **Baseline Mean:** 26.75 **Median:** 23.41 **Range:** 0.72-69.60 Immediately after last treatment **Mean:** 21.21 **Median:** 16.42 **Range:** 0.93-72.45 3 months after last treatment **Mean:** 18.93 **Median:** 12.34 **Range:** 0.00-53.38	**Funding:** Grants from Vardalsstiftelsen, Kommunala Landstingsangelagenheter, the Renee Eanders Fond, and GlaxoSmith Kline. **Limitations**: Unclear randomization and allocation concealment. No blinding of participants, care administrators. Blinding of investigators unclear. **Additional outcomes**: Headache- free periods Headache-free days

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 - Acupuncture **N:** 30 (randomised), 30 (Completed), 27 (three months after), 17 (six months after) **Age (median, range):** 35.0, 18.0-59.0 **Drop outs**: 13 **Headache duration in years (median, range):** 10.0, 2.0-35.0 **Group 3 –** Psychological therapy-Relaxation training **N:** 30 (randomised),30 (Completed), 26 (three months after), 19 (six months after) **Age (median, range):** 43.5, 22.0-59.0 **Drop outs:** 11 **Headache duration in years (median, range):** 10.0, 2.0-37.0	during a period of 10-12 weeks. **Group 3 – Psychological therapy-Relaxation training** Relaxation was performed by three registered physiotherapists who had long experience and documented skills for treating patient with relaxation training. Relaxation training programme described by Larsson and Daleflod and based on progressive and autogenic relaxation techniques was used. The group also practised progressive relaxation training(by Jacobson), autogenic relaxation training (by Schultz), relaxation and breathing techniques, stress coping techniques and techniques to relax during activity and everyday living. Eight to ten sessions of relaxation training were performed individually under the supervision of a physiotherapist once a week. Patients received an audiotape which included the last session and were instructed to train at home once daily.		**Group 3: N=**30 **Baseline** **Mean: 26.14** **Median:** 20.05 **Range:** 3.77-61.71 Immediately after last treatment **Mean:** 16.77 **Median:** 15.61 **Range:** 0.00-56.24 3 months after last treatment **Mean:** 16.14 **Median:** 11.74 **Range:** 0.00-66.64	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, CTTH= Chronic tension type headache

Migraine

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Nelson et al, 1998[586] **Study design:** RCT **Comparison:** Manual therapy (Spinal manipulation) v TCA (Amitriptyline) **Setting:** Chiropractic college outpatient clinic, USA **Duration of follow-up:** 16 weeks	**Patient group**: Adults with migraine. **Inclusion criteria**: Diagnosis of migraine with/without aura; 18-65 years of age; history of migraine headaches for at least 1 year and had at least 4 headache days per month; diagnosis of migraine headache made according to IHS criteria. **Exclusion criteria:** Pregnancy or lactation; patients under active chiropractic or medical care (e.g., taking prescription medication) within the last month; inability to attend study appointments twice a week for 8 weeks; any clinical contraindication to spinal manipulative therapy (e.g., joint instability, fractures, inflammatory disease or amitriptyline therapy (e.g., cardiac arrhythmias, glaucoma, epilepsy). **Group 1** – Spinal manipulative therapy **N:** 77 (randomised); 77 (received treatment); 59 (completed treatment) **Age in years (mean):** 36.1 (11.4)	**Group 1 Spinal manipulative therapy** Patients were treated a total of 14 times over 8 week period, with no more than 2 treatments per week by chiropractors. Spinal manipulation administered was a type describes as high-velocity, low amplitude, short-lever arm. Chiropractors treated levels of the cervical or thoracic spine for which there were clinical indications (determined by motion and static palpation and findings of localised tenderness). **Group 2 Amitriptyline** 25 mg in first week of treatment, followed by 50 mg in second week, 75 mg in third week and a maximum of 100 mg after three weeks of therapy. Patients were seen three times during treatment period. **Group 3- Combined treatment** Patients simultaneously	**Change in patient-reported headache days** [% of days with headache, mean(SD)] 4 weeks post treatment	**Group 1** n=58 Baseline: 55.1 (26.3) Final: 36.9 (29.3) **Group 2** n=47 Baseline: 51.8 (24.4) Final: 40.5(23.3) **Group 3** n=54 Baseline: 30.9 (22.8) Final: 39.9 (26.6)	**Funding:** Foundation for Chiropractic Education and Research Grant # 92-03-06 **Limitations:** Unblinded trial 5 patients from pharmacological group did not accept treatment allocation and dropped out of the trial. Different reasons for loss to follow up in both groups. Patient expectation of improvement immediately after randomization differed significantly between groups. **Additional outcomes:** Headache index calculated as the weekly sum of each patient's headache pain scores. **Notes:** All patients allowed to use over the counter medication as necessary.
			Change in patient-reported headache intensity [reported on a scale of 0-10, mean(SD)] 4 weeks post treatment	**Group 1** n=56 Baseline: 5.0 (1.3) Final: 4.4 (1.7) **Group 2** n=44 Baseline: 4.6 (1.1) Final: 4.5 (1.3) **Group 3** n=50 Baseline: 4.4 (1.1) Final: 4.3 (1.4)	
			Functional health status and health-related quality of life [SF-36 on 0-100 scale, mean(SD)] 4 weeks post treatment	**Group 1** n=58 Baseline: 67.1(14.5) Final:74.4 (15.1) **Group 2** n=50 Baseline: 66.3(13.4) Final: 71.5 (12.4) **Group 3** n=55 Baseline: 64.3 (15.7) Final:71.9 (14.1)	
			Use of acute pharmacological treatment	**Group 1** n=58 Baseline: 2.2(1.9) Final: 1.2(1.2)	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 18 (lost to follow up) **Group 2** - Amitriptyline **N:** 70 (randomised); 65 (received treatment); 49 (completed treatment) **Age in years (mean):** 37.4 (10.9) **Drop outs:** 20 (5 refused treatment allocation, 7 side effects, 8 lost to follow up) **Group 3**- Combined treatment **N:** 71 (randomised); 71 (received treatment); 56 (completed treatment) **Age in years (mean):**40.2 (9.8) **Drop outs:** 17 (13 lost to follow up, 4 had side effects)	received both spinal manipulative therapy and amitriptyline therapy for the 8 week treatment period. 4 week baseline period, followed by 8 week treatment period, followed by 4 week follow up period. Patients kept a daily headache diary for 16 weeks an recorded frequency and intensity of pain.	[use of over the counter medication, pills/day, mean(SD)] 4 weeks post treatment	**Group 2** n=47 Baseline: 1.8 (1.2) Final: 1.3 (1.3) **Group 3** n= 54 Baseline: 2.0 (1.5) Final: 1.7 (1.5)	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Tuchin et al, 2000[806] **Study design:** RCT **Comparison:** Spinal manipulation v Control **Setting:** Chiropractic research Centre of Macquarie University, Australia **Duration of follow-up:** 6 months	**Patient group**: Adults with a diagnosis of migraine **Inclusion criteria:** Aged 18-70 years; minimum of five of the following indicators: inability to continue normal activities or need to seek a quiet dark area, pain located around temples, pain described as throbbing, associated with nausea, vomiting, aura, photophobia, migraine precipitated by weather changes, migraine aggravated by head or neck movements, previous diagnosis of migraine by a specialist, family history of migraine; minimum of one migraine a month. **Exclusion criteria:** Participants experiencing daily migraine, with the initiating factor being trauma; contraindications to spinal manipulative therapy; presence of temporal arteritis, benign intracranial hypertension or space occupying lesions. **All patients** **N:** 127 **Age in years (mean):** NR **Drop outs:** 4 (1-alteration in work situation, 1-fractured ankle, 1-	**Group 1 Chiropractic spinal manipulative therapy (CSMT)** Group received two months of CSMT treatment consisting of chiropractic diversified technique at vertebral fixations determined by the practitioner. The level of spine manipulated was not specified. *CSMT is defined as a passive manual manoeuvre during which the 3-joint complex is carried beyond the normal physiologic range of movement without exceeding the boundaries of anatomic integrity. **Group 2 Control** Detuned interferential therapy consisting of electrodes being placed on the patient with no current sent through the machine. Trial consisted of three stages: 2 months of data	**Patient-reported headache frequency** [average number of migraines per month, mean(SD)]	**Group 1:** Baseline: 7.1(6.98) After treatment: 4.1 (6.55) **Group 2:** Baseline:7.3(6.53) After treatment: 6.9(6.6) **p value:** <0.005	**Funding:** NR **Limitations:** Unclear randomization and allocation concealment. Unclear if comparable at baseline. Inclusion criteria states and age range of 18-70 years, but age ranges for both groups reported elsewhere in the study include children.* **Additional outcomes:** Hours before return to normal for an average episode Duration/hours for an average episode **Notes:** Patient blinding was achieved by participants being informed that they may be randomly assigned to a control group that would receive a placebo. *Age ranges include children (confirmed by study author).
			Patient-reported intensity [100 mm VAS for average episode, mean(SD)]	**Group1:** Baseline:7.96 (1.4) After treatment: 6.9 (1.8) **Group 2:** Baseline: 7.89 (1.2) After treatment: 6.2 (1.7) **p value:** NS	
			Use of acute pharmacological treatment[average number of medications per month, mean(SD)]	**Group1:** Baseline:21.3(28.4) After treatment: 9.8 (12.4) **Group 2:** Baseline: 20.1(28.4) After treatment: 16.2(12.4) **p value:** <0.001	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	soreness after CSMT, 1-increase in migraine after CSMT) **Group 1 –** Chiropractic spinal manipulative therapy (CSMT) **N:** 83 **Age in years (mean):** 39.6(range 10-70) **Drop outs:** NR **Group 2 -** Control **N:** 40 **Age (mean):** 37.8 (range 17-66) **Drop outs:** NR	collection prior to treatment, 2 month treatment phase and 2 months follow up phase. Participants completed diaries for the 6 months of the study			

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, CSMT = Chiropractic spinal manipulative therapy, VAS=Visual Analogue Scale, NS=Not significant, IHS=International Headache Society

E.3.3 Prophylactic non-pharmacological management of primary headaches with psychological therapies

Tension type headache

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: D'Souza et al, 2008[182] **Study design:** RCT **Comparison:** Written emotional disclosure vs neutral writing control **Setting:** University psychology department **Duration of follow-up:** 3 months	**Patient group:** Undergraduate psychology students with either migraine or TTH **Inclusion criteria:** Fulfilled IHS criteria for either migraine or tension headache. Headaches at least twice per week that were of moderate or severe intensity Or migraine headache at least once a month. **Exclusion criteria:** Headaches suspected to be due to neurological disease, alcohol abuse or a primary medical disorder or those currently in psychotherapy or counselling. **All patients** **N:** 141 (51 tension headache, 90 migraine) **Drop outs:** 6 **Tension Headache group** **Age (mean, SD):** 20.27 (2.30) **M:F (n, %):** 42:9 (82.4: 17.6) **Group 1 – Written emotional disclosure** **N:** 17 **Age (mean):** NR for any group **Drop outs:** 0	**Group 1 Written emotional disclosure** Four sessions over 2 weeks (four 20 min sessions over 2 consecutive weeks). Standard instructions to write about 'a trauma or upheaval or stressful experience that you may be experiencing right now or that you experienced at some other time in your life', particularly ' the most stressful that you have experienced and is the most significant to you' and 'ideally one that you have not talked about in detail with others'. Participants were encouraged to write about the facts as well as their deepest feelings and to try to write about the same event for all four writing days. Finally they were encouraged to 'tell a story' and consider writing about how the event has affected their relationships, health or headaches. Writings were left with the research team at the end of the session. Not encouraged to practice at home. **Group 2 neutral writing control** Four sessions over 2 weeks (four 20 min	**Change in patient-reported headache frequency** (in last month (Mean SD)) Follow-up 3months (adjusted follow up adjusted for baseline value)	**Tension headache group** **Group1:** Baseline 9.94 (SD 7.22) Follow-up 12.24 (SD 7.90) Adjusted: 12.56 (SEM 1.60) **Group 2:** Baseline 9.65 (SD 6.64) Follow-up: 11.24 (SD 9.01) Adjusted: 11.74 (SEM 1.60) **Migraine group** **Group1:** Baseline: 9.65 (SD 6.46) Follow-up 9.00 (SD 5.81) Adjusted 9.37 (SEM 0.93) **Group 2:** Baseline 11.77 (SD 7.58) Follow-up 8.97 (SD 6.14) Adjusted 8.35 (SEM 0.94)	**Funding:** Arthritis Foundation and grant from National Institute of Health **Limitations:** Blinding unclear. Students were given course credit or money for participating. Migraine group headache frequency not comparable at baseline. **Additional outcomes:** Mood immediately following intervention. Physical
			Patient-reported headache intensity (0-10 scale 10=bad, mean (SD)) Follow-up 3months (adjusted for baseline value)	**Tension headache group** **Group1:** Baseline 5.47 (SD1.81) Follow up 5.00 (SD 1.62) Adjusted 5.00 (SEM 0.44) **Group 2:** Baseline 5.43 (SD 1.79) Follow up 4.71 (SD 1.80) Adjusted 4.73 (SEM 0.44) **Migraine group**	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 - Neutral writing control **N:** 17 **Drop outs:** 1 (but did complete follow-up) **Group 3 - Relaxation training** **N=**17 **Drop outs:** 0 **Migraine** **Age (mean):** 21.44 (SD 5.47) **M:F (n, %):** 80:10 (88.9: 11.1) **Group 1 – Written emotional disclosure** **N: 31** **Age (mean):** NR for any group **Drop outs:** 3 **Group 2 - neutral writing control** **N:** 31 **Drop outs:** 1 **Group 3- relaxation training** **N:** 28 (results not reported in this table)	sessions over 2 consecutive weeks). Engaged in time management writing to control for expectations, number of sessions, effort and attention from laboratory personnel received by both active groups. Participants wrote about their activities for the past week (session 1) and past 24h (session 2) and their planned activities for the next 24h (session 3) and next week (session 4). Instructions asked participants to write only about their actions but to refrain from writing about their feelings or opinions. Not encouraged to practice at home. Group 3- relaxation training results not reported in this table. **All patients** Completed prospectively a brief diary each evening during the follow-up period, recording the presence and severity of headaches each day.		**Group1:** Baseline 6.39 (SD 1.52) Follow up 5.23 (SD 2.28) Adjusted 5.25 (SEM 0.34) **Group 2:** Baseline 6.35 (SD 1.14) Follow up 5.55 (SD 1.69) Adjusted 5.60 (SEM 0.34)	symptoms. **Notes:** Randomisation: random numbers table in blocks of 6; performed separately for the tension and migraine headache samples. ACA
			Headache specific QoL (MIDAS) Follow-up 3months (adjusted follow up adjusted for baseline value)	**Tension headache group** **Group1:** Baseline 8.24 (SD 8.84) Follow up 8.35 (SD 8.89) Adjusted 9.23 (SEM 1.43 **Group 2:** Baseline 9.24 (SD 6.53) Follow-up 7.29 (SD 7.82) Adjusted 7.73 (SEM 1.42) **Migraine group** **Group1:** Baseline 13.35 (SD 11.83) Follow-up 9.87 (SD 8.79) Adjusted 10.05 (SEM 1.62) **Group 2:** Baseline 15.35 (SD 12.25) Follow up 10.13 (SD 11.49) Adjusted 9.13 (SEM 1.63)	

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Larsson & Melin, 1986[477] **Study design:** RCT **Comparison:** Relaxation training vs information contact **Setting:** 2 secondary schools, Sweden **Duration of follow-up:** 6 months (3 week baseline, 5-6 week treatment, 3-4 week Post-measurement period)	**Patient group:** Adolescents with TTH and combined TTH and migraine. **Inclusion criteria:** Age 16-18 years; Duration of headache >1 year; Symptom frequency of at least once per week (defined as chronic headache). **Exclusion criteria:** Somatic disease e.g. acute infection **All patients** **N:** 31 **Group 1 – relaxation training** **N:** 11 (10 F, 1 M) **Age (mean):** NR **Headache type:** TTH 9, combined 2 **Drop outs**: 1 **Group 2 – information contact** **N:** 13 (13 F) **Age (mean):** NR **Headache type:** TTH 11, combined 2	**Group 1 relaxation training** 9 sessions conducted by graduate students in clinical psychology (first 2 sessions) and a child psychiatrist (next 5 sessions) administered for 45 minutes twice a week for 5 weeks, following the guidelines of Bernstein and Borkovec, with minor modifications to tailor the treatment to the pupils' everyday problems and needs. The purpose was to teach a rapid relaxation method, 'cue-controlled' or applied to be used regularly in everyday situations in early headache symptoms or increased bodily tensions, particularly in the head muscles. During the first 4 sessions, in a group format of 3-4 individuals, training focussed on teaching discrimination between a tensed and relaxed state of different muscle groups throughout the body. In the following sessions the relaxation training was aimed at teaching and encouraging the pupils to apply the rapid relaxation technique paired with their breathing during which a cue word was subvocalised. The importance of regular home practice, at least twice a day, for 15-20 min, was emphasised. No taped or written instructions were provided for the pupils throughout the study. **Group 2 information contact** During the first 4 sessions the pupils met 2 clinical psychologists and were informed about the outlines of the treatment, prevalence and sex differences in chronic headache, and performed a behavioural analysis in which factors like stress and types of situations in which headache was likely to occur, were particularly noted. The information from this self-performed analysis was discussed with the pupils during the sessions without any direct suggestions	**Patient-reported headache frequency** (baseline and final values, mean) Post treatment ~9 weeks **Patient-reported headache intensity** (baseline and final, mean) on a scale of 0-5, with 5 being the worst Peak intensity recorded Post treatment ~9 weeks	**Group1:** 5.6 at baseline, 3.3 post-treatment, 2.2 at 6 months **Group 2:** 5.1 at baseline, 4.5 post-treatment, 4.2 at 6 months **Difference:** 2,28-6.4 **P value:** <0.01 **Group1:** 3.4 at baseline, 2.6 post-treatment, 3.1at 6 months **Group 2:** 3.4 at baseline, 3.3 post-treatment, 3.1 at 6 months	**Funding:** Swedish Board of Education **Limitations:** Randomisation and allocation concealment unclear. Investigator not blind to treatment. Unclear if assessor was blinded. Average age per group not reported. Not all outcomes reported. Participants were paid. **Additional outcomes:** Headache sum Headache-free days Headache duration Stress Medicine intake (data not reported) **Notes:** Mixed headache types. ACA

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 2 **Group 3 self-registration** **Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, TTH=tension type headache****Drop outs:** 0	from the therapist to change the situation. At the end of the first sessions the pupils' experiences for therapeutic improvement were rated. During the following 5 sessions the child psychiatrist briefly discussed common psychological and physiological causes of migraine and TTH and summed up the results of each individual's medical examination and headache diagnosis. No attempt was made to give the pupils specific, individual advice related to their headache complaints and particular questions raised were answered deliberately on a common sense level. Group 3 self-registration - Results not reported in this table **All patients** The pupils were given several psychological tests, aimed at assessing anxiety, depression and the experience of stress. Following these, a medical-neurological examination was performed and baseline phase was initiated, they kept a headache diary, where headache activity was recorded 4 times/day. Pupils continued to keep their headache diaries for at lest 3 weeks after completed treatment. The participants in the relaxation group were encouraged during the last session to continue to practice relaxation on a daily regular basis.			

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, TTH=tension type headache

Migraine

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: D'Souza et al, 2008[182] **Study design:** RCT **Comparison:** Written emotional disclosure vs neutral writing control **Setting:** University psychology department **Duration of follow-up:** 3 months	**Patient group:** Undergraduate psychology students with migraine or tension type headache (TTH). **Inclusion criteria:** Fulfilled IHS criteria for either migraine or TTH. Headaches at least twice per week that were of moderate or severe intensity OR migraine headache at least once a month. **Exclusion criteria:** Headaches suspected to be due to neurological disease, alcohol abuse or a primary medical disorder or those currently in psychotherapy or counselling. **All patients** **N:** 141 (51 TTH, 90 migraine) **Drop outs:** 6 **Tension Type Headache** **Age (mean, SD):** 20.27 (2.30) **M:F (n, %):** 42:9 (82.4: 17.6) **Group 1 – Written emotional disclosure (WED)** **N:** 17 **Age (mean):** NR	**Group 1 Written emotional disclosure (WED)** 4 sessions over 2 weeks (four 20 min sessions over 2 consecutive weeks). Standard instructions to write about 'a trauma or upheaval or stressful experience that you may be experiencing right now or that you experienced at some other time in your life', particularly ' the most stressful that you have experienced and is the most significant to you' and 'ideally one that you have not talked about in detail with others'. Participants were encouraged to write about the facts as well as their deepest feelings and to try to write about the same event for all four writing days. Finally they were encouraged to 'tell a story' and consider writing about how the event has affected their relationships, health or headaches. Writings were left with the research team at the end of the session. Not encouraged to practice at home. **Group 2 neutral writing control** 4 sessions over 2 weeks (four 20 min sessions over 2 consecutive weeks). Engaged in time management writing to control for expectations, number of sessions, effort and attention from	**Change in patient-reported headache frequency** (in last month (Mean SD)) Follow-up 3months (adjusted follow up adjusted for baseline value) **Patient-reported headache intensity** (0-10 scale 10=bad, mean (SD)) Follow-up 3months (adjusted follow up adjusted for baseline value)	**Tension headache** **Group1:** 9.94 (SD 7.22) at baseline, 12.24 (SD 7.90) at follow-up, 12.56 (SEM 1.60) adjusted follow-up **Group 2:** 9.65 (SD 6.64) at baseline, 11.24 (SD 9.01) at follow-up, 11.74 (SEM 1.60) adjusted follow-up **Migraine** **Group1:** 9.65 (SD 6.46) at baseline, 9.00 (SD 5.81) at follow-up, 9.37 (SEM 0.93) adjusted follow-up **Group 2**: 11.77 (SD 7.58) at baseline, 8.97 (SD 6.14) at follow-up, 8.35 (SEM 0.94) adjusted follow-up **Tension headache** **Group1:** 5.47 (SD1.81) at baseline, 5.00 (SD 1.62) at follow-up, 5.00 (SEM 0.44) adjusted follow-up **Group 2:** 5.43 (SD 1.79) at baseline, 4.71 (SD 1.80) at follow-up, 4.73 (SEM 0.44) adjusted follow-up **Migraine group** **Group1:** 6.39 (SD 1.52) at	**Funding:** Arthritis Foundation and grant from National Institute of Health **Limitations:** Blinding unclear Students were given course credit or money for participating. Migraine group headache frequency not comparable at baseline. N completing 3 month follow-up unclear. **Additional outcomes:** Mood immediately following intervention. Physical symptoms. **Notes:**

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 0 **Group 2 - neutral writing control** **N:** 17 **Age (mean):** NR **Drop outs:**1 **Group 3-relaxation training** N: **17** **Migraine** **Age (mean):** 21.44 (SD 5.47) **M:F (n, %):** 80:10 (88.9: 11.1) **Group 1 – Written emotional disclosure (WED)** **N:** 31 **Age (mean):** NR **Drop outs:** 3 **Group 2 - neutral writing control** **N:** 31 **Age (mean):** Not Reported **Drop outs:** 1 **Group 3- relaxation training** N: **28**	laboratory personnel received by both active groups. Participants wrote about their activities for the past week (session 1) and past 24h (session 2) and their planned activities for the next 24h (session 3) and next week (session 4). Instructions asked participants to write only about their actions but to refrain from writing about their feelings or opinions. Not encouraged to practice at home. Group 3- relaxation training results not reported in this table. **All patients** Completed prospectively a brief diary each evening during the follow-up period, recording the presence and severity of headaches each day.	**Headache specific QoL (MIDAS)** Follow-up 3months (adjusted follow up adjusted for baseline value)	baseline, 5.23 (SD 2.28) at follow-up, 5.25 (SEM 0.34) adjusted follow-up **Group 2:** 6.35 (SD 1.14) at baseline, 5.55 (SD 1.69) at follow-up, 5.60 (SEM 0.34) adjusted follow-up **Tension headache** **Group1:** 8.24 (SD 8.84) at baseline, 8.35 (SD 8.89) at follow-up, 9.23 (SEM 1.43) adjusted follow-up **Group 2:** 9.24 (SD 6.53) at baseline, 7.29 (SD 7.82) at follow-up, 7.73 (SEM 1.42) adjusted follow-up **Migraine** **Group1:** 13.35 (SD 11.83) at baseline,9.87 (SD 8.79) at follow-up, 10.05 (SEM 1.62) adjusted follow-up **Group 2:** 15.35 (SD 12.25) at baseline, 10.13 (SD 11.49) at follow-up, 9.13 (SEM 1.63) adjusted follow-up	Randomisation: random numbers table in blocks of 6; performed separately for the tension and migraine headache samples. ITT with last observation carried forward.

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, TTH=tension type headache, WED=written emotional disclosure

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Richter et al, 1986[666] **Study design:** RCT **Comparison:** Relaxation training / cognitive coping vs placebo **Setting:** Children's Hospital, Canada **Duration of follow-up:** 16 weeks (4 week baseline, 6 week treatment, 4 weeks post-treatment, 4 weeks follow-up)	**Patient group:** Children and adolescents with migraine **Inclusion criteria:** Age 9-18 years; Confirmation of the diagnosis of classical or common migraine by a project neurologist using the diagnostic criteria of intermittent paroxysmal headache and any 2 of the following 4 symptoms: throbbing pain, scotomata or related neurologic phenomena, nausea and/or vomiting and a positive family history; Minimum headache history of 3 months; Average frequency of once per week; No new prophylactic medication within the previous 2 months; Minimum IQ of 80 on the PPVT. **Exclusion criteria:** Allergic; purely dietary or menstrual headache; Unstable emotional or medical problems likely to require other medications. **All patients** **N:** 51 (17 M, 34 F), 42 evaluable **Age (mean):** 12.87 **Drop outs:** 8, and 1 child failed	**Group 1 – relaxation training** Closely followed the procedure developed by Cautela and Groden for children. Subjects were taught the sequential tensing and relaxing of large muscle groups and the use of deep breathing to achieve total body relaxation. They were then taught sequential relaxation without tensing, differential relaxation, self-cueing and 'mini' relaxation. They were instructed to practice daily and to use their relaxation skills as soon as they noticed stress levels rising, if they were involved in a stress-producing situation, or at the onset of a headache. **Group 2 - cognitive coping** This programme, called 'thinking straight' was developed by the authors as a downward extension of Holroyd and Andrasik's cognitive self-control programme and Bakal's cognitive-behavioural treatment. It emphasised altering maladaptive thought processes which mediate unpleasant emotions and biochemical concomitants which may precipitate the headache process. The programme used elements of cognitive restructuring, the cognitive control of pain, fantasy, simple problem solving and stress-inoculation training. Children were taught to monitor their stress reactions on a daily basis, to record and restructure thought processes, and to note the emotional correlates of their cognitive patterns. They were instructed to use the procedures in all stress-provoking situations as well as for the control of headache pain. Personalised cards containing coping statements were prepared for each subject. **Group 3 - placebo**	**Change in patient-reported headache frequency** baseline and final values, mean (SD)) Follow up at 14 weeks **Change in patient-reported headache intensity** (baseline and final values, mean (SD)) Peak intensity on a scale of 0-5 Follow up at 14 weeks	**Group1:** Baseline 9.03 (8.05) Follow-up 2.91 (3.40) **Group 2:** Baseline 8.14 (7.82) Follow-up 2.52 (2.94) **Group 3:** Baseline 7.26 (6.12) Follow-up 4.68 (5.83) **Group1:** Baseline 3.60 (1.08) Follow-up 2.08 (1.73) **Group 2:** Baseline 3.37 (0.77) Follow-up 1.96 (1.23) **Group 3:** Baseline 3.58 (0.76) Follow-up 2.02 (1.39)	**Funding:** Ontario Ministry of Health and the Ontario Ministry of Community and Social Services **Limitations:** Randomisation method unclear **Additional outcomes:** Headache duration Headache index **Notes:** Available case analysis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	to monitor adequately during follow-up **Group 1 – relaxation training** **N:** 15 **Age (mean):** NR **Drop outs:** not stated **Group 2 – cognitive coping** **N:** 15 **Age (mean):** NR **Drop outs:** NR **Group 3 – placebo** **N:** 12 **Age (mean):** NR **Drop outs:** NR	Attention-control or non-specific condition, 'stress reduction training'. Structurally identical to the experimental groups, i.e. it provided information on the causes of migraine, a credible treatment rationale, expectations for improvement, a set of sham 'coping skills' and daily homework. Subjects were taught to recognise and label their emotions, to relate them to the situation in which they occurred, and to discuss their feelings daily with a friend o parent. Considered a credible placebo, not unlike non-directive psychotherapy with no theoretically active treatment components. **All patients** Baseline phase: patients were taught to monitor headache activity 4 times daily using a headache diary. All subjects received 1hour of individual therapy weekly which followed detailed treatment manuals to standardised procedures. In the first session all groups were given information about the nature of migraine, the role of stress and other triggers, and the specific treatment rationale was explained. The 3 rationales were identical except for slight differences in explaining the respective mechanisms of action. All treatments were presented as stress-coping techniques which could be used to reduce tension and anxiety and thereby short-circuit the migraine process.			

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Varkey et al, 2011[819] **Study design:** RCT **Comparison:** Exercise vs topiramate vs relaxation **Setting:** Specialist headache clinic, Sweden **Duration of follow-up:** 3 and 6 months after treatment.	**Patient group:** Patients with migraine recruited from newspaper adverts and headache clinic. **Inclusion criteria:** Aged 18-65; migraine with or without aura according to ICHD-II criteria; frequency of 2-8 attacks per month; had migraine for at least 1 year before participating in the study and before the age of 50. **Exclusion criteria:** Interval headaches not distinguishable from migraine; medication overuse headache; regular exercise (once or more per week during the 12 weeks prior to the study); earlier practice of relaxation, pregnancy, breastfeeding or use of daily migraine prophylaxis in the 12 weeks prior to the study; inability to understand Swedish; use of antipsychotic or antidepressive medication in the 12 weeks prior to the study; drug or alcohol abuse;, topiramate intolerance. **All patients** **N:** 91 **Age (mean):** 44.4 (11.3) **Drop outs**: 44	**Group 1 - Exercise** Trained with a registered physiotherapist for 40 minutes three times/ week. Exercise programme based on indoor cycling and the rate of perceived exertion was used to set the intensity of the exercise programme. Training session included 15 min warm up, 20 min exercise programme, 5 min cool down. There was opportunity to discuss the exercise programme with the therapist after the session. If participant was absent they exercised at home or a local gym. All forms of continuous aerobic exercise were then accepted, participants instructed to reproduce same intensity and duration of exercise used in the programme. Participants who exercised 1/ week at clinic and >2/ week were considered adhering to treatment. **Group 2 - Topiramate** Visited neurologist before starting a course of topiramate. Dosage was increased by 25mg/week until the dosage	**Responder rate** (50% reduction in migraine attack frequency) at 3 months	**Group 1:** 9/30 **Group 2:** 8/31 **Group 3:** 7/30 **p value:** NR	**Funding:** Swedish research council, Gothenburg research and development council, Swedish association of physiotherapists, Renee Eander fund, Neurological research foundation, Olle Engkvists Byggmastare foundation, Glaxosmithkline, Astrazeneca. **Limitations:** Single blind (evaluator only). >10% dropped out of study at 3 month follow up, but similar in all groups. Unclear for how long patients trained with a physical therapist- reads as though only at the beginning then participant took control of exercise programme for at least 2 of the 3 sessions per week. Study based on a self selected sample. Patients who already undertook regular exercise were excluded. **Additional outcomes:** Body weight VO_2max Data at 6 months
			Change in patient-reported migraine days (n/month, least squares mean (SE)) **[SD] Change from baseline at 3 months	**Group 1:** -2.23 (0.55) **[3.01] **Group 2:** -2.08 (0.54) **[3.01] **Group 3:** -1.47 (0.55) **[3.01] **p value:** NR	
			Change in patient-reported migraine frequency (attacks†/month, least squares mean (SE)) **[SD] Change from baseline at 3 months	**Group 1:** -0.98 (0.58) **[1.53] **Group 2:** -0.68 (0.28) **[1.56] **Group 3:** -0.94 (0.28) **[1.53] **p value:** NR	
			Change in patient-reported migraine intensity (VAS 0-100, least squares mean (SE)) **[SD] Change from baseline at 3 months	**Group 1:** -7.1 (3.5) **[19.17] **Group 2:** -13.7 **[18.93] **Group 3:** -5.1 (3.5) **[19.17] **p value:** NR	
			Headache specific QoL Swedish version of	**Group 1:** 5.0 (2.3) **[12.60] **Group 2:** 2.4 (2.3)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 – Exercise **N:** 30 **Age (mean):** 47 (10.8) **Drop outs:** 8 at 3 months, 5 withdrew (1 lack of time, 4 non-compliance) 3 no data, 14 at 6 months. **M/F:** 5/ 25 **Disease duration (years):** 28.8 (11.0) **Migraine frequency (days/month):**7 (3.8) **Migraine frequency (attacks†/month):**4.3 (2.0) **Frequency of headache medication used (doses/month):** 6.9 (4.1) **Intensity of pain (median, IQR):** 50 (26-64) **MSQoL (median, IQR):** 60 (43-77) **Group 2 - topiramate** **N:** 31 **Age (mean):** 44.4 (9.2) **Drop outs: :** 11 at 3 months, 10 withdrew (7 refused drugs, 3 adverse events) 1 no data, 14 at 6 months. **M/F:**2/29 **Disease duration (years):** 25.1 (11.4) **Migraine frequency (days):** 7.5 (3.9) **Migraine frequency (attacks):**3.6 (1.6)	reached the highest dose that the individual could tolerate, maximum of 200mg/day. Allowed to call neurologist any time of day during the treatment period to book a scheduled visit if needed. At least 1 follow up visit was scheduled. Adherence defined as using the medicine for > 2 months in accordance with prescription and was measured using self reports. **Group 3 – Relaxation** Scheduled individual appointment with a registered physiotherapist once a week. The programme was based on common forms of relaxation, breathing and stress-management techniques (described by Larsson and Andrasik) and includes a series of 6 exercises, each of which is based on the one before. Each lasted between 5-20minutes and verbal and written information was given before the introduction of a new relaxation exercise. After each session there was an opportunity to discuss their progress with the	the migraine specific QoL questionnaire [Scale 1- 100] least squares mean (SE) **[SD] **Use of acute pharmacological treatment** (doses/ month) least squares mean (SE) **[SD] **Incidence of adverse events (%)** **NB none were serious**	**[12.81] **Group 3:** 3.1 (2.4) **[13.15] **p value:** NR **Group 1:** -2.72 (0.55) **[3.01] **Group 2:** -2.71 (0.54) **[3.01] **Group 3: -**2.84 (0.54) **[2.96] **p value:** NR **Group1:** 0/30 **Group 2:** 3/31* **Group 3:** 0/30 **p value:** NR	**Notes:** ANCOVA used to adjust for baseline differences (these results are reported) ** SD calculated by NCGC ITT analysis undertaken with last observation carried forward for missing data. *3 patients state AE as reason for withdrawal. 8 patients reported AEs in total. No serious AEs reported. Participants randomised after the baseline period. Randomisation by independent person by a lottery method. †Migraine attack defined as concomitant days with migraine headache and distinct attacks were counted if separated by ≥24 hours.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Frequency of headache medication used (doses): 7.1 (5.3) **Intensity of pain (VAS) (median, IQR):** 40 (29-58) **MSQoL (median, IQR):** 60 (48-73) **Group 3 – relaxation** (N=30) **N:** 30 **Age (mean):** 41.5 (11.4) **Drop outs:** 7 at 3 months, 4 withdrew (2 not satisfied, 1 lack of time, 1 unexplained) 1 no data, 16 at 6 months. **M/F:** 2/28 **Disease duration (years):** 22.2 (11.8) **Migraine frequency (days/month):**7.6 (3.8) **Migraine frequency (attacks†/month):**4.2 (1.6) **Frequency of headache medication used (doses/month):** 6.5 (4.6) **Intensity of pain (median, IQR):** 39 (26-55) **MSQoL (median, IQR):** 58 (51-67)	physiotherapist. Between sessions they practised at home every day with a CD. Adherence was defined as participating in 6 or more sessions at the clinic. Verbal confirmation of practice at home was also required. **All groups** 4- 12 week baseline period, followed by 12 week treatment period. All participants were allowed to contract the physiotherapist or neurologist with questions (telephone or visit). No restriction was made on the use of concomitant acute medication.			

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, MSQoL=Migraine specific quality of life, ICHD=International Classification of Headache Disorders

E.3.4 Prophylactic non-pharmacological management of primary headaches with dietary supplements and herbal remedies

Dietary supplements

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Peikert et al, 1996[617] **Study design:** RCT **Comparison:** Magnesium vs placebo **Setting:** outpatients **Duration of follow-up:** 4 weeks baseline, 12 weeks treatment	**Patient group** Adults meeting IHS criteria for migraine with or without aura **Inclusion criteria:** Patients aged 18-65 years IHS criteria for migraine with or without aura **Exclusion criteria:** Pregnancy or nursing, known ammonium-phosphate-calculus-diastheses, kidney function disorders with serum creatinine higher than 1.5 mg/dL, other interfering medical disorders, known allergies to any of the components of the preparations, serious psychiatric diseases, tendencies towards substance-dependent or abusive behaviour, and inability to distinguish migraine from other headaches. **All patients** **N:** 81 **Group 1** – Magnesium [mean, SD] **N:** 43 **Age (mean):** 43.8 (10.7) **Drop outs:** 7 **Duration since onset (month):** 203.2 (130.8) **Frequency of attacks/ 4 weeks:** 3.63 (1.76) **No of days with migraine/ 4 weeks:** 4.95 (2.69)	**Group 1 600mg (24 mmol) magnesium** (trimagnesium dicitrate magnesium diasporal, Germany) water soluble granular powder every morning **Group 2 - magnesium free placebo powder** for 12 weeks	**Change in patient-reported migraine days** Mean (SD) Group1 n=43 Group 2 n=38	**Group1:** -2.49 (0.05) **Group 2:** -1.16 (3.89) **p value:** 0.04	**Funding:** NR **Limitations:** **Additional outcomes:** More than 50% reduction in migraine days **Notes:** Analysis carried out on ITT population, apart from responder rate outcome which was undertaken on PP analysis. All figures are mean reduction-no baseline and final values available). No prophylaxis 3 months prior to study. Acute medication allowed (monotherapy and polytherapy, including acetylsalicylic acid, sumatriptan, metoclopramide, simple analgesics + codeine, ergot + caffeine).
			Change in patient-reported migraine intensity (intensity of attacks recorded on VAS) Group1 n=43 Group 2 n=38	**Group1:** -2.06 (2.77) **Group 2:** -1.25 (2.29) **p value:** 0.3199	
			Change in patient-reported migraine frequency mean (SD) Group1 n=43 Group 2 n=38	**Group1:** -1.51 (2.07) **Group 2:** -0.58 (2.30) **p value:** 0.0303	
			Responder rate (50% reduction in migraine days) Group1 n=36 Group 2 n=32	**Group1:** 19/36 (52.7%) **Group 2:** 11/32 (34.4%) **p value:** 0.149	
			Change in use of acute pharmacological treatment Group1 n=43	**Group1:** -5.07 (6.58) **Group 2:** -2.40 (6.59) **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Duration of attacks (days): 1.42 (0.76) **Severity of attacks (VAS):** 6.02 (1.87) **Group 2 - Placebo** **N:** 38 **Age (mean):** 47.6 (10) **Drop outs:** 6 **Duration since onset (months):** 181.6 (125.5) **Frequency of attacks/ 4 weeks:** 3.66 (1.71) **No of days with migraine/ 4 weeks:** 5.47 (3.19) **Duration of attacks (days):** 1.66 (1.22) **Severity of attacks (VAS):** 6.35 (1.92)		Group 2 n=38 (Mean reduction Per patient, (number of single doses)) **Incidence of serious adverse events** Patients dropped out due to AE	 **Group1:** 3/43 (7%) **Group 2:** 0/38 **p value:** NR	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, PP=per protocol, CI=confidence interval, AE=adverse event, IHS=International Headache Society, VAS=visual analogue scale

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Schoenen et al, 1998[706] **Study design:** RCT **Comparison:** Riboflavin vs Placebo **Setting:** NR **Duration of follow-up:** 1 month baseline then randomised to 3 months treatment	**Patient group:** Adults with, migraine with or without aura defined by IHS **Inclusion criteria:** Patients aged 18-65 years, migraine with or without aura defined by IHS. History of migraine at least 1 year, between 2 and 8 attacks per month, had no more than 5 days of interval headaches per month, had no analgesic or ergotamine over-consumption, no serious organic or psychiatric disease. Women required to have adequate contraception. **Exclusion criteria:** NR **All patients** **N=** 54 **Group 1 – Riboflavin** [mean, range] **N:** 28 **Age (mean):** 36.9 (18-62) **Drop outs:** 1 **No of women:** 21 **Attack frequency (/month):** 3.83 (2-6) **Attack duration (hr):** 35.42 (6-84) **Migraine history:** with aura: 23, without aura: 1, both: 4 **Disease duration:** 11.8 (1-40) **Group 2 - Placebo**	**Group 1 Riboflavin** – oral 400mg (Riboflavinum D 2914A, Federa, Brussels) **Group 2 – Placebo** (Avicel RC 581 850mg + betacarotene 0.4733 mg)	**Change in patient-reported headache frequency** Median (5th -95th percentiles) Group 1 n=28 Group 2 n=26	**Group1:** -2.0 (-.4, 1) **Group 2:** 0 (-2.0, 2.0) **p value:** 0.0001	**Funding:** Belgian Migraine society **Limitations:** Uses headache days and migraine days interchangeably. **Additional outcomes:** None **Notes:** Randomised in 10 blocks of 10 packages, each block comprised 5 placebo and 5 active treatments. All figures for outcomes are medians No baseline and final values available- only change values. p values Mann Whitney U test, Fisher's exact test (two tailed) for responder rate. Four point scale used to determine severity of migraine. Patients took acute medications including oral or rectal analgesics with antiemetics, oral or subcutaneous sumatriptan, and some took ergotamine-containing preparations. *calculated by NCGC
			Change in patient-reported headache days Median (5th -95th percentiles) Group 1 n=28 Group 2 n=26	**Group1:** -3.0 (-9.0, 1) **Group 2:** 0.50 (-5.0, 7.0) **p value:** 0.0001	
			Change in patient-reported headache intensity Severity- four point scale, Median (5th - 95th percentiles) Group 1 n=28 Group 2 n=26	**Group1:** 0 (-2.5, 0.43) **Group 2:** 0.05 (-1.0, 1) **p value:** 0.031	
			Responder rate 50% reduction in migraine days Group 1 n=28 Group 2 n=26	**Group1:** 17/ 28* (59%) **Group 2:** 4/26* (15%) **p value:** 0.002	
			Use of acute pharmacological treatment Per migraine day	**Group1:** 0 (-1.67, 1.25) **Group 2:** 0 (-0.75, 1.30)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 26 **Age (mean):** 35.2 (19-53) **Drop outs:** 3 **No of women:** 21 **Attack frequency (/months):** 3.71 (2-7) **Attack duration (hr):** 32.35 (6-72) **Migraine history:** with aura: 19, without aura: 2, both: 5 **Disease duration:** 13.9 (1-47)		Median (5th -95th percentiles) Group 1 n=28 Group 2 n=26	**p value:** 0.369	

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

Herbal remedies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Lipton et al, 2004[506] **Study design:** RCT **Comparison:** Butterbur vs placebo **Setting:** 9 primary care or specialist centres in USA and Germany **Duration of follow-up:** 4 week baseline, randomised to treatment for 16 weeks	**Patient group:** Adults with migraine with or without aura. **Inclusion criteria:** Aged 18-65. Range of 2-6 attacks per month for 3 months prior to study. Age at onset of migraine was younger than 50. Patients required to have a minimum of 2 attacks during baseline phase. Other prophylactic medication had to be discontinued at least 3 months prior to study participation. Participants excluded if they had more than 6 non-migraine headaches per month during the previous3 months prior to the study. **Exclusion criteria:** Non- migraine attacks for >6 days per month during the previous 3 months prior to start of the study. women who were pregnant, breast feeding, or of child bearing potential not using medically accepted birth control measures were excluded. **All patients** **N:** 245 **Drop outs:** 31 **Group 1 – 50 mg bid [mean, range]** **N:** 79 **Age (mean, range):** 41 (22-60) **Female (%):** 87 **Drop outs:** 8 **Type of migraine: with aura:** 16	**Group 1 – 50 mg bid butterbur root extract** Single capsule, twice a day **Group 2 – 75 mg bid butterbur root extract** Single capsule, twice a day **Group 3 - placebo** Single capsule, twice a day 4 week baseline then, 16 week treatment	**Change in patient-reported headache/migraine frequency** Mean % change in headache frequency	**Month 3** **Group1:** 42 **Group 2:** 58 **Group 3:** 26 **Month 4** **Group1:** 40 **Group 2:** 51 **Group 3:** 32	**Funding:** NR **Limitations:** >10% study population dropped out. Reported as mean % change therefore data cannot be pooled. **Notes:** Patients taking <80% of medication considered non compliant. Randomisation schedule performed by computer program. Each centre allocated a block of patient numbers and associated treatments. Double blind study medication assembled for each patient number according to the randomisation code prepared by an independent statistician. Analyses carried out on ITT population. *n calculated by NCGC.
			Responder rate* 50% reduction in migraine attack frequency per month relative to baseline	**Month 3** **Group1:** 47/79 (59%) **Group 2:** 53/75 (71%) **Group 3:** 39/75 (52%) **Month 4** **Group1:** 44/79 (56%) **Group 2:**51/75 **(**68%) **Group 3:** 37/75 (49%)	
			Incidence of serious adverse events (number of patients) None judged to be treatment related	**Group1:** 0/79 **Group 2:** 3/75 (4%) **Group 3**: 3/75 (4%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	without aura: 55 **both:** 0 **Attack frequency:** 3 (2-6) **Attack days/month:** 3 (2-7) **Attack duration (h):** 13 (4-61) **Attack intensity score:** 2 (1.5-3) **<u>Group 2</u> - <u>75 mg bid</u> [mean, range]** **N:** 77 **Female (%):** 79 **Age (mean, range):** 42 (22-60) **Drop outs:** 9 **Type of migraine:with aura:** 19 **without aura:** 49 **both:** 0 **Attack frequency:** 3 (2-7) **Attack days/month:** 3 (2-7) **Attack duration (h):** 12 (4-45) **Attack intensity score:** 2 (1.5-3) **<u>Group 3 – placebo</u> [mean, range]** **N:** 77 **Female (%):** 79 **Age (mean, range)**: 42 (22-58) **Dropout:** 14 **Type of migraine: with aura:** 12 **without aura:** 48 **both:** 3 **Attack frequency:** 3 (2-7) **Attack days/month:** 3 (2-8) **Attack duration (h):** 11 (2-46) **Attack intensity score:** 2 (1.7-2.7)				

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Grossman & Schmidramsl, 2000[344] **Study design:** Double blind RCT **Comparison:** Butterbur (Petasites) vs placebo **Setting:** Outpatients, Department of neurology of municipal hospital, Munich-Harlaching **Duration of follow-up:** 4 week run in , 12 week therapy	**Patient group:** Adults with migraine with or without aura. **Inclusion criteria:** Aged 18- 60 years. Minimum of 3 attacks per month within the last 3 months prior to the start of the study and a minimum of 2 attacks in the run-in phase after 4 weeks without trial medication necessary for recruitment. Other inclusion criteria defined by IHS. **Exclusion criteria:** Treatment with other agents known to have an effect on migraine within 4 weeks prior to the start of the run-in phase and regular consumption of analgesics for more than 12 days per month. Other exclusion criteria defined by IHS. **<u>All patients</u>** **N:** 60 **Drop outs:** 2 **<u>Group 1 –</u> 150 mg Petasites hybridus (Butterbur) [mean, SD]** **N:** 33 **Age (mean):** 29 (9.26) **Drop outs:** 2 **Gender % (m/f):** 51/49 **Age at first attack:** 17.6 (4.82) **Attacks per month:** 3.4 (1.06) **Previous therapy (months):** 13.8 (17.23) **Attacks per month:** 3.4 (1.48) **Days with attacks per month:** 3.6	**Group 1- 150 mg Petasites hybridus (butterbur root extract) Diener states 2 x 50 mg per day** 2 capsules twice daily **Group 2- Placebo** 2 capsules twice daily Both groups Patients seen at 4 week intervals	**Patient-reported migraine frequency** Number of days with attacks per 4 weeks (Mean, SD)	**<u>Baseline:</u>** **Group1:** 3.6 (1.93) **Group 2:** 3.0 (1.27) **<u>12 weeks:</u>** **Group1:** 1.8 (0.95) **Group 2:** 2.6 (1.15) **p value:** 0.7172	**Funding:** NR **Limitations:** Grossman 2000 randomisation and AC NR, Diener 2004C both reported. Discrepancy between what Grossman and Diener report in intervention group. **Additional outcomes:** Change in migraine duration. Mean number of accompanying symptoms. **Notes:** Diener 2004C was a reanalysis of Grossman 2000. Re-analysed using Mann Whitney U as data skewed. Reported mean (SD) as first publication did. Figures from Diener 2004C. *n calculated by NCGC.
			Patient-reported migraine intensity Mean per month, SD (VAS)	**<u>Baseline:</u>** **Group1:** 3.9 (0.91) **Group 2:** 3.6 (0.73) **<u>12 weeks:</u>** **Group1:** 3.1 (1.73) **Group 2:** 3.4 (1.08) **p value:** 0.6257	
			Responder rate* 50% reduction in migraine attacks per month from baseline	**Group1:** 16/33 (48%) **Group 2:** 4/27 (15%) **p value:** NR	
			% of patients using acute pharmacological treatment*	**<u>Baseline:</u>** **Group1:** 15/33 (44%) **Group 2:** 7/27 (27%) **<u>12 weeks:</u>** **Group1:** 6/33 (18%) **Group 2:** 7/27 (26%) **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	(1.93) **Duration of attacks per month:** 9.4 (3.32) **Intensity of attacks per month:** 3.9 (0.91) **Attacks with acute medication (%) during 4 week run in period:** 20.6 (31.51) **<u>Group 2 - Placebo</u>** **N:** 27 **Age (mean):** 29.1 (9.46) **Drop outs:** 0 **Gender (m/f):** 55/45 **Age at first attack:** 19.7 (5.15) **Attacks per month:** 3.1 (0.85) **Previous therapy (months):** 13.1 (18.51) **Attacks per month:** 2.9 (1.15) **Days with attacks per month:** 3.0 (1.27) **Duration of attacks per month:** 9.3 (3.94) **Intensity of attacks per month:** 3.6 (0.73) **Attacks with acute medication (%):** 12.8 (25.41)				

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Pfaffenrath et al, 2002[625] **Study design:** RCT **Comparison:** Feverfew vs placebo **Setting:** Outpatients, 10 centres in Germany. **Duration of follow-up:** 84 days	**Patient group:** Adults with migraine with or without aura **Inclusion criteria:** Male or female outpatients between 18 and 65 years. Diagnosis of migraine with or without aura according to IHS, migraine attacks for at least 1 year and age of onset <50 years, average of 2 to 6 migraines per month, within the last 3 months prior to study entry, 2-6 migraine attacks within the 4 week baseline period, a total of at least 36 hrs with migraine during the baseline period, stable drug treatment regimen of migraine attacks, patients ability to distinguish between migraine and other headaches, no prophylactic migraine treatment within 4 weeks prior to screening. **Exclusion criteria:** Hypersensitivity to study medication, pregnancy, intake of analgesics, ergot preparations or other established drugs for acute migraine attack on >10 days per month, the use of antidepressants, neuroleptics, tranquilisers, medications for headache prophylaxis, medications with headache as side effect, magnesium containing drugs as well as additional non drug therapies for migraine, >10 days with headaches other than migraine per month, experience with more that 3 different migraine prophylactic drugs in the past, drug misuse or dependency, expected lack of compliance, psychiatric disorders according to DSM-IV, confirmed diagnosis of GI or CV complaints, other severe disease, participation in clinical trials within the last 3 months or simultaneous participation in another clinical investigation.	**Group 1 – 2.08 mg Feverfew** **Group 2 - 6.25 mg Feverfew** **Group 3 – 18.75 mg Feverfew** **Group 4- placebo**	**Patient-reported migraine frequency** Mean (SD) **Group 1 n=28** **Group 2 n=28** **Group 3 n=29** **Group 4 n=25**	**<u>Baseline</u>** **Group1:** 2.8(1.2) **Group 2:** 4.0(1.4) **Group 3:** 3.0(0.9) **Group 4:** 3.3(1.2) **<u>Individual last visit</u>** **Group1:** 2.6(1.8) **Group 2:** 3.2(1.4) **Group 3:** 2.7(1.7) **Group 4:** 2.6(2.1) **<u>Mean change</u>** **Group1:** -0.2(1.3) **Group 2:** -0.9(1.8) **Group 3:** -0.3(1.7) **Group 4:**-0.7(1.9) **95% CI:** NR **p value:** NR	**Funding:** NR **Limitations:** Allocation concealment unclear. 35 dropouts (>10%). Per protocol analysis (n=110) exclude all patients with major protocol violations. **Additional outcomes:** Maximum intensity of migraine attacks (VAS). Attacks with confinement to bed. Missed working days due to migraine. Type and amount of additionally taken medications for the treatment of migraine attacks, but NR. **Notes:** Randomisation after 4 week baseline period. Traditional effective dose 1.05g, equivalent to 6.25 mg extract. Medications prepared as soft gelatine capsules identical in appearance weight size taste and smell. Randomisation in centre
			Responder rate * (More than 50% improvement of migraine attack frequency) N=147	**Group1:** 6/37 (16.2) **Group 2:** 10/36 (27.8) **Group 3:** 9/39 (23.1) **Group 4:** 11/35 (31.4) **95% CI:** NR **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	<u>All patients</u> **N:** 147 **<u>Group 1 –</u> Feverfew 2.08 mg [mean (SD)]** **N:** 37 **Age (mean):** 42 (15) **Drop outs:** 11 **m/f:**2/7 **attacks of migraine: total #:**2.9+/-1.1 **total duration (h/month**): 86+/-53.1 **attack duration (h):** 33 (21.3) **max intensity (cm/ vas):** 7.3 (1.4) **max severity (score):** 3.3 (0.6) **Days with accompanying migraine symptoms:** 1.7 (1.3) **Missed working days due to migraine:** 0.6 (1.2) **<u>Group 2</u> - Feverfew 6.25 mg [mean (SD)]** **N:** 36 **Age (mean):** 44 (10) **Drop outs:** 8 **m/f:** 5/14 **attacks of migraine: total #:** 3.7 (1.4) **total duration (h/month):** 89.5 (54.6) **attack duration (h):** 26.7 (19.3) **max intensity (cm/ vas):** 7.6 (1.7) **max severity (score):** 3.3 (0.7) **Days with accompanying migraine symptoms:**1.5 (2.0) **Missed working days due to migraine:** 1.3 (1.7) **<u>Group 3</u> - Feverfew 18.75 mg [mean (SD)]** **N:** 39 **Age (mean):** 49 (9)				specific blocks on basis of randomisation code generated by alphamed. Assignment of random numbers to patients was carried out in consecutive order according to time of enrolment into study. -1 serious AE in placebo group- hospitalisation due to ovarian cyst- not related to drug treatment *n calculated by NCGC

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 7 **m/f:** 1/7 **attacks of migraine: total #:** 3 (1.1) **total duration (h/month):** 96 (69.6) **attack duration (h):** 31.4 (15.7) **max intensity (cm/ vas):** 7.3 (1.5) **max severity (score):** 3.2 (0.6) **Days with accompanying migraine symptoms:** 2.0 (3.1) **Missed working days due to migraine:** 1.2 (2.0) **<u>Group 4 - Placebo</u> [mean (SD)]** **N:** 35 **Age (mean):** 45 (13) **Drop outs:** 9 **m/f**:5/8 **attacks of migraine:** **total #:** 3.2 (1.3) **total duration (h/month):** 92 (63) **attack duration (h):** 30.5 (20.1) **max intensity (cm/ vas):** 7.4 (1.7) **max severity (score):**3.3 (0.7) **Days with accompanying migraine symptoms:** 1.7 (2.2) **Missed working days due to migraine**: 0.9 (1.6)				

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, GI=castrointestinal, CV=cardiovascular, VAS=visual analogue scale

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Diener et al, 2005A[224] **Study design:** RCT **Comparison:** Feverfew vs Placebo **Setting:** Outpatients, 10 centres in Germany, 4 in France **Duration of follow-up:** 112 days	**Patient group:** Adults with migraine with or without aura. **Inclusion criteria:** 18 and 65 years. Diagnosis of migraine with or without aura according to IHS, migraine attacks for at least 1 year and age of onset <50 years, average of 2 to 6 migraines per month, within the last 3 months prior to study entry, 2-6 migraine attacks within the 4 week baseline period, a duration of migraine attacks within the baseline period of 4-72 hr, patients ability to distinguish between migraine and other headaches, discontinuation of prophylactic migraine treatment at least 4 weeks (8 weeks for flunarizine) prior to beginning of baseline period. **Exclusion criteria:** Hypersensitivity to study medication, pregnancy, intake of analgesics, ergot preparations or triptans for acute migraine attack on >10 days per 4 weeks, >10 days with headaches other than migraine per month, drug misuse or dependency, expected lack of compliance, psychiatric disorders according to DSM-IV, confirmed diagnosis of GI or CV complaints, other severe disease, participation in clinical trials within the last 3 months or simultaneous participation in another clinical investigation. **<u>All patients</u>**	**Group 1 6.25 mg feverfew (MIG-99)** three times a day for 16 weeks **Group 2 placebo** three times a day for 16 weeks 4 week baseline without migraine prophylaxis followed by 16 week active treatment phase	**Patient-reported migraine days** (baseline and final values) **Mean (SE) [SD*]** Group 1 n=89 Group 2 n=81	**<u>Baseline</u>** **Group1:** 7.04 **Group 2:** 7.04 **<u>3 months</u>** **Group1:** 4.74(0.3) [2.83*] **Group 2:** 5.33(0.31) [2.79*] **<u>4 months</u>** **Group1:** 4.53(0.3) [2.83*] **Group 2:** 5.60(0.31) [2.79*]	**Funding:** Grant from Schaper & Brummer (manufacturer of MIG 99). **Limitations:** Group 1, 22 dropouts (1 early study termination, 18 major violation of inclusion criteria, 3 major violation during treatment phase). Group 2, 35 dropout (2 early termination, 27 major violation of inclusion criteria, 6 major violation during treatment phase). Data unavailable for 45 patients that were randomised without fulfilling IHS criteria (218 patients randomised, ITT n=170 and per protocol n=161). Change in patient-reported headache days- not very clear what population this was calculated from. **Notes:** Randomisation after 4 week baseline period. Randomisation of 4 in centre-specific blocks on the basis of randomisation code generated by Alphamed.
			Responder rate Patients with a >50% decrease of migraine attacks Based on ITT population Average of periods p2 and p3 (2nd and 3rd 28 days)	**Group1:** 27/89 (30.3%) **Group 2:** 14/81 (17.3%) **95% CI:** NR **p value:** 0.047	
			Number of patients with serious adverse events (%) Paper states they had no relationship to study medication	**Group1:** 3/108 (2.7%) **Group 2:** 2/110 (1.8%) **p value:** NR	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 218 **Age (mean):** 43.1 (12) **<u>Group 1 – Feverfew</u>** **N:** 108 **Age (mean):** 43.5 (12) **Drop outs:** 19 **m/f:** 18/ 89 **Migraine without aura (%):** 90 (84.1) **Age of first onset of migraine:** 21.7 (9.3) **Average duration of migraine attack:** 27.1 (21.4) **Average number of migraine attacks per 4 weeks:** 4.7 (1.0) **<u>Group 2</u>** - <u>Placebo</u> **N:** 110 **Age (mean, SD):** 42.7 (12) **Drop outs:** 29 **m/f:** 19/89 **Migraine without aura (%):** 87 (80.6) **Age of first onset of migraine:** 22.1 (11.2) **Average duration of migraine attack (h):** 25.3 (19) **Average number of migraine attacks per 4 weeks:** 5.0 (1.7)				Assignment of random numbers to patients was carried out in consecutive order according to time of enrolment into study. ITT analysis on 170 patients and per protocol analysis on 161 patients. SD* values calculated by NCGC.

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

E.3.5 Prophylactic non-pharmacological management of primary headaches with exercise

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: John et al, 2007[401] **Study design:** RCT **Setting:** Health care clinic **Duration of follow-up:** 3 months	**Patient group:** Patients with migraine without aura. **Inclusion criteria:** 20-25 years. Willing to be randomised and attend sessions regularly. No prophylactic medication for the previous 2 months. 4-15 (and no more) attacks a month. Literate in English. Included patients with mild depression and anxiety. **Exclusion criteria:** >15 attacks/month. Co-morbid condition. Unstable medical/psychiatric condition (including those on antidepressants, pregnant women headaches related to diet /allergy or menstruation). Receiving other treatments for migraine. Participated in yoga program in the 6 months prior to enrolment in study. Those unwilling to participate and practice regularly. **All patients** **N:** 72 **Age (mean)**: NR **Drop outs**: 7	**Group 1- yoga** Treatment phase 12 weeks. Patients taught a self administered set of practises under the guidance of a trained yoga therapist. Participants were given handouts of techniques to practice during the prodromal stage of migraine when possible. Patients told not to practice during headache, resolution, and postdrome stage. An integrated approach to yoga therapy was used including yoga postures, breathing practices yoga breathing, relaxation practices and meditation for 5 days per week for 60 minutes. Kriya taught once a week with deep relaxation **Group 2 –self care** Treatment phase 12 weeks	**Mean change in migraine frequency** ± SD (days) Per month	**Baseline** **Group1:** 10.22 ± 2.59 **Group 2:** 9.82 ± 2.31 **Follow up** **Group 1:** 4.56 ± 1.79 **Group 2:** 10.18 ± 2.14 **p value:** 0.001	**Funding:** NMP medical research institute Jaipur Rajasthan, India **Limitations:** Allocation concealment NR. Participants and investigators not blinded. Participants in the intervention group charged registration fee to participate. Mean headache frequency is patient reported outcome. Migraine frequency: baseline doesn't state whether this is no. of attacks per week in the previous month. **Additional outcomes:** Migraine duration Hospital anxiety depression scale **Notes:** * Average age is given for the patients who completed the study excluding drop outs. A random number generator (version1) computer programme was used for randomisation. Patients in the intervention group
			Mean change in migraine intensity ± SD (McGill Pain Questionnaire) 0-10 numerical scale	**Baseline** **Group1:** 2.94 ±0.91 **Group 2:** 3.33 ±0.92 **Follow up** **Group 1:** 1.69 ±0.47 **Group 2:** 3.97 ±0.58 **p value:** 0.001	
			Mean use of acute pharmacological treatment ± SD (prescribed by neurologist but not use of any other symptomatic medication)	**Baseline** **Group1:** 2.69 ± 1.31 **Group 2:** 2.91 ± 1.13 **Follow up** **Group 1:** 1.37 ± 1.01 **Group 2:** 3.94 ± 0.94 **p value:** 0.001	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 mean (SD) **N:** 36 **Age (mean):** 34.38 (8.74)* **Drop outs**: 4 **Male/ female**: 10/22 **Non prescribed medication:** 2.69 (1.31) **Average pain:** 7.32 (1.03) **Frequency of attacks in last month:** 10.22 (2.59) **Group 2 mean (SD)** **N:** 36 **Age (mean):** 34.21 (9.66)* **Drop outs:** 3 **Male/ female:** 6/27 **Non prescribed medication**: 2.92 (1.13) **Average pain**: 7.62 (0.91) **Frequency of attacks in last month**: 9.82 (2.31)	Participants contacted 1 per month for an educational session on migraine, its types, causes and triggering factors given by a healthcare provider. Also handouts provided with info on self care strategies such as avoiding triggers, life style modifications in diet and sleep. Patients asked to make entries in a headache diary.			were charged a registration fee and asked to acquire the necessary equipment Patients allowed to take similar acute medications prescribed by neurologists. Not to use other symptomatic medications including over the counter drugs. Outcome data calculated on ACA basis- Group 1 n=32, Group 2 n=33

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Varkey et al, 2011[819] **Study design:** RCT **Comparison:** Exercise vs topiramate vs relaxation **Setting:** Specialist headache clinic, Sweden **Duration of follow-up:** 3 and 6 months after treatment.	**Patient group:** Patients with migraine recruited from newspaper adverts and headache clinic. **Inclusion criteria:** Aged 18-65; migraine with or without aura according to ICHD-II criteria; frequency of 2-8 attacks per month; had migraine for at least 1 year before participating in the study and before the age of 50. **Exclusion criteria:** Interval headaches not distinguishable from migraine; medication overuse headache; regular exercise (once or more per week during the 12 weeks prior to the study); earlier practice of relaxation, pregnancy, breastfeeding or use of daily migraine prophylaxis in the 12 weeks prior to the study; inability to understand Swedish; use of antipsychotic or antidepressive medication in the 12 weeks prior to the study; drug or alcohol abuse;, topiramate intolerance. **All patients** **N:** 91 **Age (mean):** 44.4 (11.3) **Drop outs**: 44	**Group 1 - Exercise** Trained with a registered physiotherapist for 40 minutes three times/ week. Exercise programme based on indoor cycling and the rate of perceived exertion was used to set the intensity of the exercise programme. Training session included 15 min warm up, 20 min exercise programme, 5 min cool down. There was opportunity to discuss the exercise programme with the therapist after the session. If participant was absent they exercised at home or a local gym. All forms of continuous aerobic exercise were then accepted, participants instructed to reproduce same intensity and duration of exercise used in the programme. Participants who exercised 1/ week at clinic and >2/ week were considered adhering to treatment. **Group 2 - Topiramate** Visited neurologist before starting a course of topiramate. Dosage was increased by 25mg/week until the dosage	**Responder rate** (50% reduction in migraine attack frequency) at 3 months	**Group 1:** 9/30 **Group 2:** 8/31 **Group 3:** 7/30 **p value:** NR	**Funding:** Swedish research council, Gothenburg research and development council, Swedish association of physiotherapists, Renee Eander fund, Neurological research foundation, Olle Engkvists Byggmastare foundation, Glaxosmithkline, Astrazeneca. **Limitations:** Single blind (evaluator only). >10% dropped out of study at 3 month follow up, but similar in all groups. Unclear for how long patients trained with a physical therapist- reads as though only at the beginning then participant took control of exercise programme for at least 2 of the 3 sessions per week. Study based on a self selected sample. Patients who already undertook regular exercise were excluded. **Additional outcomes:** Body weight VO_2max Data at 6 months
			Change in patient-reported migraine days (n/month, least squares mean (SE)) **[SD] Change from baseline at 3 months	**Group 1:** -2.23 (0.55) **[3.01] **Group 2:** -2.08 (0.54) **[3.01] **Group 3:** -1.47 (0.55) **[3.01] **p value:** NR	
			Change in patient-reported migraine frequency (attacks†/month, least squares mean (SE)) **[SD] Change from baseline at 3 months	**Group 1:** -0.98 (0.58) **[1.53] **Group 2:** -0.68 (0.28) **[1.56] **Group 3:** -0.94 (0.28) **[1.53] **p value:** NR	
			Change in patient-reported migraine intensity (VAS 0-100, least squares mean (SE)) **[SD] Change from baseline at 3 months	**Group 1:** -7.1 (3.5) **[19.17] **Group 2:** -13.7 **[18.93] **Group 3:** -5.1 (3.5) **[19.17] **p value:** NR	
			Headache specific QoL Swedish version of	**Group 1:** 5.0 (2.3) **[12.60] **Group 2:** 2.4 (2.3)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 – Exercise **N:** 30 **Age (mean):** 47 (10.8) **Drop outs:** 8 at 3 months, 5 withdrew (1 lack of time, 4 non-compliance) 3 no data, 14 at 6 months. **M/F:** 5/ 25 **Disease duration (years):** 28.8 (11.0) **Migraine frequency (days/month):**7 (3.8) **Migraine frequency (attacks†/month):**4.3 (2.0) **Frequency of headache medication used (doses/month):** 6.9 (4.1) **Intensity of pain (median, IQR):** 50 (26-64) **MSQoL (median, IQR):** 60 (43-77) **Group 2 - topiramate** **N:** 31 **Age (mean):** 44.4 (9.2) **Drop outs: :** 11 at 3 months, 10 withdrew (7 refused drugs, 3 adverse events) 1 no data, 14 at 6 months. **M/F:**2/29 **Disease duration (years):** 25.1 (11.4) **Migraine frequency (days):** 7.5 (3.9) **Migraine frequency (attacks):**3.6 (1.6)	reached the highest dose that the individual could tolerate, maximum of 200mg/day. Allowed to call neurologist any time of day during the treatment period to book a scheduled visit if needed. At least 1 follow up visit was scheduled. Adherence defined as using the medicine for > 2 months in accordance with prescription and was measured using self reports. **Group 3 – Relaxation** Scheduled individual appointment with a registered physiotherapist once a week. The programme was based on common forms of relaxation, breathing and stress-management techniques (described by Larsson and Andrasik) and includes a series of 6 exercises, each of which is based on the one before. Each lasted between 5-20minutes and verbal and written information was given before the introduction of a new relaxation exercise. After each session there was an opportunity to discuss their progress with the	the migraine specific QoL questionnaire [Scale 1- 100] least squares mean (SE) **[SD] **Use of acute pharmacological treatment** (doses/ month) least squares mean (SE) **[SD] **Incidence of adverse events (%)** **NB none were serious**	**[12.81] **Group 3:** 3.1 (2.4) **[13.15] **p value:** NR **Group 1:** -2.72 (0.55) **[3.01] **Group 2:** -2.71 (0.54) **[3.01] **Group 3: -**2.84 (0.54) **[2.96] **p value:** NR **Group1:** 0/30 **Group 2:** 3/31* **Group 3:** 0/30 **p value:** NR	**Notes:** ANCOVA used to adjust for baseline differences (these results are reported) ** SD calculated by NCGC ITT analysis undertaken with last observation carried forward for missing data. *3 patients state AE as reason for withdrawal. 8 patients reported AEs in total. No serious AEs reported. Participants randomised after the baseline period. Randomisation by independent person by a lottery method. †Migraine attack defined as concomitant days with migraine headache and distinct attacks were counted if separated by ≥24 hours.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Frequency of headache medication used (doses): 7.1 (5.3) **Intensity of pain (VAS) (median, IQR):** 40 (29-58) **MSQoL (median, IQR):** 60 (48-73) **Group 3 – relaxation** (N=30) **N:** 30 **Age (mean):** 41.5 (11.4) **Drop outs:** 7 at 3 months, 4 withdrew (2 not satisfied, 1 lack of time, 1 unexplained) 1 no data, 16 at 6 months. **M/F:** 2/28 **Disease duration (years):** 22.2 (11.8) **Migraine frequency (days/month):**7.6 (3.8) **Migraine frequency (attacks†/month):**4.2 (1.6) **Frequency of headache medication used (doses/month):** 6.5 (4.6) **Intensity of pain (median, IQR):** 39 (26-55) **MSQoL (median, IQR):** 58 (51-67)	physiotherapist. Between sessions they practised at home every day with a CD. Adherence was defined as participating in 6 or more sessions at the clinic. Verbal confirmation of practice at home was also required. **All groups** 4- 12 week baseline period, followed by 12 week treatment period. All participants were allowed to contract the physiotherapist or neurologist with questions (telephone or visit). No restriction was made on the use of concomitant acute medication.			

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, IQR=Interquartile range, MSQoL=Migraine specific quality of life questionnaire, VAS=visual analogue scale, ICHD=International Classification of Headache Disorders

E.3.6 Prophylactic non-pharmacological management of primary headaches with education and self-management

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Abram et al, 2007[5] **Study design:** RCT **Comparison:** Headache clinical model vs traditional clinical model **Setting:** Primary care or outpatient clinic **Duration of follow-up:** 3 months And 6 months	**Patient group:** Children and adolescents, 10-18 years. **Inclusion criteria:** Referred by primary care physician or self referred for neurological consultation at a paediatric outpatient multi-speciality clinic. Minimum of 2 month history of recurrent primary headache disorder (migraine, TTH, mixed or chronic daily). **Exclusion criteria**: Past formal neurological or psychological consultation or a known significant abnormality on a neuroimaging or neurological examination. All patients **N:** 81 **Age (mean):** 12.7 **Group 1 – Headache clinic** **N:** 41 **Age (mean):** 13.3 **Drop outs:** 16 **Male (%):** 44 **White (%):** 83 **Time from referral to initial visit (days):** 17 **Headache diagnosis (%):**	**Group 1 - Headache clinical model (HCM)** Small group appointment, 4-6 patients and their parents attended a 1 hour educational session. Included education about headache, education about role of stress in headache, potential treatments were introduced, concluded with a guided practice in deep breathing, progressive muscular relaxation and imagery. This was followed immediately by an individual consultation with a child neurologist **Group 2 –Traditional clinical model (TCM)** Individual consultation with a paediatric neurologist	**Headache specific Quality of life (QoL) pedMIDAS** Outcome data available for 50 patients at 3 months, and for 66 patients at 6 month visit	**Baseline** **Group 1:** 59 **Group 2:** 43 **p value:** 0.086 **3 months** **Group1:** -40% **Group 2:** -50% **p value:** 0.24 between groups **Baseline to 3 months p=**0.000 NS from 3 to 6 months p=0.297	**Funding:** Nemours clinical management programme, Orlando. **Limitations:** Blinding unclear, not stated whether participants or their parents knew aim of study, or which was considered the experimental treatment group. pedMIDAS n for individual groups not stated. Limited reporting of values for pedMIDAS. **Notes:** Randomised using a random number table.
			Headache specific QoL Functional Disability Inventory (FDI) parent No group or group x time effects	**Baseline** **Group 1:** 18 **Group 2:** 20 **p value:** 0.453 **3 months** **p value: 0.004** 6 months p value: 0.00	
			Headache specific QoL FDI child No group or group x time effects	**Baseline** **Group 1:** 18.41 **Group 2:** 18.6 **p value:** 0.95 **3 months** **p value:** 0.075 6 months p value: 0.002	
			Resource use Psychological	**3 months** **Group1:** 14.6%	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	Migraine: 20, Episodic tension type headache: 7, Mixed: 59, chronic daily: 15 **Group 2 – Traditional clinic** **N:** 40 **Age (mean):** 12.1 **Drop outs:**15 **Pharm treatment:** NR **Male (%):** 45 **White (%):** 90 **Time from referral to initial visit (days):** 17 **Headache diagnosis (%)** Migraine: 43, Episodic tension type headache: 7, Mixed: 35 - chronic daily: 15		**treatment** % use	**Group 2:** 7.5% **p value:** 0.271 6 months Group1: 9.1 Group 2: 3.0 p value: 0.302	
			Resource use **Calls to neurology clinic** % use	**3 months** **Group1:** 19.1 **Group 2:** 11.5 **p value:** 0.15 6 months Group1: 9.1 Group 2: 3.0 p value: 0.80	
			Resource use **Emergency department visits** % use	**3 months** **Group1:** 7.7 **Group 2:** 7.6 **p value:** 0.70 6 months Group1: 0 Group 2: 6.1 p value: 0.16	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, pedMIDAS= Paediatric Migraine Disability Assessment, FDI= Functional Disability Inventory, TTH=tension type headache

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Kohlenberg & Cahn 1981[446] **Study design:** RCT **Comparison:** Instructions on self management vs control **Setting:** NR **Duration of follow-up:** 6 weeks baseline, Followed up at 22 weeks (3 months after finishing the book)- 4 weeks of headache data was collected, then 6 month follow up where an additional 4 weeks of data were collected	**Patient group:** Patients with a diagnosis of migraine **Inclusion criteria:** At least 2 headaches per month, diagnosed as having migraine headaches by their doctor and currently be under his or her care, be willing to collect data on headaches on a daily basis, be willing to collect data for 6 weeks prior to receiving any experimental treatment. Physician to document all of the above in writing. **Exclusion criteria:** Severe psychiatric problems, high or low blood pressure, subject to strokes. **All patients** **N:** 117 **Drop outs:** 66 **Group 1 – experimental book** **N:** 58 **Age (mean):** 44.0 **Drop outs:** 36 **Number of years suffering from migraine:** 19.9	**Group 1- Experimental book** Included a liquid crystal finger temperature band. Contains 7 chapters, includes information on: physiological basis of migraine; importance of avoiding vasoconstriction; how to use the temperature device as biofeedback instrument; relaxation exercise (meditation and progressive relaxation); biofeedback exercise; and cognitive restructuring. **Group 2 –Control book** "More than 2 aspirin" (S. Diamond & W. B. Furlong) Series of case histories, question and answer session. Primary purpose of book is to provide information about symptoms, diagnosis and treatment of headaches. **Both groups** Participants told in the consent form that two different books were being	**Change in patient-reported headache frequency** % decrease figures only stated	**Group1:** 62% **Group 2:** 14% **p value:** NR F (2,94) = 6.9 (period interaction) Differences between baseline and 3 & 6 months significant within and between groups	**Funding:** NR **Limitations:** Study does not state blinding status, although appears that subjects were blind, unclear about investigartors. Patient demographics only on the 51 that completed the study. Change in patient reported headache frequency (number of headaches) only given as % decrease. Large number of dropouts (treatment 62%; control 51%), study reports this may be to do with lack of contact through study. Only 1 male participant completed the study. Partial reporting of change in headache intensity. **Additional outcomes:** Confidence ratings before and after (0-5 scale). Headache duration. **Notes:** Patients were recruited through advertisements in local
			Change in patient-reported headache intensity (headache pain) Recorded on a 0 (no pain)-5 (worst pain ever) scale	**Group1:** F(2,92) = 52 (treatment group statistically greater pain reduction than control) **Group 2:** NR Both groups significantly reduced pain ratings from the baseline period F(1,92) = 5.7	
			Use of acute pharmacological treatment Mean number of doses (tablet, capsules etc) per week	**Baseline:** **Group1:** 6.6 **Group 2:** 2.8 **3 month** **Group1:** 4.1 **Group 2:** 2.2 **6 month** **Group1:** 2.9 **Group 2:** 2.2	
			Confidence rating	**Baseline:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 – control book **N:** 59 **Age (mean):** 46.7 **Drop outs:** 30 **Number of years suffering from migraine:** 20.1	tested. People given 10 weeks to finish the book, contacted at 22 weeks after receiving the book (or 3 months after finishing the book).	(Patients perception of the usefulness of programmes)	**Group1:** 2.8 **Group 2:** 3.8 **After reading book** **Group1:** 2.6 **Group 2:** 3.5	newspapers, public service announcements on the radio asking for volunteers. Patients had to pay $25 deposit to participate in the study which they received upon completion of the study or if they withdrew. Only contact with patients was by mail or phone. Statistical tests- 3 ways analyses of variance with repeated measures- F significance. Individual mean comparisons with Scheffe test.

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

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Larsson et al, 1987[476] **Study design:** RCT **Comparison**: Therapist-assisted relaxation vs self help relaxation vs control **Setting:** High schools in Sweden **Duration of follow-up:** 5 months	**Patient group:** Adolescents aged 16-18 years, suffering from migraine, migraine and tension type headache or non-migrainous headache. **Inclusion criteria:** Headache complaints for at least once a week, having headaches for at least 1 year, not receiving psychological or pharmacological treatment for their headaches at the present time. **Exclusion criteria: NR** **All patients** **N:** 46 **Age (mean):** NR for any group **Drop outs**: 5 **Group 1 – Self help relaxation** **N:** 16 **Drop outs:** 2 **F/M:** 11/5 **Headache type:** Migraine: 1, Mixed: 2, Tension: 13 **Headache duration (years):** 1-5: 11, >5: 5 **Depression/ anxiety range 35-120 [mean, SD]:** 56 (10.7) **Stress, range 11-44 [mean, SD]:** 23.5	**Group 1 –Self-help relaxation** A series of 5 audiotapes roughly 5-10 minutes duration, developed by the experimenters. Same type of relaxation instructions as used by group 2. Treatment introduced by school nurse at initial meeting. Students urged to change the tapes once a week. Nurses contact 2 months after initial intervention to give participants a booster tape which contained instructions to practise critical steps in relaxation treatment. **Group 2 – Therapist assisted relaxation (TAR)** 9 x 45 minute sessions, twice a week during regular school hours. Sessions 1-3: Progressive relaxation training conducted in groups of 3-4 students. Session 4: rapid "cue controlled" relaxation technique was introduced. Final 2-3 sessions: practise of "cue controlled" technique and extended it to everyday	**Change in patient-reported headache days** **"Headache free days"**	**Baseline** **Group 1:** 1.8 **Group 2:** 2.1 **Group 3**: 1.4 **5 months follow up** **Group 1:** 3.6 **Group 2:** 4.9 **Group 3:** 1.7 **p value:** **Group 1:** <0.001 **Group 2:** <0.01 **Group 3:**NS	**Funding:** NR **Limitations:** Does not state what time period pre-follow up is. Restrictions applied to randomisation: classmates were assigned to the same treatment group in order to reduce the risk of contamination; subjects were evenly distributed across groups within separate schools. No allocation concealment- active selection bias. Binding not stated, appears to be open label. Not clear what scale confidence rating is assessed on. **Additional outcomes:** Headache duration. Headache sum.
			Change in patient-reported headache frequency	**Baseline** **Group 1:** 5.8 **Group 2:** 5.1 **Group 3:** 5.7 **5 months follow up** **Group 1:** 3.5 **Group 2:** 2.3 **Group 3:** 5.5 **p value:** **Group 1:** <0.001 **Group 2**: <0.001 **Group 3:**NS	
			Change in patient-reported headache intensity **Peak headache intensity**	**Baseline** **Group 1:** 3.3 **Group 2:** 3.2 **Group 3:** 3.6 **5 months follow up**	

Study Details	Patients	Interventions	Outcome measures	Effect size	Comments
	(5.5) **Group 2 – Therapist assisted relaxation** **N:** 14 **Drop outs:** 2 **Female/ male:** 13/1 **Headache type:** Migraine: 1, Mixed: 4, Tension: 9 **Headache duration (years):** 1-5: 10, >5: 4 **Depression/ anxiety, range 35-120 [mean, SD]:** 58.6 (13.3) **Stress, range 11-44 [mean, SD**]: 22.3 (5.0) **Group 3 – Self- monitoring** **N:** 11 **Drop outs:** 1 **Female/ male:** 11/0 **Headache type:** Migraine: 0, Mixed: 4, Tension: 7 **Headache duration (years):** 1-5: 5, >5: 6 **Depression/ anxiety, range 35-120 [mean, SD]:** 55.5 (6.2) **Stress, range 11-44 [mean, SD]:** 22.31 (4.4)	situation. Two booster sessions at 2 months following initial treatment. **Group 3 – Self monitoring** Perform self- recordings and did not receive any treatment. Informed of group membership by telephone by the child psychiatrist and encouraged to seek help at regular school health services in case they experienced deteriorating headache.		**Group 1:** 2.3 **Group 2:** 2.5 **Group 3:** 3.1 **<u>p value:</u>** **Group 1:** <0.01 **Group 2:** NS **Group 3:** NS	School absence. Cost effectiveness. Treatment compliance. **Notes:** Recorded headache activity on a 6-point scale (0=no headache to 5= tense incapacitating headache). Lottery used throughout the study in which participants had opportunity to win ~£2 each week after they had handed in their report card to the nurse. Groups equivalent at baseline.
			Responder rate (50% reduction in headache complaints) Outcome measured at - "pre-follow up"	**<u>Pre-follow up</u>** **Group 1:** 1/16 (8%) **Group 2:** 1/14 (9%) **Group 3:** 0/11 (0%) **p value: <**0.01	
			Use of acute pharmacological treatment	Stated as outcome but not reported	
			Confidence rating Students experience of how effectively headaches were reduced (Likert scale 1=very little, 5=very much and 1=not helpful to5= very helpful) Or Four 10 point scales (1=not at all, 10 very much) Mean (SD)	**Group 1:** 3.9 (0.5) **Group 2:** 4.1 (0.6) **Group 3:** NR	

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval, TAR=therapist assisted relaxation

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Lemstra et al, 2002[486] **Study design:** RCT **Comparison:** **Setting:** YMCA centre **Duration of follow-up:** At 6 weeks and 3 months	**Patient group:** Adults with migraine with or without aura according to IHS. **Inclusion criteria:** Patients 18 years of age or older with a chronic migraine pain for at least 6 months, meet the diagnostic criteria for migraine with or without aura according to IHS. **Exclusion criteria**: If pain was of a benign nature. **All patients** **N:** 80 **Drop outs:** 3 **Group 1 – 6 week intervention** **N:** 44 **Age (mean):** 35.59 (10.15) **Drop outs:** 3 **Gender (f/m):** 32 (72.7%)/12 (27.3%) **Education:** University or college: 16/44, High school graduate: 25/44, Less than high school graduation: 3/44 **Current self-reported health (1-5):** 3.60 (1.03) **Onset of pain (months):** 102.91 (77.75) **Days in last month with pain:** 20.20 (8.07) **Number of non prescription**	**Group 1 – 6 week intervention** (neurologist intake, physical therapist intake, 18 group supervised exercise classes with exercise therapist, 2 group lectures with a psychologist, 1 group lecture with a dietician, 2 massage therapy session, neurologist and physical therapist discharge) submaximal general exercise, education, lifestyle changes, and self-management Active participation maximised with supervised visits, telephone calls with every absence and scheduled attempts to try and to determine knowledge retention. Development of a coordinated management plan for the patient. **Group 2- waiting list control** was standard medical care with patient's family physician, control intervention was referral to medical specialist (19%), referral to treatment (11%), medication (56%), further	**Change in patient-reported headache frequency** Visual analogue scale: 100% worse to 100% improvement After intervention measurements only	**Group1:** 56.93 (9.13) **Group 2:** -2.22 (2.22) **p value:** 0.000	**Funding:** NR **Limitations:** Study not blinded. All outcomes are patient perceived change- therefore subjective. Headache frequency measured differently to other studies. Outcomes for headache frequency intensity. Functional health status health-related quality of life only reported for end of intervention, not at baseline. **Additional outcomes:** Change in pain duration. Change in average pain. Change in most pain. Change in least pain. Change in hours of pain. Change in pain disability index. Change in beck depression inventory. Change in work status (%). **Notes:** Randomisation: individual computer generated, envelope concealed under the
			Change in patient-reported headache intensity Visual analogue scale: 100% worse to 100% improvement After intervention measurements only	**Group1:** 38.18 (8.54) **Group 2:** -2.78 (1.98) **p value:** 0.001	
			Functional health status 1 (excellent health) – 5 (poor health) After intervention measurements only	**Group1:** 51.59 (7.71) **Group 2:** -0.56 (2.03) **p value:** 0.000	
			Health-related quality of life Visual analogue scale: 100% worse to 100% improvement After intervention measurements only	**Group1:** 57.05 (8.17) **Group 2:** -1.94 (1.94) **p value:** 0.000	
			Use of acute	**Group1:** 1.06 (0.22)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	medications: 1.86 (0.95) **Number of prescription medications:** 2.55 (2.17) **Expect intervention will help (%):** 12/44 (27.3) **Group 2 - Control** **N:** 36 **Age (mean):** 33.17 (13.21) **Drop outs:** 0 **Gender (f/m %):** 21(58.3%)/15(41.7%) **Education:** University or college: **12/36**, High school graduate: **23/36,** Less than high school graduation: **1/36** **Current self-reported health (1-5):** 3.67 (0.89) **Onset of pain (months):** 101.67 (128.35) **Days in last month with pain:** 21.08 (8.33) **Number of non prescription medications:** 2.0 (0.89) Number of prescription medications: 2.17 (2.09) **Expect intervention will help (%):** 13/36 (36.1)	diagnostics (0%), education (0%), nothing at all (14%)	**pharmacological treatment** non prescription drug use in the last 30 days *Before and after measurements*	**Group 2:** 0.25 (0.12) **p value:** 0.005	supervision of the data manager. Blinding of patients not considered possible, treatment credibility assessed in patients and therapists before intervention. Therapists blinded to which specific outcome variables were primarily under evaluation. Outcome assessor blinded to intervention status. ITT analysis.
			Use of acute pharmacological treatment Prescription drug use in the last 30 days *Before and after measurements*	**Group1**: 1.18 (0.24) **Group 2:** 0.22 (0.11) **p value:** 0.001	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Williamson & Reeder, 1984[852] **Study design:** RCT, 3 x 3 factorial design **Comparison:** Group relaxation vs self help vs waiting list control **Setting:** **Duration of follow-up:** 4 months (see notes and limitations*)	**Patient group:** Self-referred patients recruited by media advertisement with migraine, muscle contraction or mixed headache. **Inclusion criteria**: Diagnostic interviews indicated that the patient met the criteria to be diagnosed as either classic migraine, common migraine, muscle contraction or mixed headache, reported at least 3 headaches during a month of baseline recording, they did not report experiencing head pain every day, they agreed to complete all stages of the study and their personal physician agreed to allow them to participate in the experiment. **Exclusion criteria:** Not meeting diagnostic criteria or presented symptoms of other potential causes of head pain. **All patients** **N:** 48 **Drop outs:** 7 **Group 1 - self help relaxation**	**Group 1 self help relaxation** Divided into 3 groups; each led by one of three pairs of therapist. Met once per week for approximately 1 hour for 4 weeks. Received copies of the relaxation book (Rosen 1977) and given instructions how to use the self help guide. Purpose of sessions to promote compliance with self monitoring procedure and the relaxation programme. **Group 2 group relaxation training** Divided into 3 groups; Sessions twice a week for four weeks. Sessions lasted approximately 1.5 hours. Trained in progressive muscular relaxation using 16 muscle group relaxation. Actual practise of the technique and discussion. Provided with audiotapes of the relaxation procedure and instructed to use the tapes at least once daily. Taught abbreviated relaxation procedure and provided with tapes. Identifying stress and headaches and use of relaxation to cope with this. Practise of relaxation by recall. **Group 3 waiting list control** Met for 4x 1 hour sessions over 4 weeks to discuss physiological and psychological basis of headache. **All patients** Self monitored headache activity for 3 (or 4) weeks.	**Change in patient-reported headache frequency** **Responder rate** Greater than or equal to 50% reduction of headache activity from baseline to follow up	**F** (2, 102) = 0.55 **p value:** >0.10 **Group 1**: 5/14 (35.7%) **Group 2:** 4/13 (30.8%) **Group 3:** 1/14 (7.1%) **p value:** NR	**Funding:** NR **Limitations:** Allocation concealment and blinding NR (assumed open label). Values for change in patient-reported headache frequency not given. Outcomes are for 1 month only. Additional analyses at 2, 3, 4 months not performed as headache data for control group not available. **Additional outcomes:** Change in headache index. Response of individuals to treatment conditions (% improvement). **Notes:** Available case analyses. Initially designed as a 3x3 factorial.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 16 **Age (mean):** 39.1 **Drop outs:**2 **Male/ female:** 4/12 **Group 2 – group relaxation training** **N:** 16 **Age (mean):** 37.6 **Drop outs:** 3 **Male/ female:** 1/15 **Group 3 – waiting list control** **N:** 16 **Age (mean):** 39.5 **Drop outs:** 2 **Male/ female:** 4/12				

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

E.4 Management of medication overuse headache

Withdrawal treatment vs prophylactic treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Hagen et al, 2009[348] **Study design:** RCT **Setting:** Multicentre trial; out-patient clinics of five University hospitals in Norway **Duration of follow-up:** 4 years	**Patient group:** Patients with suspected medication overuse headache (MOH) **Inclusion criteria:** Age 18-70 years; MOH defined as headache≥15 days/month for at least 3 months combined with intake of ergots, triptans, opioids and/or combination medication (simple analgesics combined with caffeine) for ≥10 days per month, or of simple analgesics ≥15 days for a minimum of 3 months. **Exclusion criteria:** Contraindications for all types of prophylactic drugs; no improvement of headache at previous trials to stop overused medication for at least 3 weeks; history of hemicrania continua, chronic paroxysmal hemicranias or cluster headache; patient used analgesics frequently for other complaints than headache; pregnant, breastfeeding or not using effective contraception. **All patients** **N:** 64 (randomised); 61 (fulfilled inclusion criteria). **Group 1 Withdrawal** **N:** 22 (randomised); 20 (completed 1 month visit); 19 (completed 3 month visit); 18 (completed 5 month visit; 14 (completed 12 month visit)	**Group 1** **Withdrawal of medication** Advised to abruptly withdraw overused medication. If required: • allowed to use rescue medication up to 2 days per week. • offered sick leave for up to 2 weeks, offered inpatient detoxification if failed to complete the out-patient detoxification programme. • offered to start preventive treatment after three months. **Group 2** **Prophylactic treatment** Preventive treatment was started on day one. Medications used according to primary	**Change in days with acute headache medication use per month** *(mean change score, SD)*	**At 3 months:** **Group 1:** -19.1, 8.97* (n=20) **Group 2:** -13.2, 10.89*(n=17) **Group 3:** -6.9, 10.17*(n=19) **At 5 months:** **Group 1:** -18.5, 9.08*(n=20) **Group 2:** -11.6, 10.21*(n=17) **Group 3:** -6.1, 9.65*(n=19) **At 12 months:** **Group 1:** -16.1, 10.68*(n=20) **Group 2:** -14.2, 4.77* (n=17)	**Funding:** NR **Limitations:** Open label trial. Method of allocation concealment was unclear. **Additional outcomes:** Change from baseline in: Headache hours; Headache index (headache days/month x mean daily headache hours x mean daily headache severity); Sick leave days per month; and Anxiety and depression measured by HADS. **Notes:** Rescue medications for group 1 included: 10-25mg of amitryptiline (for lack of sleep), 50 mg of diclofenac or 500mg of
			Responder rate *without medication overuse and with ≥50% reduction in monthly headache days compared with baseline*	**At 5 months:** **Group 2:** 41%, (7/17) **Group 3:** 5%, (1/18) 2v3, p value: 0.010 **At 12 months:** **Group 1:** 25%, (4/14) **Group 2:** 53%, (9/16) 1v2, p value: 0.081	
			Change in patient reported headache days per month from baseline *(mean change*	**At 3 months:** **Group 1:** -4.2 , 4.38*(n=20) **Group 2:** -7.2 , 8.85*(n=17) **Group 3:** -1.6, 7.16* (n=19) **At 5 months:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 42.1 years **Drop outs:** 8 (at 12 month follow up) **No. of headache days per month (mean):** 24.1 **No. of days with analgesics/month (mean):** 22.9 **<u>Group 2 Prophylactic treatment</u>** **N:** 19(randomised); 17 (completed 1 month visit); 17 (completed 3 month visit); 17 (completed 5 month visit; 16 (completed 12 month visit) **Age (mean):** 41.6 years **Drop outs:** 3 (at 12 month follow up) **No. of headache days per month (mean):** 25.2 **No. of days with analgesics/month (mean):** 23.5 **<u>Group 3 Control group</u>** **N:** 20 (randomised); 19 (completed 1 month visit); 18 (completed 3 month visit); 18 (completed 5 month visit) **Age (mean):** 38.7 years **Drop outs:** 2 (at 5 month follow up) **No. of headache days per month (mean):** 26.8 **No. of days with analgesics/month (mean):** 23.7	diagnosis were: angiotensin II blockers β-blockers, valproate, tricyclic antidepressants (for migraine + TTH only), valproate, tricyclic antidepressants and gabapentin (for TTH only). **<u>Group 3 Control group</u>** No direct advice to stop using analgesics or start any preventive treatment. All patients used a headache diary during baseline period and after randomisation. Baseline period was for at least 3 months prior to randomisation.	*score, SD)*	**Group 1:** -4.8, 7.37* (n=20) **Group 2:** -7.3, 9.04*(n=17) **Group 3:** -2.1, 6.22* (n=19) **<u>At 12 months:</u>** **Group 1:** -5.1, 10.90* (n=20) **Group 2:** -10.3, 8.75* (n=17)	naproxen orally, and/or 20mg metoclopramide. Control group finished the study period after 5 months observation and were then offered treatment considered optimal for them (withdrawal or prophylactic). *calculated at NCGC
			Mental health component (MCS-12) mean, SD at 12 months	**Group 1:** 14.6, 18.27*(n=20) **Group 2:** 13.9, 23.14*(n=17)	
			Physical health component (PCS-12) *mean, SD at 12 months*	**Group 1:** 6.5, 19.23*(n=20) **Group 2:** 20.2, 27.33*(n=17)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, MOH=Medication overuse headache, TTH=Tension type headache, HADS=hospital anxiety and depression scale.

Outpatient withdrawal treatment vs inpatient withdrawal treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Creach et al, 2011[173] **Study design:** Randomised trial, open label **Setting:** Headache clinics, France **Duration of follow-up:** 2 years (March 2003-December 2005)	**Patient group:** Patients with suspected medication overuse headache (MOH) referred to pain clinic by their primary care physician. **Inclusion criteria:** Patient with suspected MOH defined as headache ≥15 days/month for at least 3 months combined with an intake of acute symptomatic treatments for headache ≥15 days/ month over the same period; age≥18 years, patients accepting allocation to treatment by randomisation, patients who agreed to halt their professional activity for 8 days in order to complete an abrupt drug withdrawal **Exclusion criteria:** Patients who had suffered from any significant illness or major depression in the past month, pregnancy, unable to describe precisely describe their headaches or their medication consumption, patients whose medication overuse included WHO step III opioids, no improvement after a previous well conducted withdrawal **All patients** N: 82 (randomised) **Group 1- Outpatient withdrawal group** N:41 **(randomised)**, 36 (analysed at 2 months follow up), 34 (analysed at 2 years follow up) Dropouts:5 excluded (1-spontaneous decrease of MOH, 1- desire for inpatient treatment, 3-incomplete withdrawal)	**<u>Group 1 Outpatient withdrawal therapy</u>** Outpatient withdrawal treatment Patients told to consult general practitioner if needed **<u>Group 2 Inpatient withdrawal therapy</u>** Inpatient withdrawal treatment Monitored by neurologist **In both groups:** • Both groups were seen by a neurologist on the first visit. • Patients completed a questionnaire and a daily headache diary for one month between visits 1 and 2 • A preventive treatment, chosen by the neurologist in the second visit, was introduced on the first day of withdrawal based on previous preventive treatments already used by the patient • Both groups received oral amitriptyline in progressively decreasing doses over one month and metoclopramide to minimise withdrawal syndrome • At the end of withdrawal, patients received a prescription for acute symptomatic treatment (usually triptans or NSAIDs) with instructions not to take them for more than 8 days per month.	Responder rate at 2 years follow up (n/N, %) Responder rate defined as patients who 2 months after the onset of withdrawal treatment, experienced no headache or had reverted to an episodic pattern of headache (<15 headache days /month) and whose intake of symptomatic medication was <10 days/month	Outpatient group: 16/34, 47% Inpatient group: 14/32 , 44%	**Funding:** Grants from Fondation de France and Fondation CNP **Limitations:** • Details of randomisation and allocation concealment not reported. • Open label trial **Additional outcomes:** • Reduction in percentage of headache days(numbers not extractable) • Number of patients with episodic headaches • Severity of withdrawal symptoms • Psychological distress induced by withdrawal • Craving for acute symptomatic medication • Percentage of

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age in years (mean ±SD):45±11 Duration of headache in years (mean ±SD):23.9±13.9 Number of headache days per month (mean ±SD): 27.3±4.6 Number of days per month with ATH use (mean ±SD): **26.4±5.7** **Group 2- In patient withdrawal group** N:41**(randomised)**, 35 (analysed at 2 months follow up), 32 (analysed at 2 years follow up) Dropouts: 6 excluded(3- spontaneous decrease of MOH, 1- concomitant surgery, 1- desire for outpatient withdrawal, 1- incomplete withdrawal) Age in years (mean ±SD):50±11 Duration of headache in years (mean ±SD): 25.1±13.4 Number of headache days per month (mean ±SD): 25.8±5.6 Number of days per month with ATH use (mean ±SD): 25.8±5.6				subjective improvement

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD: Standard deviation, N: Number, MOH: Medication overuse headache, WHO: world Health Organisation, ATH: Acute treatment of headaches, NSAIDs: Non steroidal anti-inflammatory drug

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Rossi et al, 2006 & 2008[670,671] **Study design:** RCT **Setting:** Headache Inpatient clinic, Grottaferrata, Italy **Duration of follow-up:** 12 months	**Patient group:** People aged 16-65 years suffering from probable medication overuse headache (MOH) plus migraine. **Inclusion criteria:** Age 16-65 years; diagnosed with MOH plus migraine according to ICHD-II criteria; attending a subspecialty headache centre(INI Headache clinic); had low medical needs and unlikely to experience problems as withdrawal treatment out-patients. **Exclusion criteria:** Current diagnosis or history of coexistent, significant and complicating medical illness (which could complicate withdrawal undertaken as an out-patient); current diagnosis (fulfilment of diagnostic criteria in the past month) of mood disorder, anxiety disorder or addiction disorder (for substances other than the overused medication); overuse of agents containing opioids, barbiturates and benzodiazepines; treatment with migraine prophylactic drugs within the past three months; previous detoxification treatments; inability to furnish reliable information about medical history and psychiatric symptoms and contraindications to the use of corticosteroids and indomethacin. **All patients** **N:** 120 (randomised), 2(diagnosed with chronic migraine and not included in analysis) 89 (successfully completed withdrawal therapy and recruited for follow up), 83 (data available for analysis at end of 1 year) **Age (mean ± SD):** 43.97±12.9 years	**Group 1 Intensive advice** Received advice to withdraw medication. Advice included explaining role of medication overuse in making headache chronic, symptoms of withdrawal, long term effects and importance of patient playing an active role in management of their headache. **Group 2 Outpatient detoxification programme** Advised to abruptly withdraw the overused medication. Prednisone for the first two 8 days (60 mg/day, 2 days; 40 mg/day, 2 days, 20mg/day, 4 days). Preventive treatment chosen on basis of patient's history and preferences. **Group 3 Inpatient detoxification programme** Advice to withdraw symptomatic medication Admitted to hospital and received following treatment: Abrupt discontinuation of overused medication; Close observation and support for 8	**Change in acute medication use** *percentage reduction in number of doses of symptomatic mediation/month (mean ± SD)*	**Group 1**: 76.6±22 **Group 2**: 71.7±32 **Group 3:** 81±13	**Funding:** NR **Limitations:** Open label study. Method of allocation concealment unclear. **Additional outcomes:** Adherence to treatment **Notes:** All outcomes after two months reported in Rossi et al, 2008. Preventive medication used: Valproic acid, β-blockers, amitriptyline and topiramate.
			Relapse back to medication overuse headache within 1 year	**Group 1:** 13.8% (4/29) **Group 2:** 23.1% (6/26) **Group 3:** 25% (7/28)	
			Responder rate patients who 2 months after the onset of withdrawal treatment, experienced no headache or had reverted to an episodic pattern of headache (<15 headache days /month) and whose intake of symptomatic medication was <10 days/month	**Group 1:** 77.5% (31/40) **Group 2:** 71.7% (28/39) **Group 3:** 76.9% (30/39)	
			Change in patient reported headache days *percentage reduction*	**Group 1:** 67.6 ± 25 **Group 2:** 61.2 ± 34	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 13 (by second follow up visit) **<u>Group 1 Intensive advice</u>** **N:** 40 (randomised); 29 (data available at 1 year) **Age (mean ± SD):** 43.5±14.2 years **Drop outs:** 3 (7.5%)-at 12 weeks **Duration of MOH (mean ± SD):**4±5 **Number of doses of medication/month (mean ± SD**): 37±23 **<u>Group 2 Outpatient detoxification</u>** **N:** 39 (randomised), 26 (data available at 1 year) **Age (mean ± SD):** 44.1±12.8 years **Drop outs:** 5 (12.8%)-at 12 weeks **Duration of MOH (mean ± SD): 4**.4±3.6 **Number of doses of medication/month (mean ± SD):** 40±27 **<u>Group 3 Inpatient detoxification</u>** **N:** 39 (randomised); 28 (data available at 1 year) **Age (mean ± SD):** 46.1±11.9 years **Drop outs:** 5 (12.8%)-at 12 weeks Duration of MOH (mean ± SD): 4.6±4.2 **Number of doses of medication/month (mean ± SD):** 40.2±20	days; Prednisone (60 mg/day, 2 days; 40 mg/day, 2 days, 20mg/day, 4 days); Preventive treatment chosen on basis of patient's history and preferences; Parenteral fluid replacement and administration of antiemetics (metoclopramide 10 mg i.v twice daily).	*in number of headache days/ month (mean ± SD)*	**Group 3:** 73 ± 19	

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

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Suhr et al, 1999[769] **Study design:** RCT **Setting:** Headache clinic , Germany **Duration of follow-up:** 5.9±4.0 years	**Patient group:** Patients with drug induced headache **Inclusion criteria:** Diagnosis of drug induced headache according to IHS criteria and admitted between 1983 and 1995; had discontinuation of chronic headache after withdrawal therapy; if admitted before 1989, enrolled only if a diagnosis of drug induced headache could be made from the history. **Exclusion criteria:** NR **All patients:** **N:** 257 (identified with drug induced headache and randomised); 101(enrolled for follow up study) **Age (mean):** 46.0±12.0 years **Drop outs:** 39(lost to follow-up); 117 (did not answer questionnaire/interview sufficiently) **Group 1 Outpatient withdrawal therapy (ambulatory)** **N:** 110 (randomised); 41 (data available at follow up)- 40.6% **Age (mean):** NR **Drop outs:** 69 **Group 2 Inpatient withdrawal therapy (Stationary)** **N:** 147 (randomised); 60 (data available at follow up)- 59.4% **Age (mean):** NR **Drop outs:** 87	**Group 1 Outpatient withdrawal therapy (ambulatory)** Analgesic medication stopped abruptly Patients observed regularly during 4 week treatment as outpatients **Group 2 Inpatient withdrawal therapy (Stationary)** Analgesic medication stopped abruptly Patients observed regularly during 2 week treatment in hospital. **In both groups:** No analgesic intake was allowed during the withdrawal therapy. 10% received antidepressants and 20% received migraine prophylactic agents. After successful withdrawal therapy, treatment of primary headache was started in accordance with the principles recommended by the German Migraine and Headache Society. Follow up done in 1995 by standard interview (postal questionnaire, personal examination or telephone interview) to evaluate history of headache and its treatment after withdrawal therapy.	**Relapse back to medication overuse headache**	**Group 1:** 14.6% (6/41) **Group 2:** 25% (15/60) P value<0.2	**Funding:** NR **Limitations:** Unclear randomisation. No blinding of participants, care administrators or investigators. Significant loss to follow up and no reasons outlined. Unclear what the interventions were- no details reported other than abrupt withdrawal of medication. **Additional outcomes:** Maximal pain intensity, rate of drug intake after withdrawal therapy in patients with relapse and patients without relapse (not separated by group).
			Change in patient reported headache days/ month	**Group 1:** 9.6±10.1 **Group 2:** 12.6±11.3 P value<0.2	
			Change in patient reported headache intensity *visual analogue scale from 1 to 10 (mean*±SD*)*	**Group 1:** 6.4±2.6 **Group 2:** 6.5±2.2 P value<1.0	

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

E.5 Management during pregnancy and contraceptive use

E.5.1 Management of primary headaches during pregnancy

Triptans

Study details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
Author & Year Shuhaiber et al, 1998[721] **Study design:** Prospective cohort **Setting:** Motherisk (Toronto), Pregnancy healthline (USA), Fetal risk assessment programme (UK), Pregnancy exposure information service (USA). **Duration of**	**Patient group:** Women using sumatriptan during pregnancy. **Inclusion criteria:** Pregnant women using sumatriptan who contacted a teratogen information service (TIS) requesting counselling on potential teratogenicity of drugs for migraine. **Exclusion criteria:** NR **All patients** **N:** 288 **Drop outs:** NR **Group 1- Women taking triptans** **N:** 96 **Age (mean):** 32.3 (4.9) **Exposed in 1st trimester:** 95/96 (98.9%) **Number of maternal doses:** 5.5 (0.5 -100) Used drug once: 57/96 (59.4%), Used drug >1: 38/96 (39.6%) **Smokers:** 15/96 (15.6%) **Group 2 Disease-matched controls.** **N:** 96	**Group 1** All patients contacted by telephone within 2 years of the expected date of confinement and asked details about the outcomes of pregnancy, birth weight, presence or absence of birth defects and perinatal and post natal complications. One centre (Motherisk) confirmed the data obtained from the follow ups by requesting written documentation from the child's physician. **Group 2 Disease-matched controls.** Pregnant women contacting motherisk who had migraine headache and used other drugs such as acetaminophen, NSAIDs, narcotic analgesics). **Group 3 Non teratogen**	**Live born infants** N (%)	**Group1:** 82/96 (85.4%) **Group 2:** 90/96 (93.7%) **Group 3:** 91/96 (94.8%) **p value:** NR	**Funding:** NR **Limitations:** Modest sample size. Limited ability to determine migraine case status. All outcomes apart from major birth defects (MBD) analysed on ITT basis; MBD analysed on ACA basis. No confounding factors identified. Adjusted OR not reported. Drug use self reported, therefore may be underestimated. **Additional outcomes**: Individual MBDs reported. **Notes:** Major birth defects defined as those being potentially life threatening, resulting in major cosmetic defects or having a major impact on social
			Spontaneous abortion N (%)	**Group1:** 11/96 (11.5%) **Group 2:** 6/96 (6.3%) **Group 3:** 4/96 (4.2%) **p value:** NR	
			Therapeutic abortion N (%)	**Group1:** 4/96 (4.2%) **Group 2:** 2/96 (2.1%) **Group 3:** 1/96 (1.1%) **p value:** NR	
			Gestational age <37weeks N (%)	**Group1:** 8/96 (8.4%) **Group 2:** 16/96 (16.8%) **Group 3:** 5/96 (5.2%)	

Study details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
follow-up: Up to 2 years	**Age (mean):** 31.7 (4.5) **Smokers:** 21/96 (21.9%) **Group 3 Non teratogen controls.** **N:** 96 **Age (mean):** 31.2 (4.8) **Smokers:** 12/96 (12.5%)	**controls.** Pregnant women who contacted motherisk requesting counselling about medications known to be safe in the human fetus.		**p value:** NR	acceptability of the child. No Odds Ratios stated in study. Study states that there was no significant difference in any outcome. Continuous outcomes analysed using ANOVA.
			Major birth defects N (%)	**Group1:** 1/82 (1.2%) **Group 2:** 1/90 (1%) **Group 3:** 1/91 (1%) **p value:** NR	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, NSAID= non steroidal anti-inflammatory drugs, MBD= major birth defects; s.c= subcutaneous, OR=odds ratio

Study details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
Author & Year: Nezvalova-Henriksen el al, 2010[588] **Study design:** Prospective cohort **Setting:** Norway (Mother and child cohort study and medical birth registry) 1999-2007 **Duration of follow-up:** Follow up to birth of infant	**Patient group:** Data collected from the Medical birth registry of Norway between 1999- 2007. **Inclusion criteria:** Pregnant women living in Norway between 1999- 2006. **Exclusion criteria:** NR **All patients** **N:** 69,929 pregnant women **Age (mean):** NR **Drop outs:** NR **Group 1** **N:** 1535 **Age (mean):** NR **Drop outs:** NR **Maternal age:** <20: 1/1535 (0.07%), 20-29: 166/1535 (10.8%), 30-39: 202/1535 (13.2%), >40: 4/1535 (0.3%) **Parity:**-0: 190/1535 (12.4%), >1: 183/1535 (0.3%) **Plurality:** 1: 366/1535 (23.8%), >1: 7/1535 (0.5%) **Married/ cohabiting:** 364/1535 (23.7%) **BMI prior to pregnancy:** <18.5: 18/1535 (1.2%), 18.5- 25:	**Group 1 - triptan exposure in 1st trimester** Women who used triptans during the 1st trimester of pregnancy **Group 2 - triptan exposure during the 2nd or 3rd trimesters** **Group 1 and 2 – triptan exposure any time during pregnancy** **Group 3 - migraine control** Triptan use in the 6 months prior to pregnancy **Group 4 - non-migraine control** Women with migraine who had not reported any triptan use during pregnancy **All groups:** Two self administered questionnaires. Pregnant women live in Norway between 1999 – 2006 received a postal invitation prior to first ultrasound	**Any congenital malformation** N (%) Crude odds ratio presented unless **	**Group1:** 69/1387 (5%) **Group 2:** 49/1000 (4.9%) **Group 1 and 2:** 75/1535 (4.9%) **Group 3:** 22/373 (5.9%) **Group 4:** 3405/68021 (5%) **Odds ratios & CI** **Group 1 vs 4:** 1 [0.7-1.2] **Group 2 vs 4:** 0.9 [0.7-1.3] **Group 1 &2 vs 4:** 0.9 [0.7-1.2] **Group 3 vs 4:** 1.1 [0.7-1.8] **p value:** NR	**Funding:** Norwegian Ministry of health NIH/NIEHS grant and Norwegian research council/FUGE grant **Limitations:** Low exposure numbers. Based on self reported migraine pharmacotherapy with possible under-reporting of drug use. 2nd questionnaire only covered triptan use up to gestational age 30 weeks, may be loss of data on triptan use after this point. Migraine diagnosis not validated. Categorisation of the three study groups dependent on the accuracy of the women's reporting. Only 42% of invited months agreed to participate in this study. **Additional outcomes:** Concomitant drug use during pregnancy. Individual triptans used by women. Maternal health during
			Major congenital malformation N (%) Crude odds ratio presented unless **	**Group1:** 43/1387 (3.1%) **Group 2:** 30/1000 (3%) **Group 1 and 2:** 46/1535 (3%) **Group 3:** 11/373 (2.9%) **Group 4:** 2003/68021 (2.9%) **Odds ratios & CI** **Group 1 vs 4:** 1 [0.7-1.4] **Group 2 vs 4:** 1 [0.7-1.4] **Group 1 &2 vs 4:** 1 [0.7-1.3] **Group 3 vs 4:** 0.9 [0.5-1.7] **p value:** NR	
			Live birth N (%) Crude odds ratio presented unless **	**Group1:** 1376/1387 (99.2%) **Group 2:** 995/1000 (99.5%) **Group 1 and 2:**1524/1535 (99.2%) **Group 3:**368/373 (98.7%) **Group 4:** 67480/68021 (99.2%)* **Odds ratios & CI** **Group 1 vs 4:** 1 [0.6-1.9]	

Study details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
	227/1535 (14.8%), >25: 116/1535 (7.6%) **Smoking at gestational week 30**: 37/1535 (2.4%) **Caffeine consumption during pregnancy:** 342/1535 (22.3%) **Alcohol intake during pregnancy:** 174/1535 (11.3%) **Group 2** **N:** 1897 **Age (mean):** NR **Drop outs:** NR **Maternal age:** -<20: 12/1897 (0.6%), 20-29: 625/1897 (32.9%), 30-39: 872/1897 (46%), >40: 26/1897 (1.4%) **Parity:** 0: 723/1897 (38.1%), >1: 812/1897 (42.8%) **Plurality:** 1: 1513/1897 (79.8%), >1: 22/1897 (1.2%) **Married/ cohabiting:** 1496/1897 (78.9%) **BMI prior to pregnancy:** <18.5: 40/1897 (2.1%), 18.5- 25: 886/1897 (46.7%), >25: 580/1897 (30.6%) **Smoking at gestational week 30:** 142/1897 (7.5%) **Caffeine consumption during pregnancy:** 1405/1897 (74.1%) **Alcohol intake during pregnancy:**	scan between gestational weeks 17 – 18. The invitation contained the fist questionnaire which covered sociodemographic data, maternal medical history, drug exposure other exposures in the 6 months prior to pregnancy and during the 1st 18 weeks of the current pregnancy. 2nd questionnaire given out at gestational week 30- covered lifestyle and medical data during the 2nd and 3rd trimesters. Information from the medical birth registry of Norway was obtained from mandatory standardised forms containing information about the mother and the newborn. These forms are filled out by midwives, obstetricians and/or paediatricians at each delivery, information on the mother is obtained from the mother's pregnancy medial records.		**Group 2 vs 4:**1.6 [0.6-3.8] **Group 1 &2 vs 4**:1.1 [0.6-2.0] **Group 3 vs 4:** 0.7 [0.3-1.7] **p value:** NR	pregnancy. Obstetric complications. Chronic conditions. **Notes:** Multiple pregnancies were included, but only data on the first born infant were used. *paper states 6748, but 99.2%, assumed a type error. **adjusted for possible confounding factors- maternal socio-demographic data, medical characteristics (including concomitant drug use), maternal health, pregnancy complications. Provides OR- adjusted for variable including: parity, plurality, maternal BMI prior to pregnancy, caffeine and alcohol intake during pregnancy , paracetamol and or codeine in combination with paracetamol use during pregnancy, pre eclampsia, eclampsia, polyhydramnios, placenta previa, abruption placentae and caesarean section by birth weight >4500g and vaginal bleeding during pregnancy).
			Still birth (intrauterine death after gestational week 20) N (%) Crude odds ratio presented unless **	**Group1:** 0/1387 **Group 2:** 0/1000 **Group 1 and 2:** 0/1535 **Group 3:** 2/373** (0.5%) **Group 4:** 19/68021 (0.03%) **Odds ratios & CI** **Group 1 vs 4:** NA **Group 2 vs 4:** NA **Group 1 & 2 vs 4:** NA **Group 3 vs 4:** 11.7 [2.8-49.5] **p value:** NR	
			Perinatal death (death during labour or within 20 hours of delivery) N (%) Crude odds ratio presented unless **	**Group1:** 6/1387 (0.4%) **Group 2:** 3/1000 (0.3%) **Group 1 and 2:** 6/1535 (0.4%) **Group 3:**3/373 (0.8%) **Group 4:** 314/68021 (0.4%) **Odds ratios & CI** **Group 1 vs 4:** 0.9 [0.4-2.0] **Group 2 vs 4:** 0.7 [0.2-2.1] **Group 1 &2 vs 4:** 0.8 [0.4-1.8] **Group 3 vs 4:** 1.5 [0.5-4.8] **p value:** NR	
			Death during the 1st 12 months of life N (%)	**Group1:** 5/1387 (0.3%) **Group 2:** 2/1000 (0.2%) **Group 1 and 2:** 5/1535 (0.3) **Group 3:** 0/373	

Study details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
	819/1897 (43.1%) **Group 3** **N:** 68,021 **Age (mean):** NR **Drop outs:** NR **Maternal age**: <20: 742/68,021 (1.1%), 20-29: 30007/68,021 (44.1%), 30-39: 35973/68,021 (52.9%), >40: 1299/68,021 (1.9%) **Parity:** 0: 29508/68,021 (43.4%), >1: 38507/68,021 (0.05%) **Plurality:** 1: 66760/68,021 (98.1%), >1: 1261/68,021 (1.9%) **Married/ cohabiting:** 66072/68,021 (97.1%) **BMI prior to pregnancy:** <18.5: 2073/68,021 (3.0%), 18.5-25: 43431/68,021 (63.8%), >25: 20551/68,021 (30.2%) **Smoking at gestational week 30:** 6156/68,021 (9.1%) **Caffeine consumption during pregnancy:** 59581/68,021 (87.6%) **Alcohol intake during pregnancy:** 35058/68,021 (51.5%)		Crude odds ratio presented unless **	**Group 4:** 192/68021 (0.3%) **Odds ratios & CI** **Group 1 vs 4:** 1.3 [0.5-3.1] **Group 2 vs 4:** 0.7 [0.2-2.9] **Group 1 &2 vs 4:** 1.2 [0.5-2.8] **Group 3 vs 4:** NA **p value:** NR	
			Birth weight <2500g N (%) Crude odds ratio presented unless **	**Group1:** 63/1387 (4.5%) **Group 2:** 40/1000 (4%) **Group 1 and 2**:65/1535 (4.2%) **Group 3:** 19/373 (5.1%) **Group 4:** 2663/68021 (3.9%) **Odds ratios & CI** **Group 1 vs 4:** 1.2 [0.8-1.7] **Group 2 vs 4:** 1.1 [0.7-1.8] **Group 1 &2 vs 4:** 1.1 [0.8-1.6] **Group 3 vs 4:** 1 [0.5-1.8] **p value:** NR	
			Gestational age <37 weeks N (%) Crude odds ratio presented unless **	**Group1:** 82/1387 (5.9%) **Group 2:** 55/1000 (5.5%) **Group 1 and 2:**86/1535 (5.6%) **Group 3:** 30/373 (8.0%) **Group 4:** 4148/68021 (6.1%) **Odds ratios & CI** **Group 1 vs 4:** 0.8 [0.6-1.0] **Group 2 vs 4:** 0.8 [0.6-1.0] **Group 1 &2 vs 4:** 0.8 [0.6-1.0] **Group 3 vs 4:**1.2 [0.8-1.8] **p value:** NR	
			Apgar score <7 at 1	**Group1:** 81/1387 (5.8%)	

Study details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
			minute N (%) Crude odds ratio presented unless **	**Group 2:** 55/1000 (5.5%) **Group 1 and 2**:88/1535 (5.7%) **Group 3:**18/373 (4.8%) **Group 4:** 3708/68021 (5.5%) **Odds ratios & CI** **Group 1 vs 4: 1 [0.8-1.2]** **Group 2 vs 4:** 0.9 [0.7-1.2] **Group 1 &2 vs 4:** 1 [0.8-1.2] **Group 3 vs 4:** 0.8 [0.5-1.2] **p value:** NR	
			Apgar score <7 at 5 minutes N (%) Crude odds ratio presented unless **	**Group1:** 20/1387 (1.4%) **Group 2:** 11/1000 (1.1%) **Group 1 and 2:**22/1535 (1.4%) **Group 3:** 4/373 (1.1%) **Group 4:** 925/68021 (1.4%) **Odds ratios & CI** **Group 1 vs 4:** 1 [0.6-1.6] **Group 2 vs 4:** 0.8 [0.4-1.4] **Group 1 &2 vs 4:** 1 [0.7-1.6] **Group 3 vs 4:** 0.6 [0.2-1.7] **p value:** NR	

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

Study Details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
Author & Year: Oleson et al, 2000[597] **Study design:** Prospective cohort **Setting:** Denmark **Duration of follow-up**: To birth of infant	**Patient group:** Pregnant women who redeemed a prescription for sumatriptan from 1991 – 1996 **Inclusion criteria:** Women redeeming a prescription for sumatriptan identified through the prescription database. Healthy controls identified through the Danish national birth registry Exclusion criteria: **All patients** **N:** 35950 (total number of births) **Age (mean):** NR **Drop outs:** NR in any group **Group 1** **N:** 34 **Age (mean):** 29.6 **Smoking:** 11/34 (32.4%) **Marital status (women living with child's father):** 23/34 (64.6%) **Parity (proportion of primiparous women):**10/34 (29.4%) **Group 2** **N:** 89 **Age (mean):** 28.4 **Smoking:** 33/89 (37.0%) **Marital status (women living with child's father):** 59/89 (66.3%)	**Group 1- women exposed to sumatriptan** Women exposed to Sumatriptan during their pregnancy were identified. **Group 2- migraine control group** Women who redeemed at least one prescription for sumatriptan or ergotamine 52 – 12 weeks prior to conception, but not during pregnancy. **Group 3 -Healthy women** Women who did not redeem any prescriptions during pregnancy **All groups** All prescriptions redeemed in North Jutland county, Denmark from January 1991 – 1996, using the countries prescription database. Using the prescription database, identified all prescriptions for women who had given birth in the county of North Jutland from 1991- 1996. Prescription data was linked to the national birth registry.	**Low birth weight (<2500g)** N (%) *Adjusted OR	**Group1:** 1/34 (2.4%) **Group 2:** 5/89 (5.6%) **Group 3:** 291/15,995 (1.8%) **Odds ratios & CI** **Group 1 vs 2:** 2.3 [0.3-17.6] **Group 1 vs 3:** 0.9 [0.1-11.8] **Group 2 vs 3:** 3.2 [1.3-8.1] **p value:** NR	**Funding:** EU BIOMED programme, Danish medical research council, 1991 pharmacy foundation, North Jutland Research council. **Limitations:** Exposure to sumatriptan may be underestimated because the use of drugs during hospital admission is not included and prescriptions redeemed prior to pregnancy may have been used during pregnancy. Severity of illness that led to the prescriptions could have been a confounding variable. **Additional outcomes:** NR **Notes:** *All OR reported were adjusted for parity, smoking, maternal age and marital status. Logistic regression used to estimate association between sumatriptan use and preterm delivery and low
			Preterm (<37 weeks) N (%) Adjusted OR	**Group1:** 5/34 (14.7%) **Group 2:** 3/89 (3.4%) **Group 3**: 950/15,995 (5.9%) **Odds ratios & CI** **Group 1 vs 2:** 3.3 [1.3-8.5] **Group 1 vs 3:** 6.3 [1.2-32.0] **Group 2 vs 3:** 0.6 [0.2-1.9] **p value:** NR	
			Still births N (%) Adjusted OR	**Group 1**:0 **Group 2:** NR **Group 3:** NR	
			Birth defects N (%) Adjusted OR	**Group 1**:0 **Group 2:** NR **Group 3:** NR	

Study Details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
	Parity (proportion of primiparous women): 37/89 (41.6%) **Group 3** **N:** 15,995 **Age (mean):** 27.9 **Smoking:** 4846/15,995 (30.3%) **Marital status (women living with child's father):** 13,116/15,995 (82%) **Parity (proportion of primiparous women):** 8717/15,995 (54.5%)	Data obtained from official reports filled in by midwives attending deliveries.			birth weight. Association with low birth weight assessed in pregnancies that reached full term only.

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

Verapamil

Study Details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
Author & Year: Weber-Schoendorfer et al, 2008[842] **Study design:** Prospective observational study **Setting:** Multicentre study (11 centres) **Duration of follow-up:** Birth or end of pregnancy	**Patient group:** Pregnant women in their first trimester **Inclusion criteria: NR** **Exclusion criteria: NR** **Group 1** **N:** 299 (62 to verapamil) **Maternal age (median):** 33 (16-48) **Group 2** **N:** 806 **Maternal age (median):** 30 (17-44)	**Group 1**: verapamil Pregnant women with first trimester exposure to calcium channel blockers (CCBs) whose physician contacted a Teratology Information Service (TIS) that was a member of the European Network of Teratology Information Services (ENTIS) between 1986 and 2003 **Group 2**: all calcium channel blockers As above but includes several calcium channel blockers including verapamil **Group 3:** controls Pregnant women who had been counselled during pregnancy about exposures known to be to non-teratogenic. Controls enrolled in the same country and year as exposed pregnancies. **Confounding factors:** More women using CCBs: Smoked (26.5% vs 11.%5) Smoked >5 cigarettes/day (23.1% vs 7.9%) Previous miscarriages (24% vs 13.2%)	**Miscarriage (after exclusion of elective termination of pregnancy)** N (%)	**Group1:** 4/62 (6.9%) **Group 2:** 39/299 (14.6%) - adjusted odds ratio 2.21 (1.39, 3.50)* **Group 3:** 59/806 (7.6%)	**Funding**: German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArm) **Limitations:** Not stated if exposed patients and controls were selected consecutively. Unclear how controls were selected. Reports baseline characteristics for all CCB patients but not verapamil alone. *States outcomes parameters were adjusted for: maternal age, concomitant medication, alcohol and cigarette consumption, previous miscarriage and birth defects in previous offspring. Unclear if this refers to the adjusted odds ratios for calcium channel blockers as a whole. **Additional outcomes:** Live pregnancies, gestational age at delivery, birth weight **Notes:** Data collected by similarly structured questionnaire used by all centres to record following data at the first contact (early pregnancy before outcome known): drug exposure, demographics, medical & obstetric
			Still births (after exclusion of elective termination of pregnancy) N (%)	**Group1:** 1/62 (1.7%) **Group 2:** 6/299 (2.2%) - adjusted odds ratio 2.98 (1.02, 8.72)* **Group 3:** 6/806 (0.8%)	
			Elective termination of pregnancy (ETOP) N (%)	**Group1:** 4/62 (6. 5%) **Group 2:** 31/299 (10.4%) **Group 3:** 30/806 (3.7%)	
			Preterm children (<37 weeks) N (%)	**Group1:** 12/62 (21.8%) **Group 2:** 54/299 (23.8%) - adjusted odds ratio 4.63 (2.94, 7.27)* **Group 3:** 47/806 (6.5%)	
			All birth defects N (%)	**Group1:** 6/62 (10.7%) including 1 ETOP **Group 2:** 15/299 (6.6%) including 2 ETOPs - adjusted odds ratio 1.58 (0.81, 3.07)* **Group 3:** 33/806 (4.6%) including 2 ETOPs	
			Major birth defects (excluding chromasomal anomalies/syndromes)	**Group1:** 2/62 (3.6%) **Group 2:** 8/299 (3.5%) including 1 ETOP - adjusted odds ratio 2.27 (0.90, 5.69)* **Group 3:** 14/806 (1.9%)	

Study Details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
		Had additional diseases - not defined (85.6% vs 27.3%)	N (%)	including 1 ETOP	history. Follow up after expected date of delivery by mailed questionnaire or telephone interview.

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

E.5.2 Combined hormonal contraceptive use in girls and women with migraine

Study details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
Author & Year: Chang et al, 1999[143] **Study design:** Hospital based case-control study **Setting:** Hospital based case control study. Eight cities from five European centres (UK, Germany, Hungary, Slovenia, Yugoslavia) **Duration of follow-up:** 3 years	**Patient group:** Women aged 20-44 who had had a stroke. **Inclusion criteria:** Female; Aged 20-44 years; admitted to a participating hospital between June 1990 and January 1993; had a discharge diagnosis of stroke (cases); Controls had to have been admitted to the same hospital as the case, with one of the 27 diagnoses considered to have no association with use of oral contraceptives. **Exclusion criteria:** Had a transient ischaemic attack; died within 24 hours of admission; had a history of stroke, deep vein thrombosis, pulmonary embolism, acute myocardial infarction, or natural or surgical menopause; recent history (within 6 weeks) of pregnancy; had a major illness causing prolonged bed rest or surgery. **Cases** **N:** 291 (had a stroke and completed supplementary questionnaire); 86 (ischaemic stroke), 187 (haemorrhagic stroke), 18 (unclassified). **Cases with migraine** **N (History of migraine):** 74/291 **Age in years (mean ± SD):** 36.1±5.6 **Current oral contraceptive use:** 18 (24.3%) **Controls**	**Group 1** Women with migraine who took oral contraceptives **Group 2** Women with migraine who did not take oral contraceptives **Group 3** Women with no migraine who did not take oral contraceptives **Cases (as defined by study)** Stroke cases which were classified into seven types: Intracerebral (including intraventricular, intraparenchymal, and intracerebellar), subarachnoid haemorrhage, undifferentiated haemorrhage, ischaemic stroke with or without possible cardiac source of embolus, unclassified and venous. **Controls (as defined by study)** Up to three hospital based controls were recruited for each case matched by 5 year age bands and time of admission.	**Adjusted* odds ratio of ischaemic stroke** (OR, 95% CI)	**Group 1/ Group 3:** 16.9 (2.72 to 106) No. of cases/controls: 10/3 **Group 2/ Group 3:** 2.27 (0.69 to 7.47) No. of cases/controls: 16/23	**Funding:** United Nations Development Programme/ United Nations Population Fund/WHO /World Bank/National institutes of health **Limitations:** Information on use of oral contraceptives and past history is primarily based on interview and may be subject to recall bias. Validation of information on exposure is difficult, and may be incomplete. **Notes:** Study calculated odds ratios of stroke for Groups 1 and 2 in comparison to women who did not have a history of migraine and did not use oral contraceptives. †Stroke was fitted as the dependent variable, and known risk factors and migraine status were independent variables.
			Adjusted* odds ratio of haemorrhagic stroke (OR, 95% CI)	**Group 1/ Group 3:** 1.10 (0.40 to 2.97) No. of cases/controls: 8/16 **Group 2/ Group 3:** 1.13 (0.60 to 2.12) No. of cases/controls: 30/45	

Study details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
	N:736 (matched controls); 220 (matched for ischaemic stroke), 471 (matched for haemorrhagic stroke), 44(matched for unclassified stroke) **Controls with migraine** **N(History of migraine):** 96/736 **Age in years (mean ± SD):** 35.7±6.2 **Current oral contraceptive use:** 20 (20.8%)				*Adjusted for high blood pressure, education, smoking, family history of migraine, alcohol consumption, and social class.

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

Study details	Patients	Prognostic factors	Outcome measures	Effect size	Comments
Author & Year: Lidegaard & Kreiner, 2002[496] **Study design:** Prospective case-control study **Setting:** Danish National Patient Register **Duration of follow-up:** Five years starting in 1994	**Patient group:** Women with cerebral thrombo-embolic attacks (CTA) **Inclusion criteria:** **Cases -** Women aged 15-44 years who had a CTA; registered diagnosis in the Danish National Patient Register. **Controls -** For the period 1994-1995, control group of 600 women, age matched to CTA patients. For the period 1996-1998, 1200 randomly selected women from the Central Person Register (CPR) aged 15-44 years. **Exclusion criteria:** Women with CTA or other thrombotic diseases before 1994 were identified in the register and excluded to include only first-ever events. **All patients** **Cases** **N:** 626 **Cases with migraine** **N:** 107 (17.1%) **Controls** **N:** 4054 **Controls with migraine** **N:** 258 (6.4%)	**Group 1** Cases with migraine **Group 2** Controls with migraine	**Risk of cerebral thrombo-embolism** Crude odds ratio (Group 1 vs Group 2) **Cerebral thrombo-embolism** Adjusted odds ratio (Group 1 vs Group 2) *adjusted for oral contraceptive use	**OR:** 3.2 ***Adjusted OR:**3.2 **95% CI:** 2.5-4.2	**Funding:** Organon International, Wyeth-Ayerst, and Schering AG. **Limitations:** Difference in responses between cases and controls due to potential recall bias. Oral contraceptive users may be more likely to be investigated for stroke which may affect effect size. Differences in prescription of oral contraceptives (third generation versus older generation pills) may affect effect size. **Notes:** Women registered more than once during the 5-year period were recorded according to their first discharge diagnosis. Both cases and controls received same questionnaire regarding use of oral contraceptive pills and other factors.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients in group, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, NPR=National Patient Register ICD= International Classification of Diseases, CTA= Cerebral thrombo-embolic attack, CPR= Central Person Register (includes all Danish people older than 5 days).

Appendix F: Evidence tables – Economic evidence

Brown JS, Papadopoulos G, Neumann PJ, Price M, Friedman M, Menzin J. Cost-effectiveness of migraine prevention: the case of topiramate in the UK. Cephalalgia 2006, 26(12):1473-82. (Guideline Ref ID: BROWN2006)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** the model was based on a decision tree structure where the difference in costs and outcomes for each strategy were driven by probabilities of probabilities of major, moderate and limited clinical response[1] and withdrawal associated with topiramate and usual care. **Perspective:** UK NHS **Time horizon:** 1 year **Treatment effect duration:** 1 year **Discounting:** NA	**Population:** Adults who are candidates for migraine prevention using topiramate. The base-case monthly migraine frequency was assumed to be six. Migraineurs with moderate-severe migraine frequency. **Intervention 1:** Topiramate **Intervention 2:** Usual care (defined as 'no preventive treatment') .	**Total costs per year (mean per patient):** Intvn 1: £502 Intvn 2: £254 Incremental (1-2): £248 (p=NR) **Currency & cost year:** 2005 UK pounds inflated to 2010 costs using PSSRU[180] **Cost components incorporated:** Drugs, GP consultations, hospitalisation, emergency room visits.	**Primary outcome measure:** QALYs: Intvn 1 vs Intvn 2: 0.0384 *Incremental number of migraines averted (Mean per patient):* Intvn 1 vs Intvn 2: 1.81	**Primary ICER (Intvn 1 vs Intvn 2):** ICER: £6,457 per QALY gained **Analysis of uncertainty** One way sensitivity analysis was carried out. 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%) Topiramate was found to be cost effective for all one way sensitivity analyses. No probabilistic sensitivity analysis was conducted.

Data sources				
Health outcomes: numbers of migraines averted per month and discontinuation rate were obtained from a meta-analysis of RCTs; all of the RCTs used to inform the effectiveness estimates were included in our clinical review, though our clinical review included also more recent studies. **Quality-of-life weights:** Utility gain for major, moderate and limited clinical response was derived using trial data and the SF-36 measure. The author's state that SF-36 data was "collected as part of the trials", but do not mention specifically which one, meaning, presumably the data was collected from all the RCTs informing the model. **Cost sources:** cost of topiramate and triptans from BNF; cost of GP visits, hospitalisation, and emergency room visits from previous UK economic studies and National Statistics.				
Comments				
Source of funding: NR **Limitations:** 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 1.01. However, a value of 0.91migraines 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.				
Overall applicability*: Directly applicable Overall quality: Minor limitations**				

Abbreviations: CUA = cost utility analysis; ICER = incremental cost-effectiveness ratio; Intvn = intervention; NA = not applicable; NR = not reported; QALYs =quality-adjusted life years.
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations.*
1 Limited response: <50% reduction in migraine frequency; Moderate response: 50-75% reduction in migraine frequency; Major response: >75% reduction in migraine frequency.

Howard L, Wessely S, Leese M, Page L, McCrone P, Husain K et al. Are investigations anxiolytic or anxiogenic? A randomised controlled trial of neuroimaging to provide reassurance in chronic daily headache. J Neurol Neurosurg Psychiatry 2005, 76(11):1558-64. (Guideline Ref ID: HOWARD2005)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA **Study design:** RCT **Perspective:** UK NHS **Follow-up:** 1 year **Discounting:** NA	**Population:** Consecutive English speaking patients who fulfilled the criteria for chronic daily headache (at least 15 days per month of headache for more than 6 months), presenting as new patients to a headache clinic in London. Patients were excluded if there was a clinical justification for neuroimaging or if there was a medical contraindication to MRI scan. Subgroup A: Patients unlikely to have a psychiatric disorder Subgroup B: Patients very likely to have a psychiatric disorder as detected by the Hospital Anxiety and Depression Scale (HADS) **Intervention 1:** Offer of a screening MRI scan. In case of an abnormal scan, patients were seen by the neurologist. N = 76 Mean age = 37 M/F = 59/17 Drop outs: not clear, 5 did not have scan **Intervention 2:** No offer a MRI scan. N = 74 Mean age = 40 M/F = 57/17 Drop outs: unclear, 3 demanded a scan.	**Total costs (mean per patient):** Subgroup A Intvn 1: £464 Intvn 2: £352 Incremental (1-2): £112 (p=0.267) Subgroup B Intvn 1: £306 Intvn 2: £771 Incremental (1-2): -£465 (p=0.267) **Currency & cost year:** 2005 UK pounds **Cost components incorporated:** Cost of CT scan [£119] was used instead of MRI because this is what would be used in routine practice; GP visits, neurologist, psychiatrist/therapist visits, outpatient and inpatient care, other tests.	**Primary outcome measure** 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 See clinical evidence table in E.1.5 for details.	**ICER:** not calculated

Data sources
Health outcomes: from the RCT. **Cost sources:** NHS unit costs
Comments
Source of funding: The Wellcome Trust. **Limitations:** Value of health effects not expressed in terms of QALYs. Randomisation was unclear. Patients swapped groups. Allocation concealment unclear. Incomplete reporting of data.
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

Abbreviations: CCA = cost-consequence analysis; ICER = incremental cost-effectiveness ratio; Intvn = intervention; M/F = number of males/females; N = number randomised; NA = not applicable.

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations.*

Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N. Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis. Health Technology Assessment 2004, 8(48):1-50. (Guideline Ref ID: VICKERS2004)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** RCT **Perspective:** UK NHS **Time horizon:** 12 months **Treatment effect duration:** 12 months **Discounting:** NA	**Population:** Patients with migraine (95%) or TTH (5%) aged 18-65 with an average of at least 2 headaches per month. **Intervention 1:** Standard care from GP. N = 140 2 patients in the usual care arm received acupuncture. **Intervention 2:** Standard care from GP and up to 12 treatments over 3 months from an advanced member of the Acupuncture Association of Charted Physiotherapists. N = 161	**Total costs (mean per patient):** Intvn 1: £113 Intvn 2: £368 Incremental (2-1):£260 Mean difference adjusted for baseline variable. **Currency & cost year:** 2002/2003 GBP cost updated using an inflator index = 1.27 (from year 2002/2003) calculated from PSSRU[180] using the Hospital and Community Health Services Pay and Prices Index. **Cost components incorporated:** Cost of acupuncture (average 9 visits per patient in acupuncture arm; 4.2 average hours of contact), GP visits, outpatient visits, non-prescription drugs.	**Primary outcome measure:** QALYs (mean per patient) Intvn 1:0.708 Intvn 2: 0.727 Incremental (2-1):0.021 Mean difference adjusted for baseline variable.	**Primary ICER (Intvn 2 vs Intvn 1):** ICER: £12,381 per QALY gained Probability cost-effective: around 80% (at a £20,000/QALY threshold) **Analysis of uncertainty:** 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.
Data sources				

Health outcomes: patients' responses to the SF-36 at baseline, 3 months and 1 year. **Quality-of-life weights:** SF-6D algorithm was used to calculate HRQoL data at baseline, 3 months and 1 year from patients' responses to the SF-36 at these time points. No imputation was done for missing HRQoL data **Cost sources:** National data.
Comments
Source of funding: NHS R&D HTA Programme; **Limitations:** Short time horizon. Acupuncture was compared to usual care instead of a specific treatment strategy or no treatment. The study was conducted in 2003. **Other:** this study was excluded from the clinical review as the comparator was usual care instead of placebo; however from an economic perspective, comparing an intervention with usual care is acceptable.
Overall applicability*: Partially applicable. Overall quality: Minor limitations**

Abbreviations: CUA = cost-utility analysis; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; Intvn = intervention; N = number randomised; NA = not applicable; QALYs =quality-adjusted life years; TTH = tension-type headache.
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations.*

Appendix G: Forest plots – Clinical evidence

G.1 Assessment and diagnosis

G.1.1 Indications for consideration of additional investigation

G.1.1.1 Comparison: HIV+ with headache vs HIV+ without headache

Figure 1: CNS opportunistic infection (at baseline)

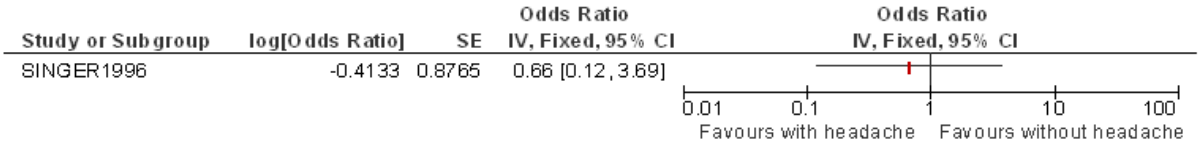
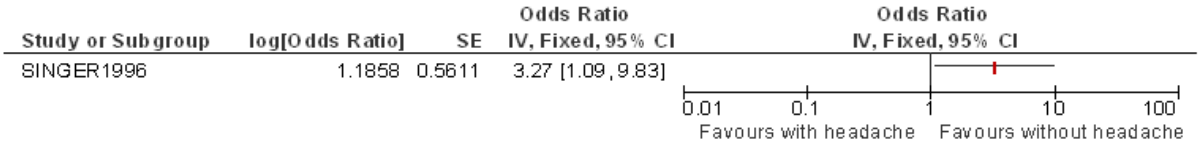


Figure 2: New HIV-1 associated neurologic disease



G.1.2 Identifying people with primary headache

G.1.2.1 ID Migraine

Figure 3: ID migraine

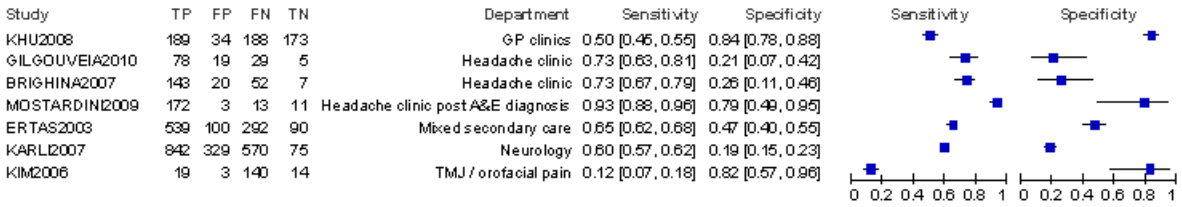


Figure 4: The structured migraine questionnaire

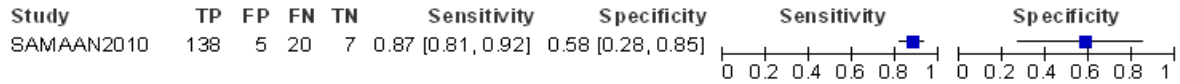
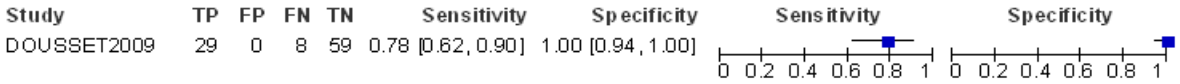


Figure 5: Cluster headache screening questionnaire



G.1.3 Imaging as a management strategy for people with primary headache

Figure 6: Resource use – GP visits

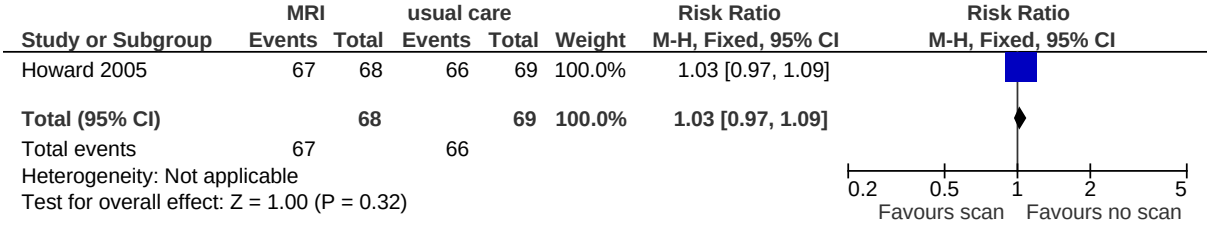


Figure 7: Resource use – neurologist visits

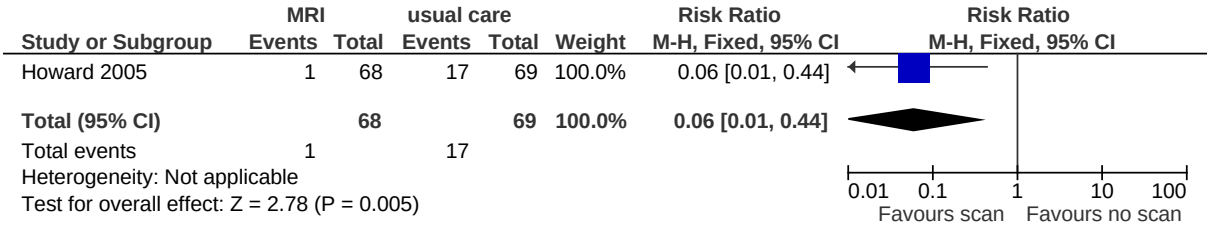


Figure 8: Resource use – psychologist / therapist visits

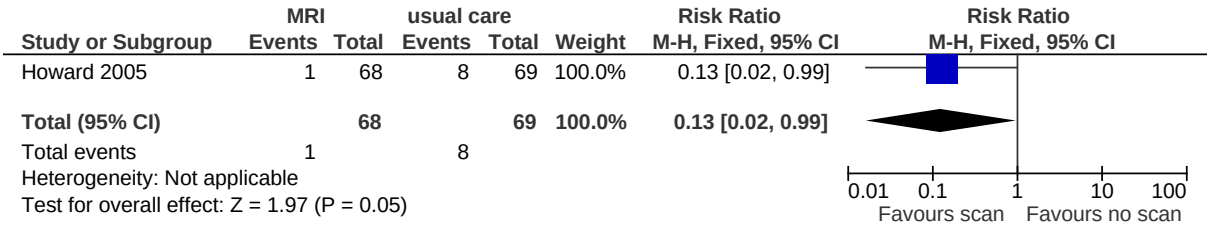


Figure 9: Resource use – outpatient visits

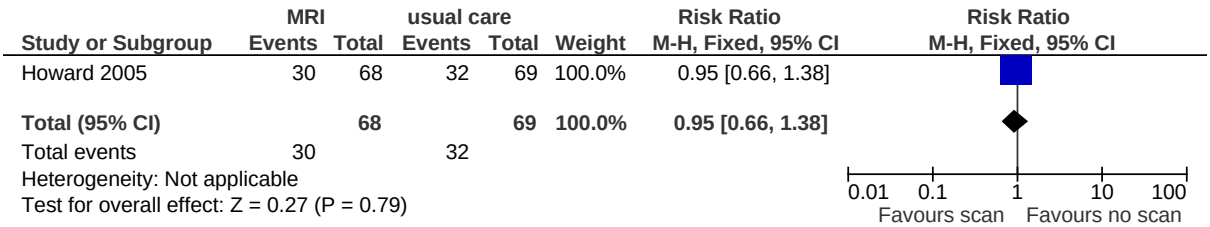


Figure 10: Resource use – other imaging

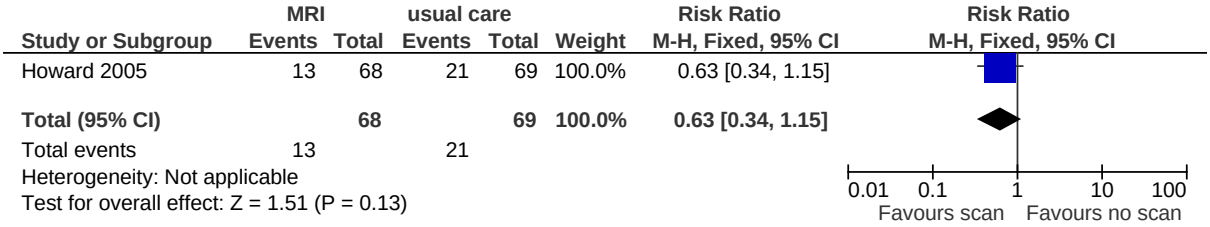


Figure 11: Resource use – tests

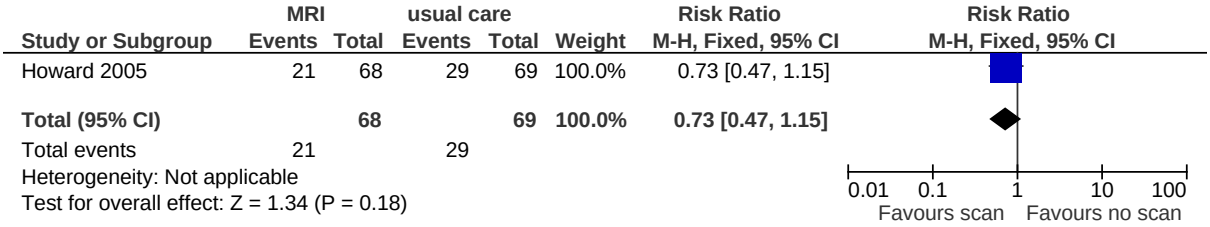


Figure 12: Resource use – inpatient care

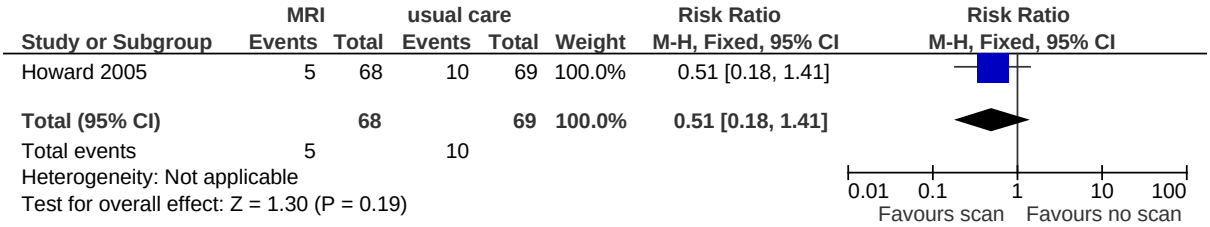


Figure 13: Resource use – other services

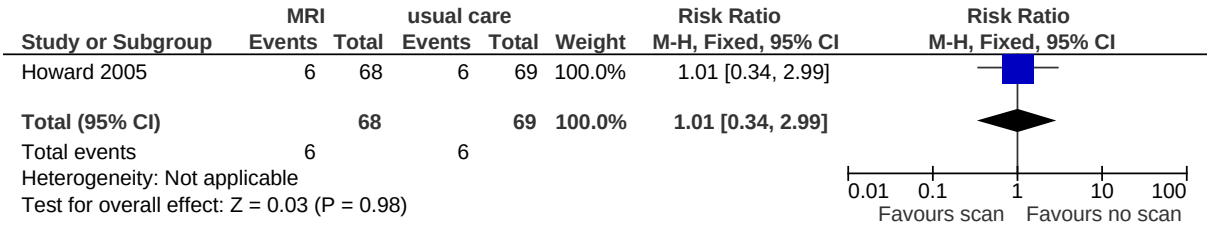


Figure 14: Resource use – sick notes

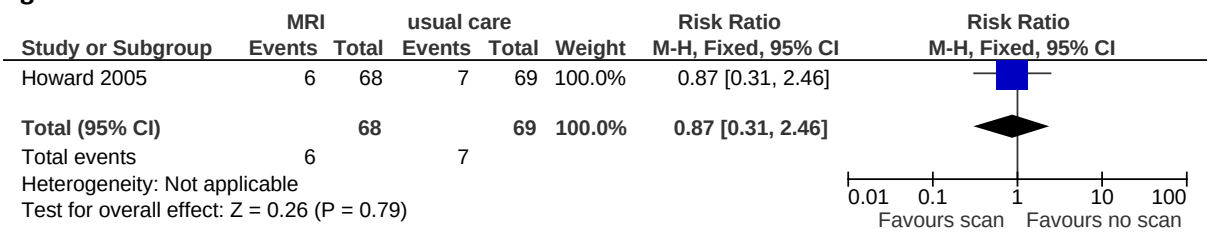


Figure 15: Change in anxiety or depression – VAS worry

Study or Subgroup	Adjusted mean difference	SE	Weight	Adjusted mean difference IV, Fixed, 95% CI
Howard 2005	-4.47	5.510204	100.0%	-4.47 [-15.27, 6.33]
Total (95% CI)			**100.0%**	**-4.47 [-15.27, 6.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)

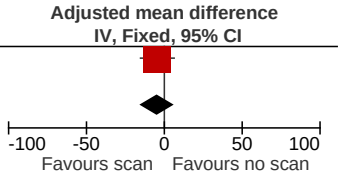


Figure 16: Change in anxiety or depression - HAQ health, worry and preoccupation

Study or Subgroup	Adjusted mean difference	SE	Weight	Adjusted mean difference IV, Fixed, 95% CI
Howard 2005	0.22	0.755102	100.0%	0.22 [-1.26, 1.70]
Total (95% CI)			**100.0%**	**0.22 [-1.26, 1.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)

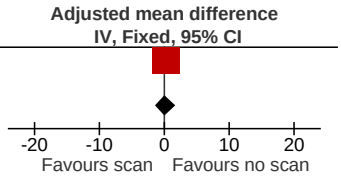


Figure 17: Change in anxiety or depression - HAQ fear of illness

Study or Subgroup	Adjusted mean difference	SE	Weight	Adjusted mean difference IV, Fixed, 95% CI
Howard 2005	0.31	0.584184	100.0%	0.31 [-0.83, 1.45]
Total (95% CI)			**100.0%**	**0.31 [-0.83, 1.45]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

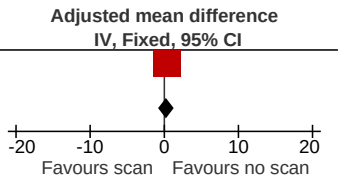


Figure 18: Change in anxiety or depression – HAQ reassurance seeking behaviour

Study or Subgroup	Adjusted mean difference	SE	Weight	Adjusted mean difference IV, Fixed, 95% CI
Howard 2005	-0.39	0.278061	100.0%	-0.39 [-0.93, 0.15]
Total (95% CI)			**100.0%**	**-0.39 [-0.93, 0.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)

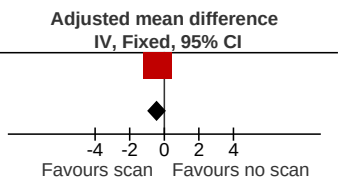
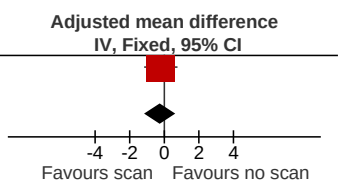


Figure 19: Change in anxiety or depression – HAQ life interference

Study or Subgroup	Adjusted mean difference	SE	Weight	Adjusted mean difference IV, Fixed, 95% CI
Howard 2005	-0.2	0.469388	100.0%	-0.20 [-1.12, 0.72]
Total (95% CI)			**100.0%**	**-0.20 [-1.12, 0.72]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)



G.2 Management

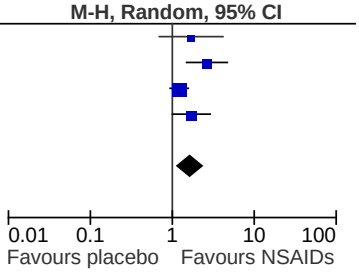
G.2.1 Acute pharmacological treatment of tension type headache

G.2.1.1 NSAID vs placebo

Figure 20: Pain free at 2 hours

Study or Subgroup	NSAIDs Events	NSAIDs Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
DAHLOF1996	17	58	5	29	13.4%	1.70 [0.70, 4.15]
KUBITZEK2003	97	467	12	153	23.1%	2.65 [1.50, 4.69]
PRIOR2002	93	295	78	301	38.7%	1.22 [0.94, 1.57]
STEINER1998	28	102	18	112	24.9%	1.71 [1.01, 2.90]
Total (95% CI)		**922**		**595**	**100.0%**	**1.66 [1.13, 2.44]**
Total events	235		113			

Heterogeneity: Tau² = 0.08; Chi² = 6.89, df = 3 (P = 0.08); I² = 56%
Test for overall effect: Z = 2.56 (P = 0.01)

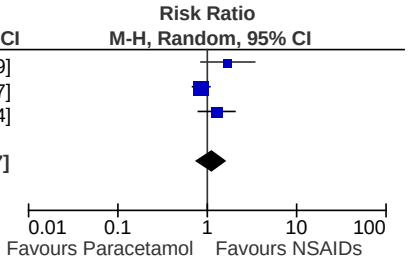


G.2.1.2 NSAID vs paracetamol

Figure 21: Pain free at 2 hours

Study or Subgroup	NSAIDs Events	NSAIDs Total	Paracetamol Events	Paracetamol Total	Weight	Risk Ratio M-H, Random, 95% CI
DAHLOF1996	17	58	10	58	20.9%	1.70 [0.85, 3.39]
PRIOR2002	93	295	112	304	47.5%	0.86 [0.68, 1.07]
STEINER1998	28	102	25	116	31.6%	1.27 [0.80, 2.04]
Total (95% CI)		**455**		**478**	**100.0%**	**1.12 [0.75, 1.67]**
Total events	138		147			

Heterogeneity: Tau² = 0.07; Chi² = 5.06, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 0.56 (P = 0.58)

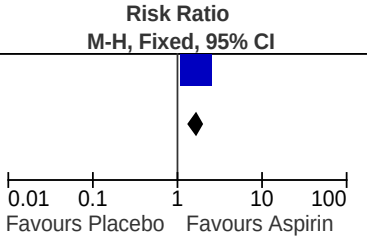


G.2.1.3 Aspirin vs placebo

Figure 22: Pain free at 2 hours

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
STEINER2003	156	214	49	112	100.0%	1.67 [1.33, 2.09]
Total (95% CI)		**214**		**112**	**100.0%**	**1.67 [1.33, 2.09]**
Total events	156		49			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.44 (P < 0.00001)

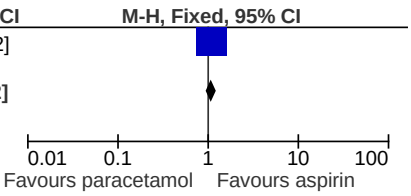


G.2.1.4 Aspirin vs paracetamol

Figure 23: Pain free at 2 hours

Study or Subgroup	Aspirin Events	Aspirin Total	Paracetamol Events	Paracetamol Total	Weight	Risk Ratio M-H, Fixed, 95% CI
STEINER2003	156	214	146	216	100.0%	1.08 [0.95, 1.22]
Total (95% CI)		**214**		**216**	**100.0%**	**1.08 [0.95, 1.22]**
Total events	156		146			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)

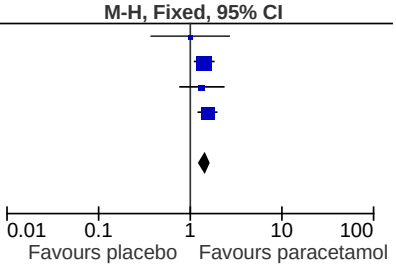


G.2.1.5 Paracetamol vs placebo

Figure 24: Pain free at 2 hours

Study or Subgroup	Paracetamol Events	Paracetamol Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DAHLOF1996	10	58	5	29	4.0%	1.00 [0.38, 2.66]
PRIOR2002	112	304	78	301	46.7%	1.42 [1.12, 1.81]
STEINER1998	25	116	18	112	10.9%	1.34 [0.78, 2.32]
STEINER2003	146	216	49	112	38.4%	1.54 [1.23, 1.94]
Total (95% CI)		**694**		**554**	**100.0%**	**1.44 [1.23, 1.69]**
Total events	293		150			

Heterogeneity: Chi² = 0.96, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 4.54 (P < 0.00001)

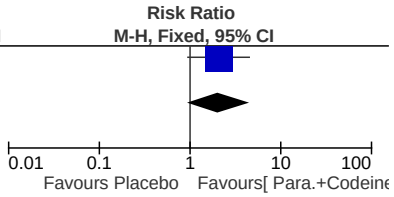


G.2.1.6 Paracetamol and codeine vs placebo

Figure 25: Pain free at 2 hours

Study or Subgroup	Paracetamol + Codeine Events	Paracetamol + Codeine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRIEDMAN1987	16	65	8	67	100.0%	2.06 [0.95, 4.48]
Total (95% CI)		**65**		**67**	**100.0%**	**2.06 [0.95, 4.48]**
Total events	16		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)



G.2.2 Acute pharmacological treatment of migraine

Oral, nasal & subcutaneous treatments

G.2.2.1 Aspirin vs NSAID

Figure 26: Headache response at up to 2 hours

Study or Subgroup	Aspirin Events	Aspirin Total	NSAID Events	NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DIENER2004	116	221	127	221	100.0%	0.91 [0.77, 1.08]
Total (95% CI)		**221**		**221**	**100.0%**	**0.91 [0.77, 1.08]**
Total events	116		127			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

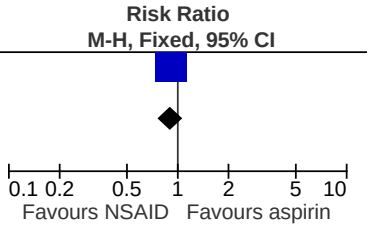
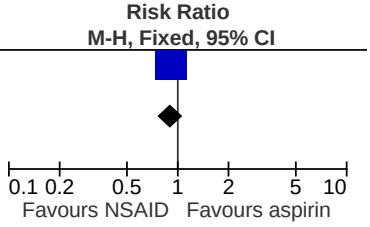


Figure 27: Pain free at up to 2 hours

Study or Subgroup	Aspirin Events	Aspirin Total	NSAID Events	NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DIENER2004	116	221	127	221	100.0%	0.91 [0.77, 1.08]
Total (95% CI)		**221**		**221**	**100.0%**	**0.91 [0.77, 1.08]**
Total events	116		127			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)



G.2.2.2 Aspirin vs triptan

Figure 28: Headache response at up to 2 hours

Study or Subgroup	Aspirin Events	Aspirin Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DIENER2004	116	221	124	224	64.2%	0.95 [0.80, 1.13]
DIENER2004B	72	146	66	135	35.8%	1.01 [0.79, 1.28]
Total (95% CI)		**367**		**359**	**100.0%**	**0.97 [0.84, 1.12]**
Total events	188		190			

Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)

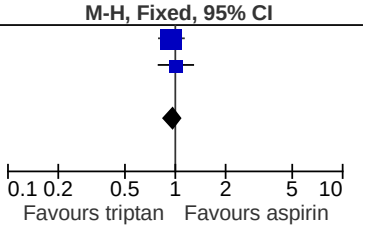
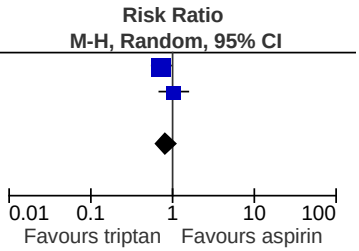


Figure 29: Pain free at up to 2 hours

Study or Subgroup	Aspirin Events	Aspirin Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Random, 95% CI
DIENER2004	60	221	83	224	59.7%	0.73 [0.56, 0.96]
DIENER2004B	37	146	33	135	40.3%	1.04 [0.69, 1.56]
Total (95% CI)		**367**		**359**	**100.0%**	**0.84 [0.60, 1.18]**
Total events	97		116			

Heterogeneity: Tau² = 0.03; Chi² = 1.92, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 1.00 (P = 0.32)



G.2.2.3 Ergot vs triptan

Figure 30: Headache response at up to 2 hours

Study or Subgroup	Ergot Events	Ergot Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Random, 95% CI
DIENER2002A	65	197	253	415	31.7%	0.54 [0.44, 0.67]
LAINEZ2007A	85	182	105	182	32.4%	0.81 [0.66, 0.99]
WINNER1996	106	145	128	150	35.8%	0.86 [0.76, 0.96]
Total (95% CI)		**524**		**747**	**100.0%**	**0.73 [0.54, 0.98]**
Total events	256		486			

Heterogeneity: Tau² = 0.06; Chi² = 17.06, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 2.12 (P = 0.03)

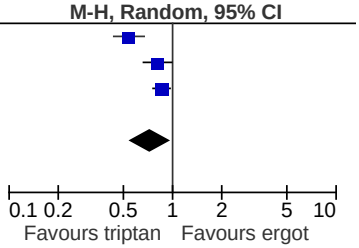


Figure 31: Pain free at up to 2 hours

Study or Subgroup	Ergot Events	Ergot Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Random, 95% CI
DIENER2002A	20	197	137	415	50.5%	0.31 [0.20, 0.48]
LAINEZ2007A	25	182	38	182	49.5%	0.66 [0.41, 1.04]
Total (95% CI)		**379**		**597**	**100.0%**	**0.45 [0.21, 0.95]**
Total events	45		175			

Heterogeneity: Tau² = 0.25; Chi² = 5.66, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 2.08 (P = 0.04)

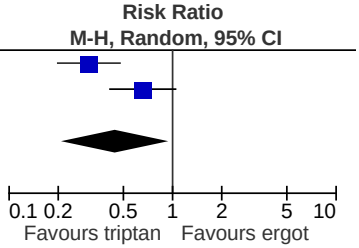


Figure 32: Sustained headache response at 24 hours

Study or Subgroup	Ergot Events	Ergot Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Random, 95% CI
DIENER2002A	55	201	191	419	40.0%	0.60 [0.47, 0.77]
TOUCHON1996	104	266	144	266	60.0%	0.72 [0.60, 0.87]
Total (95% CI)		**467**		**685**	**100.0%**	**0.67 [0.56, 0.80]**
Total events	159		335			

Heterogeneity: Tau² = 0.01; Chi² = 1.40, df = 1 (P = 0.24); I² = 29%
Test for overall effect: Z = 4.35 (P < 0.0001)

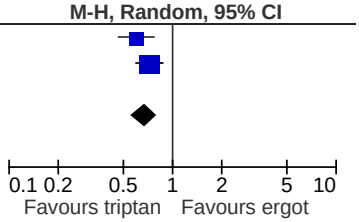
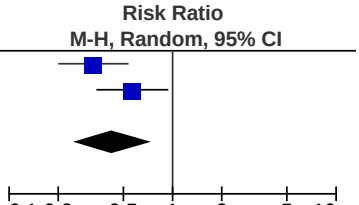


Figure 33: Sustained freedom from pain at 24 hours

Study or Subgroup	Ergot Events	Ergot Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Random, 95% CI
DIENER2002A	17	201	108	419	50.5%	0.33 [0.20, 0.53]
LAINEZ2007A	21	182	37	182	49.5%	0.57 [0.35, 0.93]
Total (95% CI)		**383**		**601**	**100.0%**	**0.43 [0.25, 0.74]**
Total events	38		145			

Heterogeneity: Tau² = 0.09; Chi² = 2.47, df = 1 (P = 0.12); I² = 60%
Test for overall effect: Z = 3.04 (P = 0.002)



G.2.2.4 NSAID vs triptan

Figure 34: Headache response at up to 2 hours

Study or Subgroup	NSAID Events	NSAID Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	157	356	200	362	28.6%	0.80 [0.69, 0.93]
BRANDES2007A ii	158	364	182	362	26.3%	0.86 [0.74, 1.01]
DIENER2004	127	221	125	224	17.9%	1.03 [0.88, 1.21]
MISRA2007	28	53	39	53	5.6%	0.72 [0.53, 0.97]
MYLLYLA1998	33	43	33	42	4.8%	0.98 [0.78, 1.23]
SMITH2005	114	248	111	226	16.7%	0.94 [0.77, 1.13]
Total (95% CI)		**1285**		**1269**	**100.0%**	**0.88 [0.82, 0.95]**
Total events	617		690			

Heterogeneity: Chi² = 8.19, df = 5 (P = 0.15); I² = 39%
Test for overall effect: Z = 3.20 (P = 0.001)

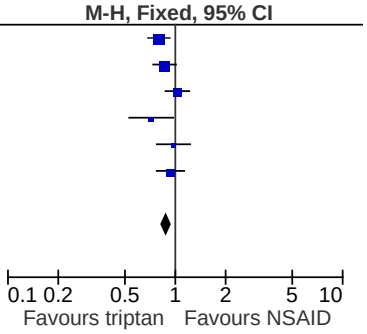


Figure 35: Pain free at up to 2 hours

Study or Subgroup	NSAID Events	NSAID Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	157	356	200	362	28.6%	0.80 [0.69, 0.93]
BRANDES2007A ii	158	364	182	362	26.3%	0.86 [0.74, 1.01]
DIENER2004	127	221	125	224	17.9%	1.03 [0.88, 1.21]
MISRA2007	28	53	39	53	5.6%	0.72 [0.53, 0.97]
MYLLYLA1998	33	43	33	42	4.8%	0.98 [0.78, 1.23]
SMITH2005	114	248	111	226	16.7%	0.94 [0.77, 1.13]
Total (95% CI)		**1285**		**1269**	**100.0%**	**0.88 [0.82, 0.95]**
Total events	617		690			

Heterogeneity: Chi² = 8.19, df = 5 (P = 0.15); I² = 39%
Test for overall effect: Z = 3.20 (P = 0.001)

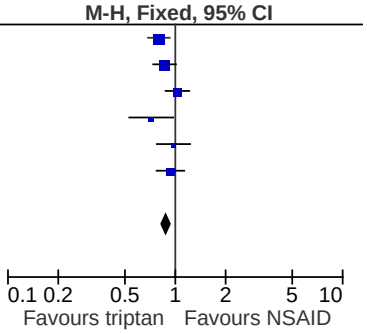


Figure 36: Sustained headache response at 24 hours

Study or Subgroup	NSAID Events	NSAID Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	107	356	127	362	39.8%	0.86 [0.69, 1.06]
BRANDES2007A ii	102	364	121	362	38.4%	0.84 [0.67, 1.04]
SMITH2005	62	248	66	226	21.8%	0.86 [0.64, 1.15]
Total (95% CI)		**968**		**950**	**100.0%**	**0.85 [0.74, 0.97]**
Total events	271		314			

Heterogeneity: Chi² = 0.02, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)

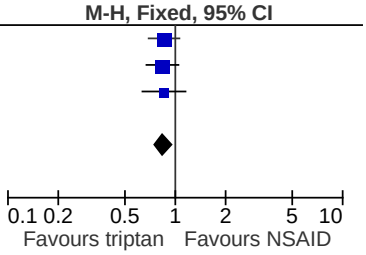


Figure 37: Sustained freedom from pain at 24 hours

Study or Subgroup	NSAID Events	NSAID Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	37	356	59	362	53.4%	0.64 [0.43, 0.94]
BRANDES2007A ii	37	364	51	362	46.6%	0.72 [0.48, 1.07]
Total (95% CI)		**720**		**724**	**100.0%**	**0.68 [0.51, 0.89]**
Total events	74		110			

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.77 (P = 0.006)

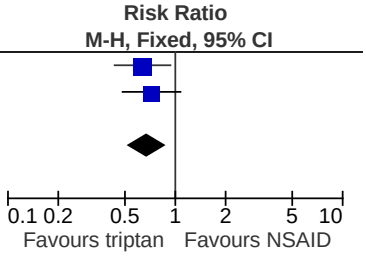
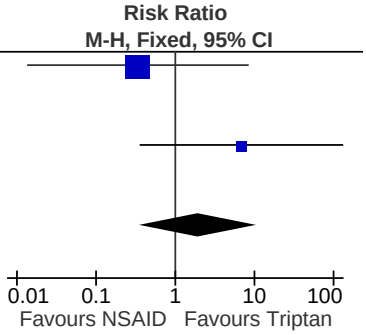


Figure 38: Incidence of serious adverse events

Study or Subgroup	NSAID Events	NSAID Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	0	361	1	365	74.7%	0.34 [0.01, 8.25]
BRANDES2007A ii	0	371	0	370		Not estimable
MISRA2007	0	55	0	57		Not estimable
MYLLYLA1998	3	47	0	46	25.3%	6.85 [0.36, 129.10]
SMITH2005	0	250	0	242		Not estimable
Total (95% CI)		**1084**		**1080**	**100.0%**	**1.99 [0.36, 10.81]**
Total events	3		1			

Heterogeneity: Chi² = 1.87, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 0.79 (P = 0.43)



G.2.2.5 Paracetamol vs triptan

Figure 39: Headache response at up to 2 hours

Study or Subgroup	Paracetamol Events	Paracetamol Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	30	43	33	43	100.0%	0.91 [0.70, 1.17]
Total (95% CI)		**43**		**43**	**100.0%**	**0.91 [0.70, 1.17]**
Total events	30		33			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)

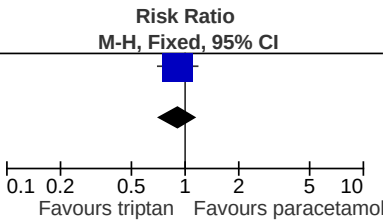


Figure 40: Pain free at up to 2 hours

Study or Subgroup	Paracetamol Events	Paracetamol Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	11	43	17	43	100.0%	0.65 [0.34, 1.21]
Total (95% CI)		**43**		**43**	**100.0%**	**0.65 [0.34, 1.21]**
Total events	11		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)

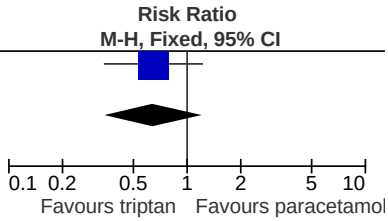


Figure 41: Sustained headache response at 24 hours

Study or Subgroup	Paracetamol Events	Paracetamol Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	18	43	23	43	100.0%	0.78 [0.50, 1.23]
Total (95% CI)		**43**		**43**	**100.0%**	**0.78 [0.50, 1.23]**
Total events	18		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)

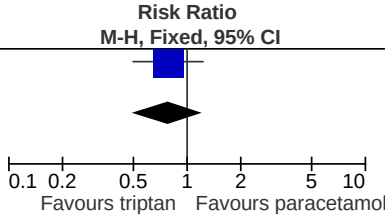
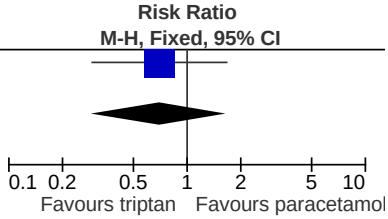


Figure 42: Sustained freedom from pain at 24 hours

Study or Subgroup	Paracetamol Events	Paracetamol Total	Triptan Events	Triptan Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	7	43	10	43	100.0%	0.70 [0.29, 1.67]
Total (95% CI)		**43**		**43**	**100.0%**	**0.70 [0.29, 1.67]**
Total events	7		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)



G.2.2.6 Aspirin with an antiemetic vs ergot

Figure 43: Headache response at up to 2 hours

Study or Subgroup	Aspirin+Antiemetic Events	Aspirin+Antiemetic Total	Ergot Events	Ergot Total	Weight	Risk Ratio M-H, Fixed, 95% CI
LEJEUNE1999	73	134	48	132	100.0%	1.50 [1.14, 1.97]
Total (95% CI)		**134**		**132**	**100.0%**	**1.50 [1.14, 1.97]**
Total events	73		48			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.90 (P = 0.004)

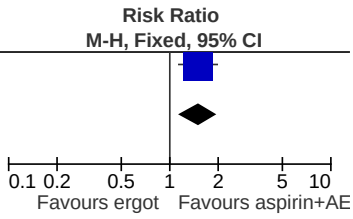
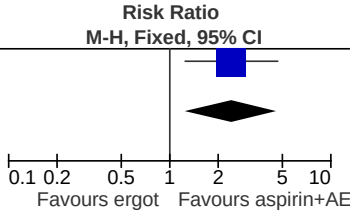


Figure 44: Pain free at up to 2 hours

Study or Subgroup	Aspirin+Antiemetic Events	Aspirin+Antiemetic Total	Ergot Events	Ergot Total	Weight	Risk Ratio M-H, Fixed, 95% CI
LEJEUNE1999	27	134	11	132	100.0%	2.42 [1.25, 4.67]
Total (95% CI)		**134**		**132**	**100.0%**	**2.42 [1.25, 4.67]**
Total events	27		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.63 (P = 0.009)



G.2.2.7 Aspirin with an antiemetic vs triptan

Figure 45: Headache response at up to 2 hours

Study or Subgroup	Aspirin+Antiemetic Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
OSAMCSC1992	62	138	74	133	51.2%	0.81 [0.64, 1.03]
TFELTHANSEN1995	63	119	76	133	48.8%	0.93 [0.74, 1.16]
Total (95% CI)		**257**		**266**	**100.0%**	**0.87 [0.73, 1.02]**
Total events	125		150			

Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)

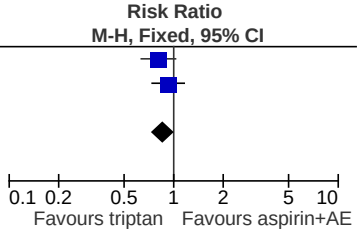
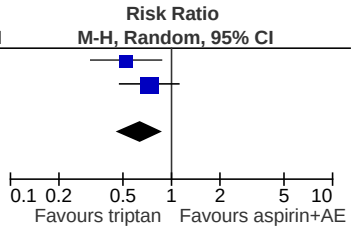


Figure 46: Pain free at up to 2 hours

Study or Subgroup	Aspirin+Antiemetic Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
OSAMCSC1992	19	138	35	133	41.3%	0.52 [0.32, 0.87]
TFELTHANSEN1995	29	135	36	122	58.7%	0.73 [0.48, 1.11]
Total (95% CI)		**273**		**255**	**100.0%**	**0.64 [0.46, 0.88]**
Total events	48		71			

Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)

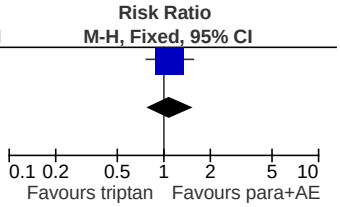


G.2.2.8 Paracetamol with an antiemetic vs triptan

Figure 47: Headache response at up to 2 hours

Study or Subgroup	Paracetamol+Antiemetic Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DOWSON2000	43	118	39	117	100.0%	1.09 [0.77, 1.55]
Total (95% CI)		**118**		**117**	**100.0%**	**1.09 [0.77, 1.55]**
Total events	43		39			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)

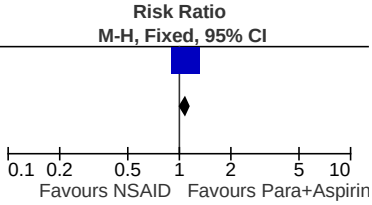


G.2.2.9 Paracetamol with aspirin vs NSAID

Figure 48: Headache response at up to 2 hours

Study or Subgroup	Paracetamol+Aspirin Events	Total	NSAID Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOLDSTEIN2006	448	669	413	666	100.0%	1.08 [1.00, 1.17]
Total (95% CI)		**669**		**666**	**100.0%**	**1.08 [1.00, 1.17]**
Total events	448		413			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.89 (P = 0.06)

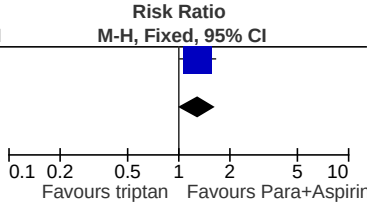


G.2.2.10 Paracetamol with aspirin vs triptan

Figure 49: Headache response at up to 2 hours

Study or Subgroup	Paracetamol+Aspirin Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOLDSTEIN2005	42	50	30	46	100.0%	1.29 [1.01, 1.64]
Total (95% CI)		**50**		**46**	**100.0%**	**1.29 [1.01, 1.64]**
Total events	42		30			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)



G.2.2.11 Triptan with an NSAID vs NSAID

Figure 50: Headache response at up to 2 hours

Study or Subgroup	Triptan+NSAID Events	Total	NSAID Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	237	364	157	356	36.9%	1.48 [1.28, 1.70]
BRANDES2007A ii	207	362	158	364	36.6%	1.32 [1.14, 1.53]
SMITH2005	163	250	114	248	26.6%	1.42 [1.21, 1.67]
Total (95% CI)		**976**		**968**	**100.0%**	**1.40 [1.29, 1.53]**
Total events	607		429			

Heterogeneity: Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 7.72 (P < 0.00001)

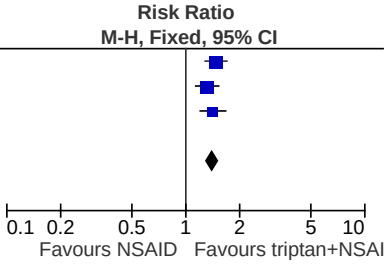


Figure 51: Pain free at up to 2 hours

Study or Subgroup	Triptan+NSAID Events	Total	NSAID Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	125	364	53	356	34.4%	2.31 [1.73, 3.07]
BRANDES2007A ii	107	362	57	364	36.5%	1.89 [1.42, 2.51]
SMITH2005	85	250	45	248	29.0%	1.87 [1.37, 2.57]
Total (95% CI)		**976**		**968**	**100.0%**	**2.03 [1.71, 2.40]**
Total events	317		155			

Heterogeneity: Chi² = 1.26, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 8.14 (P < 0.00001)

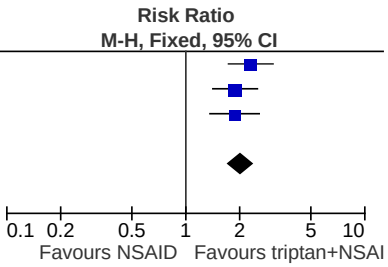


Figure 52: Sustained headache response at 24 hours

Study or Subgroup	Triptan+NSAID Events	Total	NSAID Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	174	364	107	356	39.8%	1.59 [1.31, 1.93]
BRANDES2007A ii	158	362	102	364	37.4%	1.56 [1.27, 1.91]
SMITH2005	115	250	62	248	22.9%	1.84 [1.43, 2.37]
Total (95% CI)		**976**		**968**	**100.0%**	**1.64 [1.45, 1.85]**
Total events	447		271			

Heterogeneity: Chi² = 1.13, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 7.91 (P < 0.00001)

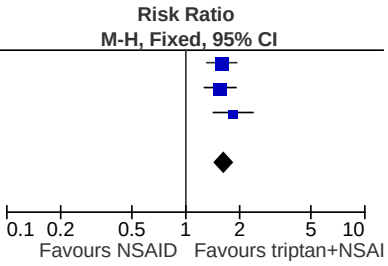
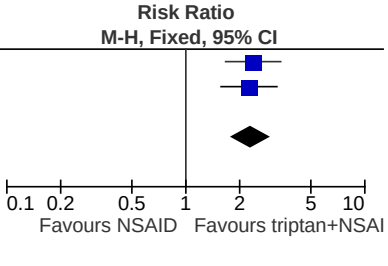


Figure 53: Sustained freedom from pain at 24 hours

Study or Subgroup	Triptan+NSAID Events	Total	NSAID Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	90	364	37	356	50.3%	2.38 [1.67, 3.39]
BRANDES2007A ii	83	362	37	364	49.7%	2.26 [1.58, 3.23]
Total (95% CI)		**726**		**720**	**100.0%**	**2.32 [1.80, 2.98]**
Total events	173		74			

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 6.54 (P < 0.00001)



G.2.2.12 Triptan with an NSAID vs triptan

Figure 54: Headache response at up to 2 hours

Study or Subgroup	Triptan+NSAID Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	237	364	200	361	37.6%	1.18 [1.04, 1.32]
BRANDES2007A ii	207	362	182	362	34.1%	1.14 [0.99, 1.30]
SCHOENEN2008	32	90	34	90	6.4%	0.94 [0.64, 1.38]
SMITH2005	163	250	111	226	21.9%	1.33 [1.13, 1.56]
Total (95% CI)		**1066**		**1039**	**100.0%**	**1.18 [1.09, 1.28]**
Total events	639		527			

Heterogeneity: Chi² = 3.68, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 4.22 (P < 0.0001)

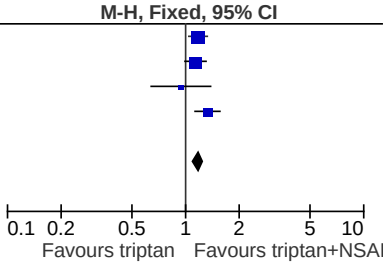


Figure 55: Pain free at up to 2 hours

Study or Subgroup	Triptan+NSAID Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	125	364	90	361	36.6%	1.38 [1.10, 1.73]
BRANDES2007A ii	107	362	82	362	33.2%	1.30 [1.02, 1.67]
SCHOENEN2008	37	90	26	90	10.5%	1.42 [0.95, 2.14]
SMITH2005	85	250	46	226	19.6%	1.67 [1.22, 2.28]
Total (95% CI)		**1066**		**1039**	**100.0%**	**1.42 [1.23, 1.63]**
Total events	354		244			

Heterogeneity: Chi² = 1.56, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 4.90 (P < 0.00001)

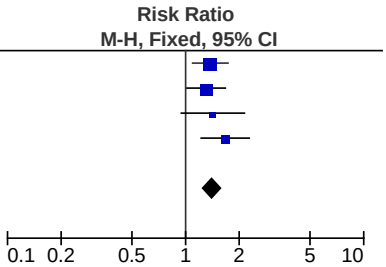


Figure 56: Sustained headache response at 24 hours

Study or Subgroup	Triptan+NSAID Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	174	364	127	361	40.1%	1.36 [1.14, 1.62]
BRANDES2007A ii	158	362	121	362	38.1%	1.31 [1.08, 1.57]
SMITH2005	115	250	66	226	21.8%	1.58 [1.23, 2.01]
Total (95% CI)		**976**		**949**	**100.0%**	**1.39 [1.24, 1.55]**
Total events	447		314			

Heterogeneity: Chi² = 1.50, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 5.64 (P < 0.00001)

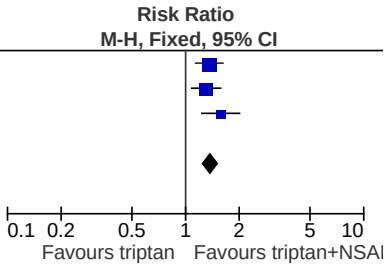
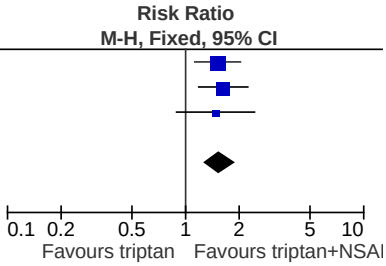


Figure 57: Sustained freedom from pain at 24 hours

Study or Subgroup	Triptan+NSAID Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRANDES2007A i	90	364	59	361	45.8%	1.51 [1.13, 2.03]
BRANDES2007A ii	83	362	51	362	39.5%	1.63 [1.19, 2.23]
SCHOENEN2008	28	90	19	90	14.7%	1.47 [0.89, 2.44]
Total (95% CI)		**816**		**813**	**100.0%**	**1.55 [1.27, 1.89]**
Total events	201		129			

Heterogeneity: Chi² = 0.16, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 4.35 (P < 0.0001)



G.2.2.13 Triptan with paracetamol vs triptan

Figure 58: Headache response at up to 2 hours

Study or Subgroup	Triptan+Paracetamol Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	43	48	33	43	100.0%	1.17 [0.96, 1.41]
Total (95% CI)		**48**		**43**	**100.0%**	**1.17 [0.96, 1.41]**
Total events	43		33			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)

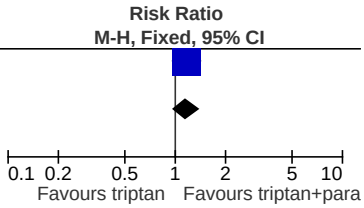


Figure 59: Pain free at up to 2 hours

Study or Subgroup	Triptan+Paracetamol Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	23	48	17	43	100.0%	1.21 [0.76, 1.94]
Total (95% CI)		**48**		**43**	**100.0%**	**1.21 [0.76, 1.94]**
Total events	23		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.43)

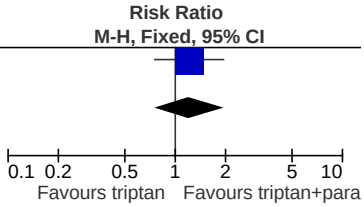


Figure 60: Sustained headache response at 24 hours

Study or Subgroup	Triptan+Paracetamol Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	30	48	23	43	100.0%	1.17 [0.82, 1.67]
Total (95% CI)		**48**		**43**	**100.0%**	**1.17 [0.82, 1.67]**
Total events	30		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)

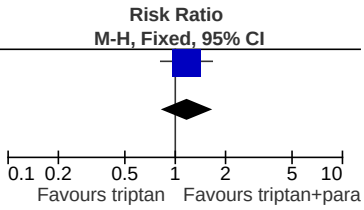
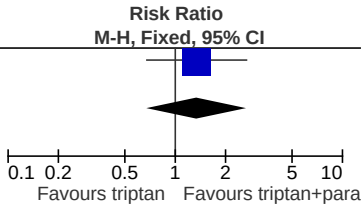


Figure 61: Sustained freedom from pain at 24 hours

Study or Subgroup	Triptan+Paracetamol Events	Total	Triptan Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	15	48	10	43	100.0%	1.34 [0.68, 2.67]
Total (95% CI)		**48**		**43**	**100.0%**	**1.34 [0.68, 2.67]**
Total events	15		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)



G.2.2.14 Triptan with paracetamol vs paracetamol

Figure 62: Headache response at up to 2 hours

Study or Subgroup	Triptan+Paracetamol Events	Total	Paracetamol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	43	48	30	43	100.0%	1.28 [1.03, 1.60]
Total (95% CI)		**48**		**43**	**100.0%**	**1.28 [1.03, 1.60]**
Total events	43		30			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.24 (P = 0.03)

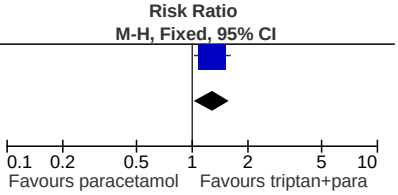


Figure 63: Pain free at up to 2 hours

Study or Subgroup	Triptan+Paracetamol Events	Total	Paracetamol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	23	48	11	43	100.0%	1.87 [1.04, 3.38]
Total (95% CI)		**48**		**43**	**100.0%**	**1.87 [1.04, 3.38]**
Total events	23		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.09 (P = 0.04)

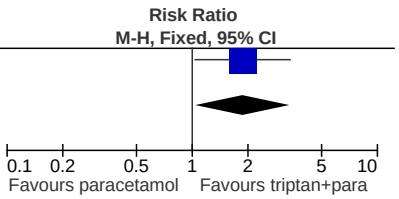


Figure 64: Sustained headache response at 24 hours

Study or Subgroup	Triptan+Paracetamol Events	Total	Paracetamol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	30	48	18	43	100.0%	1.49 [0.99, 2.26]
Total (95% CI)		**48**		**43**	**100.0%**	**1.49 [0.99, 2.26]**
Total events	30		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.89 (P = 0.06)

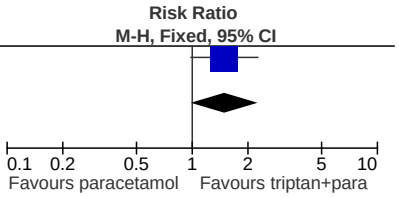
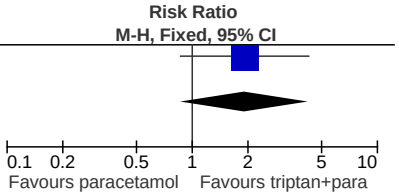


Figure 65: Sustained freedom from pain at 24 hours

Study or Subgroup	Triptan+Paracetamol Events	Total	Paracetamol Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FREITAG2008A	15	48	7	43	100.0%	1.92 [0.86, 4.26]
Total (95% CI)		**48**		**43**	**100.0%**	**1.92 [0.86, 4.26]**
Total events	15		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)



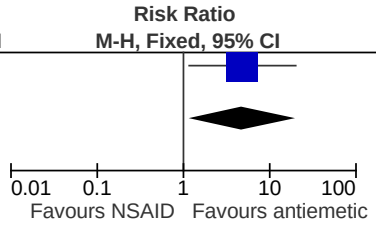
Intravenous, intramuscular and subcutaneous treatments

G.2.2.15 Antiemetic vs NSAID

Figure 66: Pain free at up to 2 hours

Study or Subgroup	Antiemetic Events	Total	NSAID Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BROUSSEAU2004	11	33	2	29	100.0%	4.83 [1.17, 20.03]
Total (95% CI)		**33**		**29**	**100.0%**	**4.83 [1.17, 20.03]**
Total events	11		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.17 (P = 0.03)

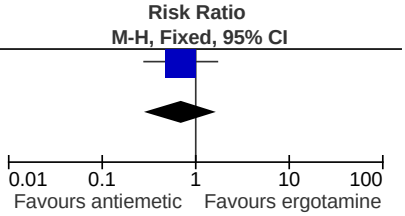


G.2.2.16 Ergot vs antiemetic

Figure 67: Pain free at up to 2 hours

Study or Subgroup	Ergotamine Events	Total	Antiemetic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BELL1990	6	26	8	24	100.0%	0.69 [0.28, 1.71]
Total (95% CI)		**26**		**24**	**100.0%**	**0.69 [0.28, 1.71]**
Total events	6		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)



G.2.2.17 NSAID vs paracetamol

Figure 68: Pain free at up to 2 hours

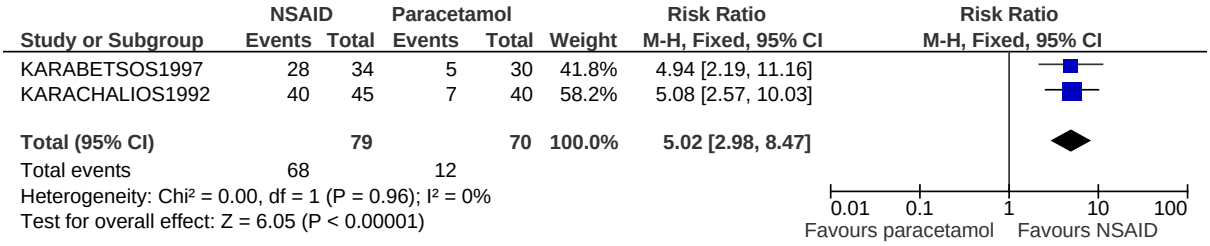
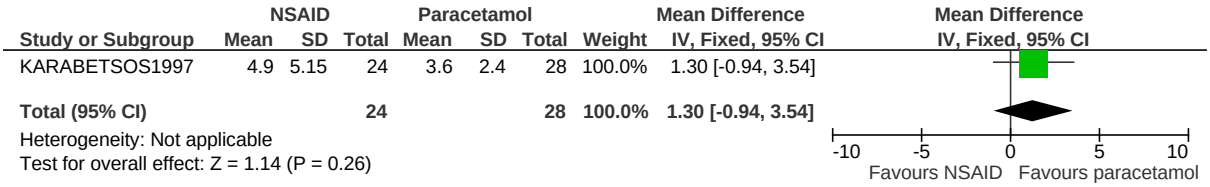
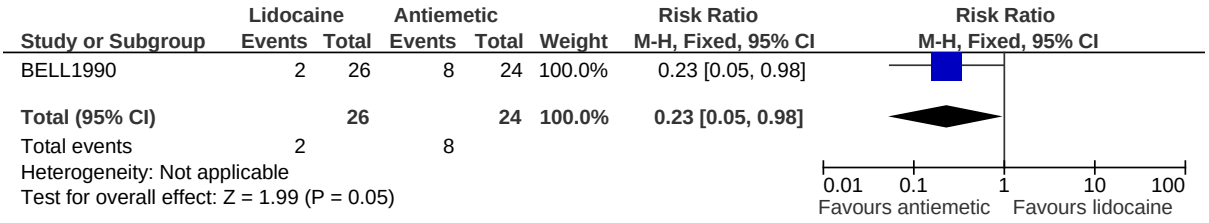


Figure 69: Time to freedom from pain



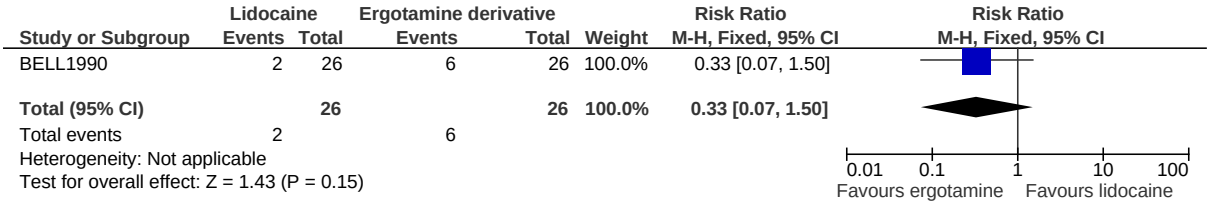
G.2.2.18 Lidocaine vs antiemetic

Figure 70: Pain free at up to 2 hours



G.2.2.19 Lidocaine vs ergot

Figure 71: Pain free at up to 2 hours



G.2.2.20 Triptan vs antiemetic

Figure 72: Pain free at up to 2 hours

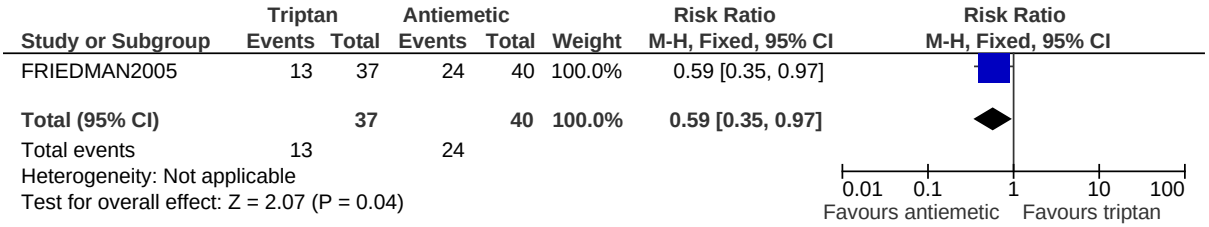
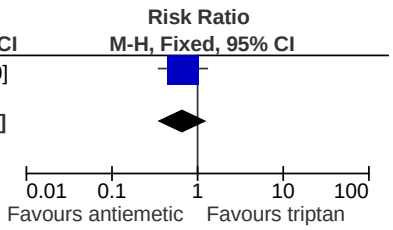


Figure 73: Sustained freedom from pain at 24 hours

Study or Subgroup	Triptan Events	Triptan Total	Antiemetic Events	Antiemetic Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FRIEDMAN2005	10	37	16	40	100.0%	0.68 [0.35, 1.30]
Total (95% CI)		**37**		**40**	**100.0%**	**0.68 [0.35, 1.30]**
Total events	10		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)



G.2.2.21 Triptan vs aspirin

Figure 74: Headache response at up to 2 hours

Study or Subgroup	Triptan Events	Triptan Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DIENER1999	104	114	88	119	100.0%	1.23 [1.09, 1.39]
Total (95% CI)		**114**		**119**	**100.0%**	**1.23 [1.09, 1.39]**
Total events	104		88			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.40 (P = 0.0007)

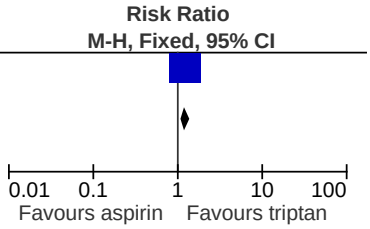


Figure 75: Pain free at up to 2 hours

Study or Subgroup	Triptan Events	Triptan Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DIENER1999	87	114	52	119	100.0%	1.75 [1.39, 2.19]
Total (95% CI)		**114**		**119**	**100.0%**	**1.75 [1.39, 2.19]**
Total events	87		52			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.79 (P < 0.00001)

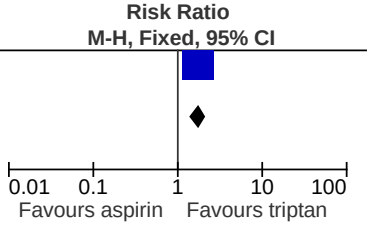
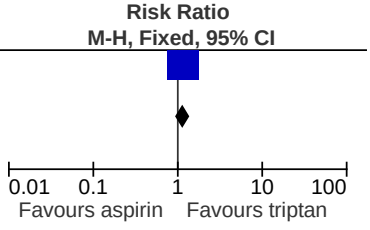


Figure 76: Sustained headache response at 24 hours

Study or Subgroup	Triptan Events	Triptan Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DIENER1999	80	114	72	119	100.0%	1.16 [0.96, 1.40]
Total (95% CI)		**114**		**119**	**100.0%**	**1.16 [0.96, 1.40]**
Total events	80		72			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)



G.2.2.22 Triptan vs ergot

Figure 77: Headache response at up to 2 hours

Study or Subgroup	Triptan Events	Triptan Total	Ergotamine derivatives Events	Ergotamine derivatives Total	Weight	Risk Ratio M-H, Fixed, 95% CI
WINNER1996	128	150	106	152	100.0%	1.22 [1.08, 1.39]
Total (95% CI)		**150**		**152**	**100.0%**	**1.22 [1.08, 1.39]**
Total events	128		106			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.19 (P = 0.001)

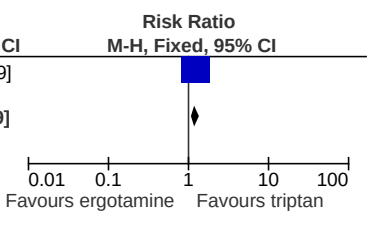
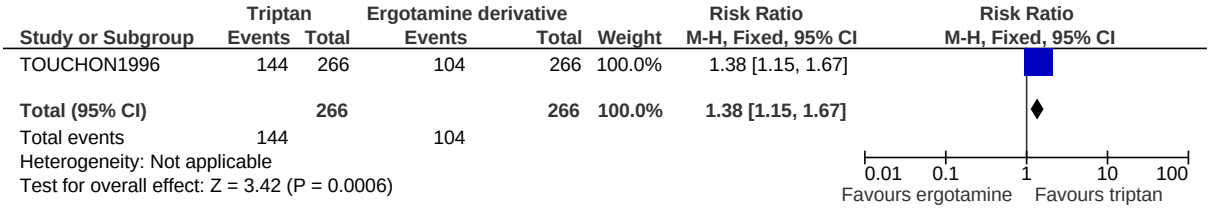
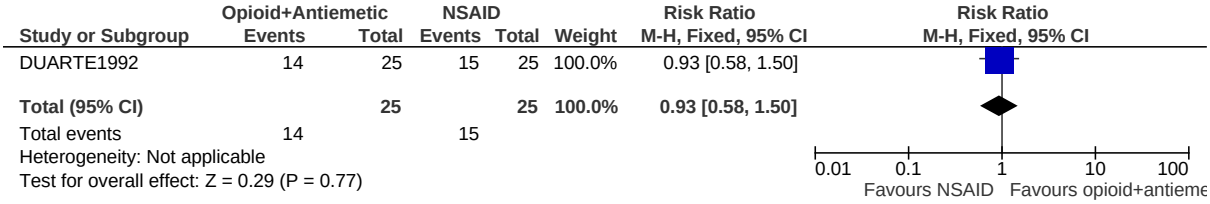


Figure 78: Sustained headache response at 24 hours



G.2.2.23 Opioid with antiemetic vs NSAID

Figure 79: Headache response at up to 2 hours



G.2.3 Acute pharmacological treatment of cluster headache

G.2.3.1 100% oxygen vs air

Figure 80: Reduction in pain at 30 minutes

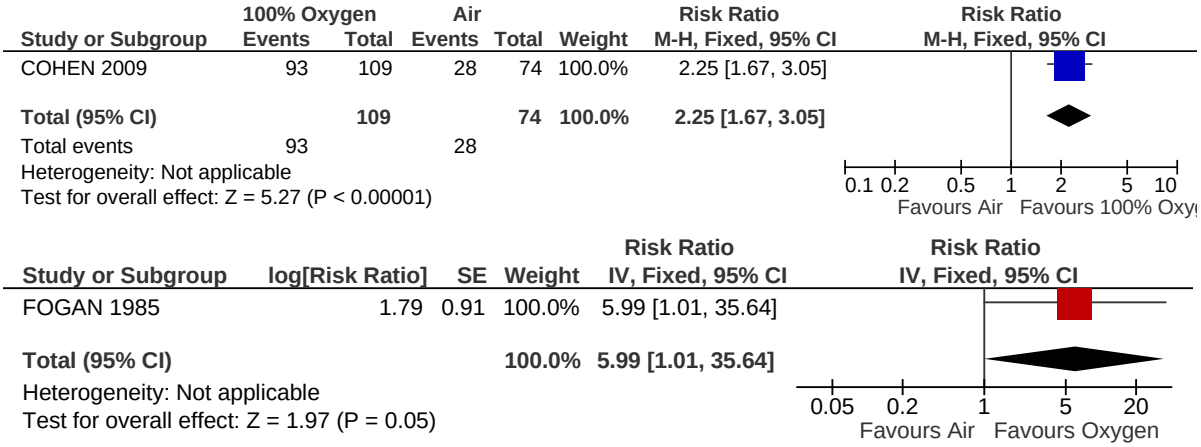
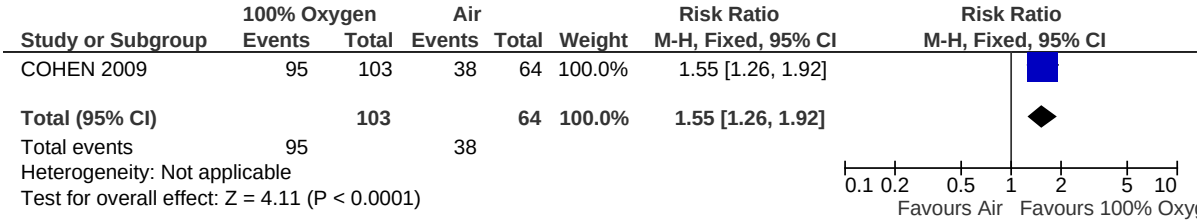


Figure 81: Headache response (up to 2 hours)

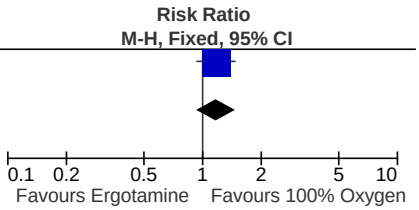


G.2.3.2 Oxygen vs ergot

Figure 82: Reduction in pain at 30 minutes

Study or Subgroup	100% Oxygen Events	Total	Ergotamine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
KUDROW 1981	41	50	35	50	100.0%	1.17 [0.94, 1.46]
Total (95% CI)		**50**		**50**	**100.0%**	**1.17 [0.94, 1.46]**
Total events	41		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)



G.2.3.3 Triptan vs placebo

Figure 83: Reduction in pain at 30 minutes

Study or Subgroup	Triptan Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CITTADINI 2006	65	128	12	61	100.0%	2.58 [1.51, 4.41]
Total (95% CI)		**128**		**61**	**100.0%**	**2.58 [1.51, 4.41]**
Total events	65		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.47 (P = 0.0005)

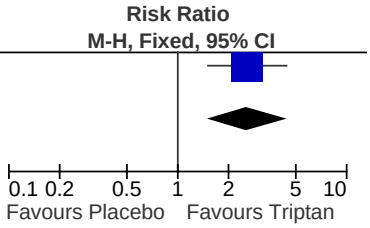
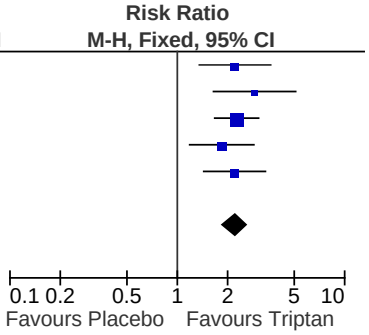


Figure 84: Headache response at up to 2 hours

Study or Subgroup	Triptan Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CITTADINI 2006	65	128	14	61	17.1%	2.21 [1.35, 3.61]
EKBOM 1991	29	39	10	39	9.0%	2.90 [1.65, 5.10]
EKBOM 1993	139	180	30	88	36.4%	2.27 [1.68, 3.06]
RAPOPORT 2007	59	104	16	52	19.3%	1.84 [1.19, 2.87]
VAN VLIET 2003	44	77	20	77	18.1%	2.20 [1.44, 3.36]
Total (95% CI)		**528**		**317**	**100.0%**	**2.22 [1.84, 2.67]**
Total events	336		90			

Heterogeneity: Chi² = 1.56, df = 4 (P = 0.82); I² = 0%
Test for overall effect: Z = 8.41 (P < 0.00001)



G.2.4 Prophylactic pharmacological treatment of tension type headache

G.2.4.1 Amitriptyline vs placebo

Figure 85: Change in headache days

Study or Subgroup	Tricyclics Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
PFAFFENRATH1994	15	10	67	16	9	64	-1.00 [-4.26, 2.26]

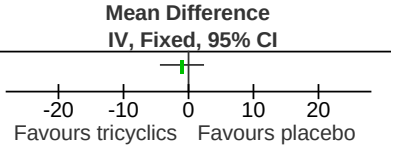


Figure 86: Change in headache intensity

Study or Subgroup	Tricyclics Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
PFAFFENRATH1994	2.8	2	67	1.7	2	64	1.10 [0.41, 1.79]

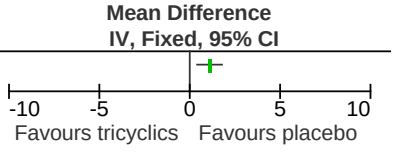
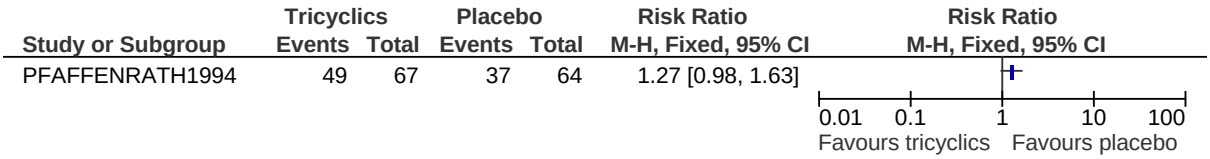


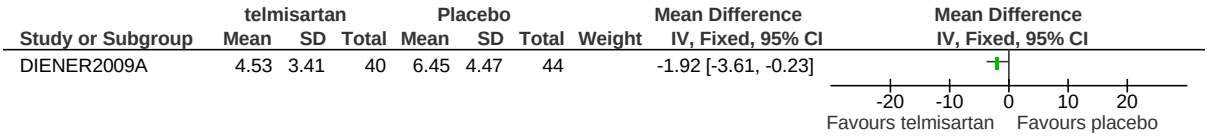
Figure 87: Incidence of serious adverse events (moderate and severe events reported together)



G.2.5 Prophylactic pharmacological treatment of migraine

G.2.5.1 ACE inhibitors / ARBs vs placebo

Figure 88: Change in patient reported migraine days



G.2.5.2 Antiepileptic vs placebo

Figure 89: Change in patient reported migraine days

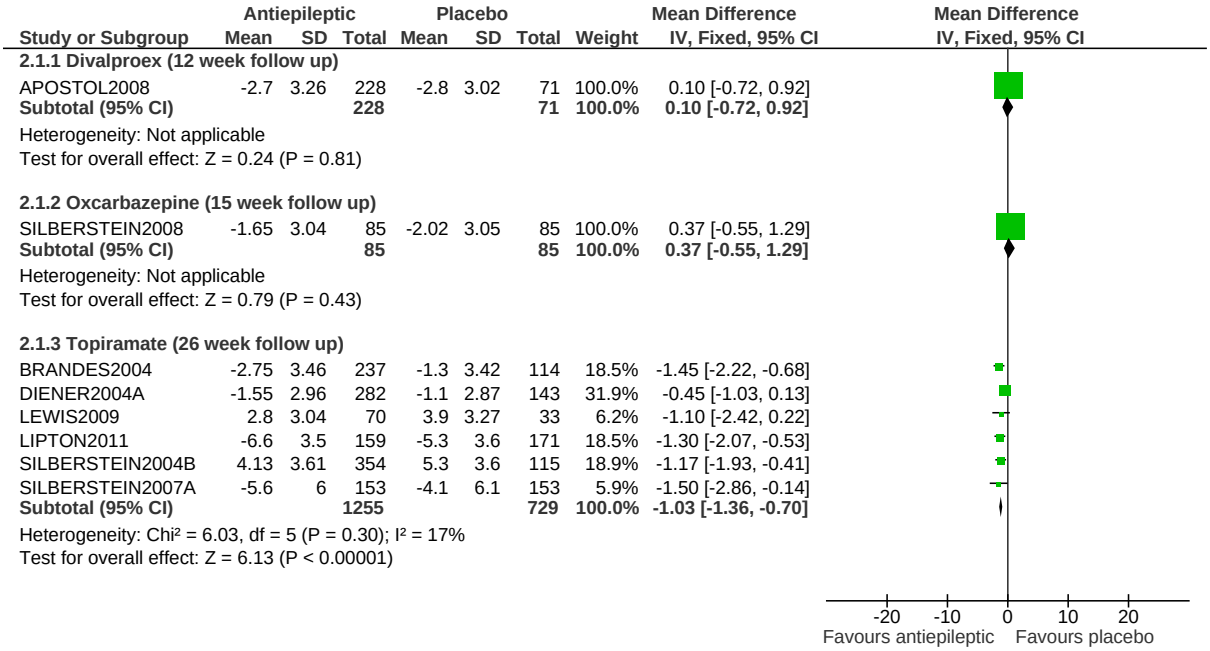


Figure 90: Responder rate

Study or Subgroup	Antiepileptic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Divalproex (12 week follow up)						
APOSTOL2008	97	227	33	71	38.3%	0.92 [0.69, 1.23]
KLAPPER1997	57	129	9	42	33.2%	2.06 [1.12, 3.80]
MATHEW1995	33	69	5	36	28.5%	3.44 [1.47, 8.06]
Subtotal (95% CI)		**425**		**149**	**100.0%**	**1.75 [0.75, 4.07]**
Total events	187		47			
Heterogeneity: Tau² = 0.46; Chi² = 13.50, df = 2 (P = 0.001); I² = 85%						
Test for overall effect: Z = 1.30 (P = 0.19)						
2.5.2 Oxcarbazepine (15 weeks follow up)						
SILBERSTEIN2008	23	85	20	85	100.0%	1.15 [0.68, 1.93]
Subtotal (95% CI)		**85**		**85**	**100.0%**	**1.15 [0.68, 1.93]**
Total events	23		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
2.5.3 Topiramate (26 week follow up)						
BRANDES2004	160	354	26	114	17.4%	1.98 [1.39, 2.83]
DIENER2004A	72	282	22	143	14.0%	1.66 [1.08, 2.56]
LEWIS2009	45	70	15	33	14.8%	1.41 [0.94, 2.14]
SILBERSTEIN2004B	169	354	26	115	17.5%	2.11 [1.48, 3.01]
SILBERSTEIN2006A	55	138	25	73	16.4%	1.16 [0.80, 1.70]
SILBERSTEIN2007A	59	153	47	153	19.9%	1.26 [0.92, 1.71]
Subtotal (95% CI)		**1351**		**631**	**100.0%**	**1.56 [1.27, 1.91]**
Total events	560		161			
Heterogeneity: Tau² = 0.03; Chi² = 9.25, df = 5 (P = 0.10); I² = 46%						
Test for overall effect: Z = 4.21 (P < 0.0001)						

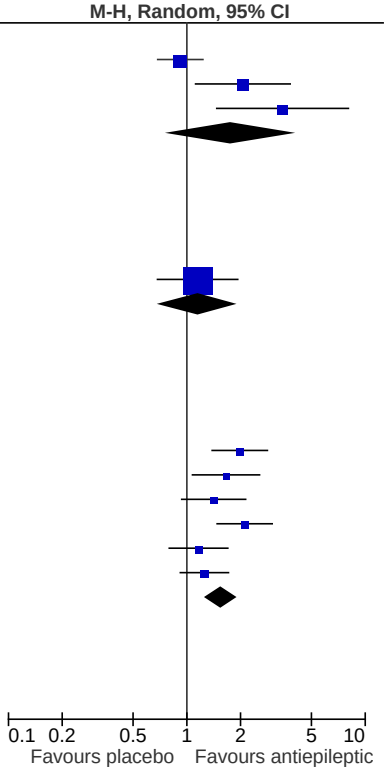


Figure 91: Change in patient reported migraine frequency

Study or Subgroup	Antiepileptic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.2.1 Divalproex (12 week follow up)								
APOSTOL2008	-1.83	1.82	228	-1.9	2.18	71	100.0%	0.07 [-0.49, 0.63]
Subtotal (95% CI)			**228**			**71**	**100.0%**	**0.07 [-0.49, 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.81)								
2.2.2 Garbapentin (12 week follow up)								
DITRIPANI2000	2.81	1.12	35	4.7	0.82	28	100.0%	-1.89 [-2.37, -1.41]
Subtotal (95% CI)			**35**			**28**	**100.0%**	**-1.89 [-2.37, -1.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.73 (P < 0.00001)								
2.2.4 Oxcarbazepine (15 week follow up)								
SILBERSTEIN2008	-1.1	1.93	85	-1.16	1.93	85	100.0%	0.06 [-0.52, 0.64]
Subtotal (95% CI)			**85**			**85**	**100.0%**	**0.06 [-0.52, 0.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.84)								
2.2.5 Topiramate (26 week follow up)								
BRANDES2004	3.53	3.2	354	4.5	2.9	114	25.6%	-0.97 [-1.60, -0.34]
DIENER2004A	-1.35	2.6	282	-0.8	2.51	143	38.6%	-0.55 [-1.06, -0.04]
LEWIS2009	1.85	1.66	70	2.4	1.93	33	17.2%	-0.55 [-1.31, 0.21]
SILBERSTEIN2004B	3.75	3.17	354	4.6	3.6	115	18.6%	-0.85 [-1.59, -0.11]
Subtotal (95% CI)			**1060**			**405**	**100.0%**	**-0.71 [-1.03, -0.40]**
Heterogeneity: Chi² = 1.34, df = 3 (P = 0.72); I² = 0%								
Test for overall effect: Z = 4.40 (P < 0.0001)								

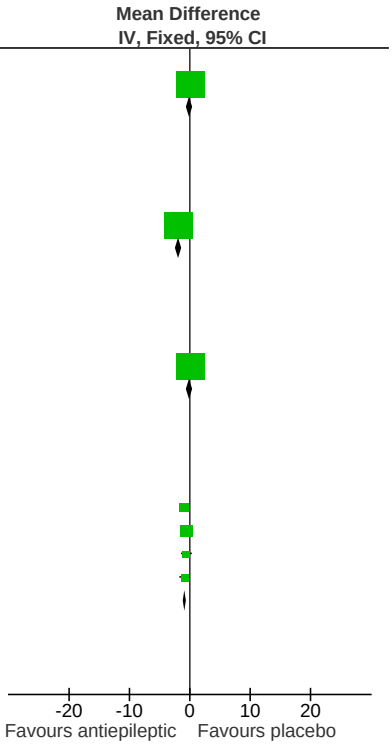


Figure 92: Change in patient reported migraine intensity

Study or Subgroup	Antiepileptic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.8.2 Garbapentin (12 week follow up)								
DITRIPANI2000	1.39	0.54	35	2.01	0.61	28	100.0%	-0.62 [-0.91, -0.33]
Subtotal (95% CI)			**35**			**28**	**100.0%**	**-0.62 [-0.91, -0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.22 (P < 0.0001)								
2.8.3 Oxcarbazepine (15 week follow up)								
SILBERSTEIN2008	0.1	0.53	85	0.04	0.53	85	100.0%	0.06 [-0.10, 0.22]
Subtotal (95% CI)			**85**			**85**	**100.0%**	**0.06 [-0.10, 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
2.8.4 Topiramate (26 week follow up)								
BRANDES2004	-0.13	0.44	354	-0.1	0.43	114	100.0%	-0.03 [-0.12, 0.06]
Subtotal (95% CI)			**354**			**114**	**100.0%**	**-0.03 [-0.12, 0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.64 (P = 0.52)								

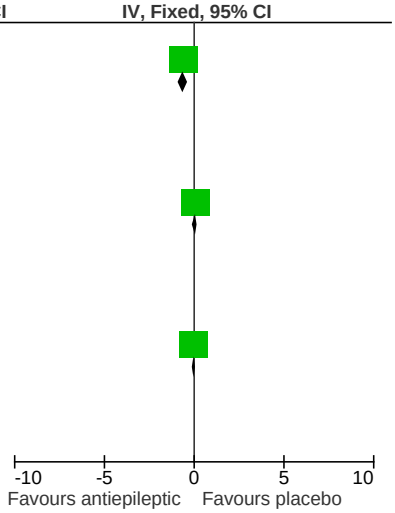


Figure 93: Headache specific quality of life (MIDAS)

Study or Subgroup	Antiepileptic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.16.1 Oxcarbazepine (15 week follow up)								
SILBERSTEIN2008	-1.16	1.59	85	-0.64	1.51	85	100.0%	-0.52 [-0.99, -0.05]
Subtotal (95% CI)			**85**			**85**	**100.0%**	**-0.52 [-0.99, -0.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.19 (P = 0.03)								
2.16.2 Topiramate (26 weeks)								
LIPTON2011	-29.7	33.05	159	-22.6	36.89	171	71.2%	-7.10 [-14.65, 0.45]
SILBERSTEIN2007A	-31.4	53.8	153	-21	52.2	153	28.8%	-10.40 [-22.28, 1.48]
Subtotal (95% CI)			**312**			**324**	**100.0%**	**-8.05 [-14.42, -1.68]**
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%								
Test for overall effect: Z = 2.48 (P = 0.01)								

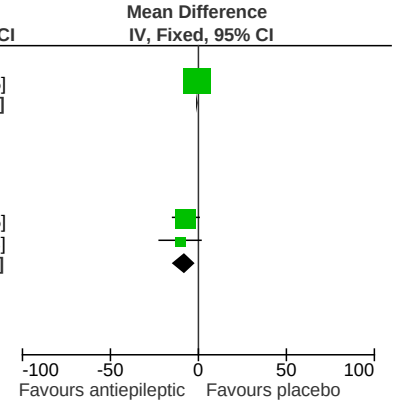


Figure 94: Use of acute pharmacological treatment

Study or Subgroup	Antiepileptic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.14.1 Oxcarbazepine (15 week follow up)								
SILBERSTEIN2008	-0.98	2.82	85	-1.53	2.82	85	100.0%	0.55 [-0.30, 1.40]
Subtotal (95% CI)			**85**			**85**	**100.0%**	**0.55 [-0.30, 1.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.27 (P = 0.20)								
2.14.2 Topiramate (26 weeks)								
BRANDES2004	-2.15	3.18	237	-1	3.1	114	22.8%	-1.15 [-1.85, -0.45]
DIENER2004A	-1.2	2.5	282	-0.8	2.39	143	46.5%	-0.40 [-0.89, 0.09]
SILBERSTEIN2004B	4.17	3.14	354	5.2	3.3	115	23.6%	-1.03 [-1.72, -0.34]
SILBERSTEIN2007A	-4.4	5.8	153	-3.4	5.3	153	7.2%	-1.00 [-2.24, 0.24]
Subtotal (95% CI)			**1026**			**525**	**100.0%**	**-0.76 [-1.10, -0.43]**
Heterogeneity: Chi² = 4.02, df = 3 (P = 0.26); I² = 25%								
Test for overall effect: Z = 4.48 (P < 0.00001)								

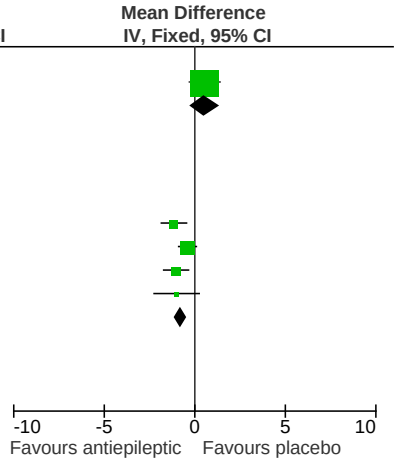
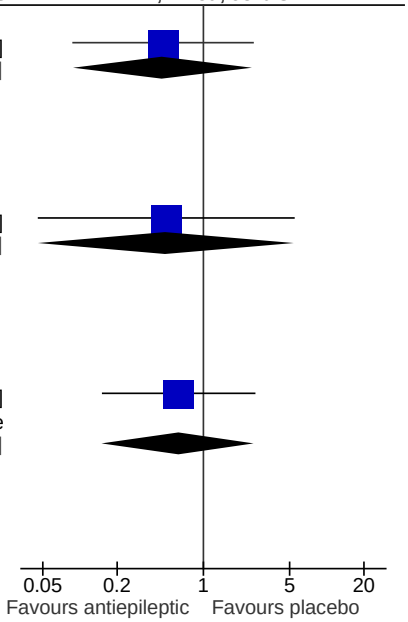


Figure 95: Incidence of serious adverse events

Study or Subgroup	Antiepileptic Events	Antiepileptic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.11.1 Divalproex						
FRIETAG2002	2	122	4	115	100.0%	0.47 [0.09, 2.52]
Subtotal (95% CI)		**122**		**115**	**100.0%**	**0.47 [0.09, 2.52]**
Total events	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
2.11.2 Oxcarbazepine						
SILBERSTEIN2008	1	85	2	85	100.0%	0.50 [0.05, 5.41]
Subtotal (95% CI)		**85**		**85**	**100.0%**	**0.50 [0.05, 5.41]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
2.11.3 Topiramate						
LIPTON2011	3	176	5	185	100.0%	0.63 [0.15, 2.60]
SILBERSTEIN2007A	0	160	0	161		Not estimable
Subtotal (95% CI)		**176**		**185**	**100.0%**	**0.63 [0.15, 2.60]**
Total events	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						



G.2.5.3 Antiepileptic vs antiepileptic (topiramate vs sodium valproate)

Figure 96: Change in patient reported migraine frequency

Study or Subgroup	Topiramate Mean	Topiramate SD	Topiramate Total	Sodium valproate Mean	Sodium valproate SD	Sodium valproate Total	Weight	Mean Difference IV, Fixed, 95% CI
AFSHARI2002	3	1.9	28	3.6	1.8	28	100.0%	-0.60 [-1.57, 0.37]
Total (95% CI)			**28**			**28**	**100.0%**	**-0.60 [-1.57, 0.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.21 (P = 0.23)								

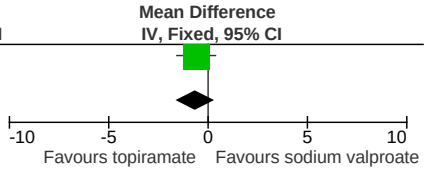
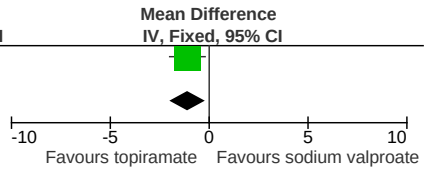


Figure 97: Change in patient reported migraine intensity (severity)

Study or Subgroup	Topiramate Mean	Topiramate SD	Topiramate Total	Sodium valproate Mean	Sodium valproate SD	Sodium valproate Total	Weight	Mean Difference IV, Fixed, 95% CI
AFSHARI2002	5.2	1.5	28	6.3	1.9	28	100.0%	-1.10 [-2.00, -0.20]
Total (95% CI)			**28**			**28**	**100.0%**	**-1.10 [-2.00, -0.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.40 (P = 0.02)								



G.2.5.4 Beta blocker vs placebo

Figure 98: Change in patient reported migraine days

Study or Subgroup	Beta-blocker Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.1.1 Mean monthly rate at 26 weeks								
DIENER2004A	-1.9	2.99	143	-1.1	2.87	143	100.0%	-0.80 [-1.48, -0.12]
Subtotal (95% CI)			**143**			**143**	**100.0%**	**-0.80 [-1.48, -0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
3.1.2 Mean monthly day rate at 10 months								
HOLROYD2010	-3.9	1.3	53	-3.3	1.13	55	100.0%	-0.60 [-1.06, -0.14]
Subtotal (95% CI)			**53**			**55**	**100.0%**	**-0.60 [-1.06, -0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.56 (P = 0.01)								
3.1.3 Mean monthly day rate at 16 months								
HOLROYD2010	-4.5	2.04	53	-3.9	1.12	55	100.0%	-0.60 [-1.22, 0.02]
Subtotal (95% CI)			**53**			**55**	**100.0%**	**-0.60 [-1.22, 0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.88 (P = 0.06)								

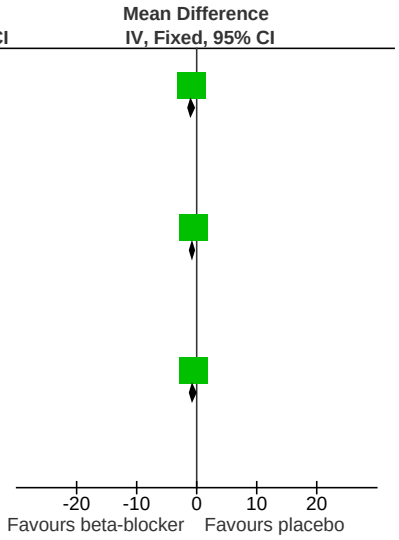


Figure 99: Responder rate

Study or Subgroup	Beta-blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 At 26 weeks						
DIENER2004A	43	143	22	143	100.0%	1.95 [1.24, 3.09]
Subtotal (95% CI)		**143**		**143**	**100.0%**	**1.95 [1.24, 3.09]**
Total events	43		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.86 (P = 0.004)						
3.4.2 At 10 months						
HOLROYD2010	18	35	22	40	100.0%	0.94 [0.61, 1.43]
Subtotal (95% CI)		**35**		**40**	**100.0%**	**0.94 [0.61, 1.43]**
Total events	18		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						

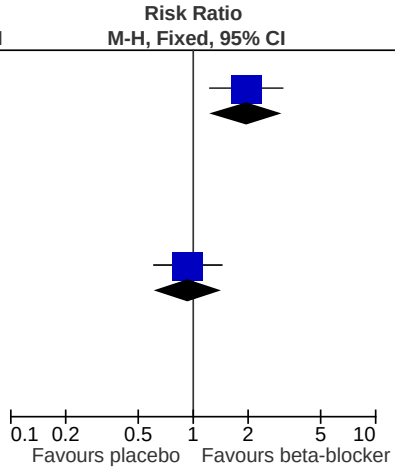


Figure 100: Change in patient reported migraine frequency

Study or Subgroup	Beta-blocker Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.2.1 Mean monthly rate at 12 to 26 weeks								
DIENER2004A	-1.6	2.51	143	-0.8	2.51	143	30.9%	-0.80 [-1.38, -0.22]
PRADALIER1989A	3.15	0.77	40	6.41	1.7	34	27.2%	-3.26 [-3.88, -2.64]
VANDEVEN1997	2.65	1.81	151	3.2	1.8	75	41.9%	-0.55 [-1.05, -0.05]
Subtotal (95% CI)			**334**			**252**	**100.0%**	**-1.37 [-1.69, -1.04]**
Heterogeneity: Chi² = 49.83, df = 2 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 8.28 (P < 0.00001)								
3.2.2 Mean monthly rate at 10 months								
HOLROYD2010	-2.1	0.56	53	-2.1	0.57	55	100.0%	0.00 [-0.21, 0.21]
Subtotal (95% CI)			**53**			**55**	**100.0%**	**0.00 [-0.21, 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.2.3 Mean monthly rate at 16 months								
HOLROYD2010	-2.5	1.11	53	-2.5	0.57	55	100.0%	0.00 [-0.33, 0.33]
Subtotal (95% CI)			**53**			**55**	**100.0%**	**0.00 [-0.33, 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								

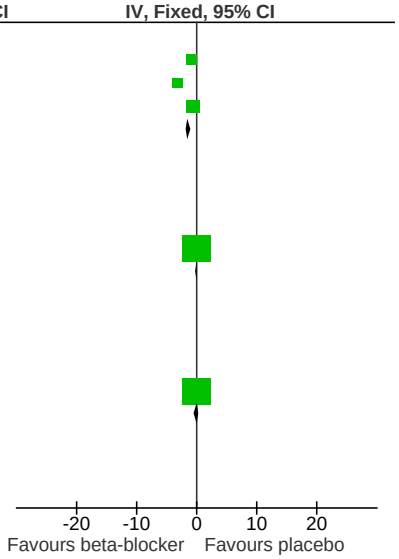
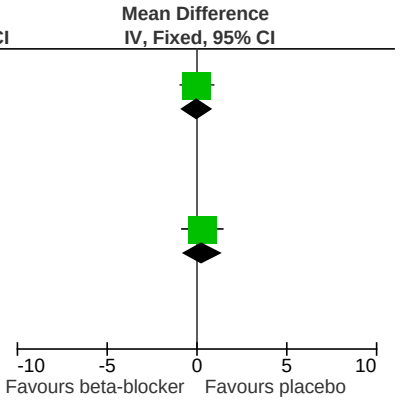


Figure 101: Migraine specific quality of life (MSQ)

Study or Subgroup	Beta-blocker Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.3.1 At 10 months								
HOLROYD2010	-7.1	2.04	53	-7.1	2.84	55	100.0%	0.00 [-0.93, 0.93]
Subtotal (95% CI)			**53**			**55**	**100.0%**	**0.00 [-0.93, 0.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.3.2 At 16 months								
HOLROYD2010	-8.5	3.34	53	-8.8	2.65	55	100.0%	0.30 [-0.84, 1.44]
Subtotal (95% CI)			**53**			**55**	**100.0%**	**0.30 [-0.84, 1.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.61)								
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%								



G.2.5.5 Antiepileptic vs beta blocker (topiramate vs propranolol)

Figure 102: Change in patient reported migraine days

Study or Subgroup	Antiepileptic Mean	SD	Total	Beta-blocker Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 Topiramate								
DIENER2004A	-1.55	2.96	282	-1.9	2.99	143	100.0%	0.35 [-0.25, 0.95]
Subtotal (95% CI)			**282**			**143**	**100.0%**	**0.35 [-0.25, 0.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.14 (P = 0.25)								

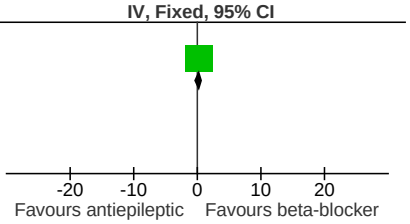


Figure 103: Responder rate

Study or Subgroup	Antiepileptic Events	Total	Beta-blocker Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Topiramate						
DIENER2004A	72	282	43	143	100.0%	0.85 [0.62, 1.17]
Subtotal (95% CI)		**282**		**143**	**100.0%**	**0.85 [0.62, 1.17]**
Total events	72		43			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

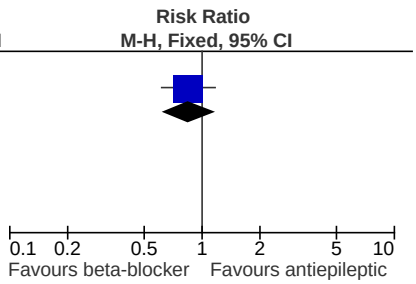


Figure 104: Change in patient reported migraine frequency

Study or Subgroup	Antiepileptic Mean	SD	Total	Beta-blocker Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.2.1 Topiramate								
DIENER2004A	-1.35	2.6	282	-1.6	2.51	143	100.0%	0.25 [-0.26, 0.76]
Subtotal (95% CI)			**282**			**143**	**100.0%**	**0.25 [-0.26, 0.76]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)

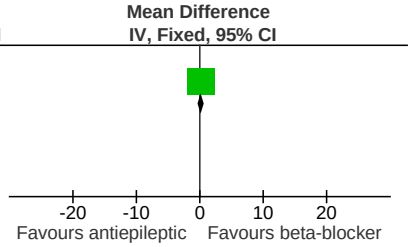
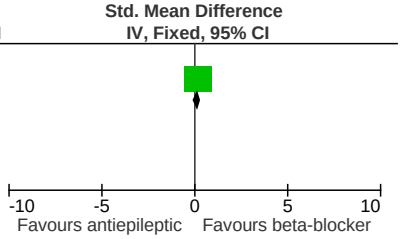


Figure 105: Use of acute pharmacological treatment

Study or Subgroup	Antiepileptic Mean	SD	Total	Beta-blocker Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
4.6.1 Topiramate								
DIENER2004A	-1.2	2.5	282	-1.6	2.51	143	100.0%	0.16 [-0.04, 0.36]
Subtotal (95% CI)			**282**			**143**	**100.0%**	**0.16 [-0.04, 0.36]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)



G.2.6 Prophylactic pharmacological treatment of menstrual migraine

G.2.6.1 Triptan vs placebo

Figure 106: Responder rate (50% reduction in frequency of headaches)

Study or Subgroup	Triptans Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
TUCHMAN2008	93	163	31	81	1.49 [1.10, 2.03]

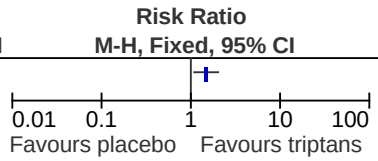


Figure 107: Use of acute pharmacological treatment (% of patients requiring medication)

Study or Subgroup	Triptans Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
BRANDES2009	167	250	137	160	0.78 [0.70, 0.87]

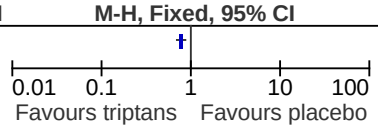
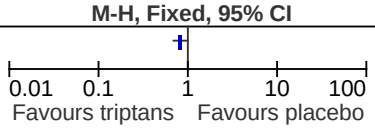


Figure 108: Use of acute pharmacological treatment (% of breakthrough attacks requiring medication)

Study or Subgroup	Triptans Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
TUCHMAN2008	100	163	60	81	0.83 [0.69, 0.99]



G.2.7 Prophylactic pharmacological treatment of cluster headache

G.2.7.1 Calcium channel blocker vs placebo

Figure 109: Responder rate (50% reduction)

Study or Subgroup	Verapamil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Leone 2000	12	15	0	15	100.0%	25.00 [1.61, 387.35]
Total (95% CI)		**15**		**15**	**100.0%**	**25.00 [1.61, 387.35]**
Total events	12		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.30 (P = 0.02)

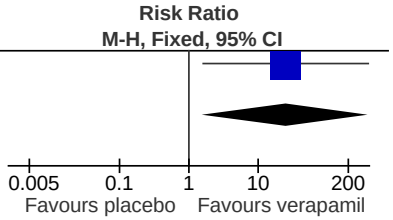


Figure 110: Change in headache frequency (no. attacks per day)

Study or Subgroup	Verapamil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Leone 2000	0.6	0.88	15	1.65	1.01	15	100.0%	-1.05 [-1.73, -0.37]
Total (95% CI)			**15**			**15**	**100.0%**	**-1.05 [-1.73, -0.37]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.04 (P = 0.002)

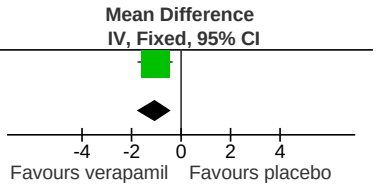
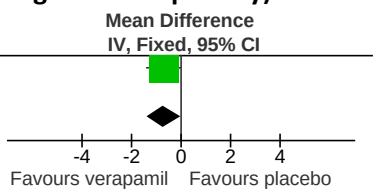


Figure 111: Use of acute pharmacological treatment (no. abortive agents used per day)

Study or Subgroup	Verapamil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Leone 2000	0.5	0.87	15	1.2	1.03	15	100.0%	-0.70 [-1.38, -0.02]
Total (95% CI)			**15**			**15**	**100.0%**	**-0.70 [-1.38, -0.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.01 (P = 0.04)



G.2.7.2 Melatonin vs placebo

Figure 112: Change in headache frequency (no. attacks per day)

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Leone 1996	1.51	7	10	2.5	0.86	10	100.0%	-0.99 [-5.36, 3.38]
Total (95% CI)			**10**			**10**	**100.0%**	**-0.99 [-5.36, 3.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

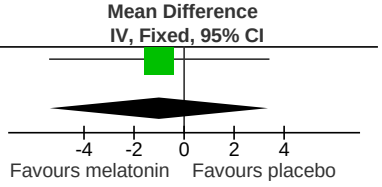
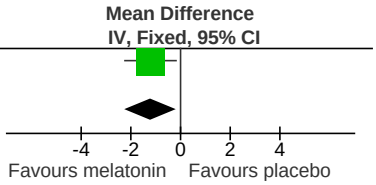


Figure 113: Use of acute pharmacological treatment (no. analgesics per day)

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Leone 1996	1.16	1.41	10	2.37	0.87	10	100.0%	-1.21 [-2.24, -0.18]
Total (95% CI)			**10**			**10**	**100.0%**	**-1.21 [-2.24, -0.18]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.31 (P = 0.02)



G.2.7.3 Sodium valproate vs placebo

Figure 114: Responder rate (50% reduction)

Study or Subgroup	Sodium valproate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El Amrani 2002	25	50	29	46	100.0%	0.79 [0.56, 1.13]
Total (95% CI)		**50**		**46**	**100.0%**	**0.79 [0.56, 1.13]**
Total events	25		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)

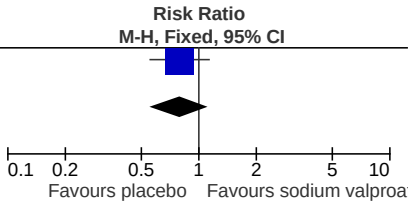


Figure 115: Change in headache intensity

Study or Subgroup	Sodium valproate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
El Amrani 2002	4.9	2.2	50	5.3	1.8	46	100.0%	-0.40 [-1.20, 0.40]
Total (95% CI)			**50**			**46**	**100.0%**	**-0.40 [-1.20, 0.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

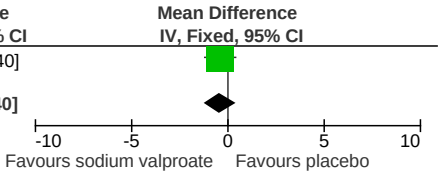


Figure 116: Acute medication use (number of people using sumatriptan)

Study or Subgroup	Sodium valproate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El Amrani 2002	18	50	24	46	100.0%	0.69 [0.43, 1.09]
Total (95% CI)		**50**		**46**	**100.0%**	**0.69 [0.43, 1.09]**
Total events	18		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.58 (P = 0.12)

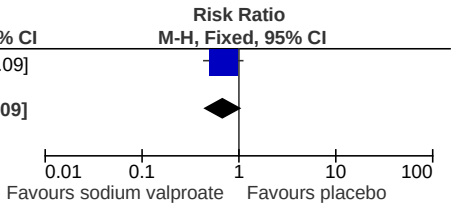
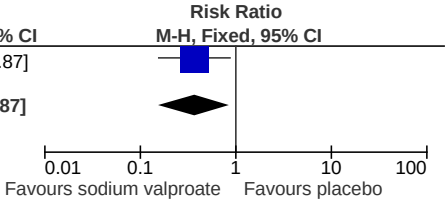


Figure 117: Acute medication use (number of people using oxygen)

Study or Subgroup	Sodium valproate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El Amrani 2002	6	50	15	46	100.0%	0.37 [0.16, 0.87]
Total (95% CI)		**50**		**46**	**100.0%**	**0.37 [0.16, 0.87]**
Total events	6		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)



G.2.7.4 Triptan vs placebo

Figure 118: Responder rate (50% reduction)

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Monstad 1995	20	89	17	79	100.0%	1.04 [0.59, 1.85]
Total (95% CI)		**89**		**79**	**100.0%**	**1.04 [0.59, 1.85]**
Total events	20		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)

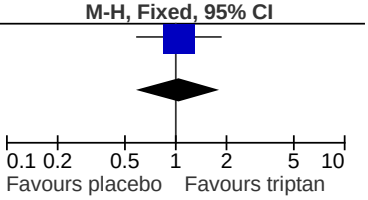
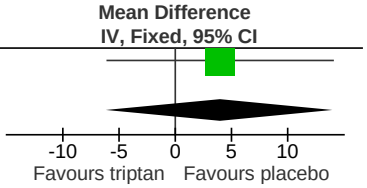


Figure 119: Change in headache frequency (attacks per week)

Study or Subgroup	Triptan Mean	Triptan SD	Triptan Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Pageler 2011	14.1	6.8	5	10.1	10.1	6	100.0%	4.00 [-6.04, 14.04]
Total (95% CI)			**5**			**6**	**100.0%**	**4.00 [-6.04, 14.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.43)



G.2.8 Prophylactic non-pharmacological management of primary headaches with acupuncture

Tension type headaches

G.2.8.1 Verum acupuncture vs sham acupuncture

Figure 120: Patient reported headache days

Study or Subgroup	Acupuncture Mean [days]	Acupuncture SD [days]	Acupuncture Total	Sham Mean [days]	Sham SD [days]	Sham Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
ENDRES 2007	6.8	6.3	199	9.1	8	192	74.0%	-2.30 [-3.73, -0.87]
KARST 2001	16.7	12	34	17.2	12	35	4.7%	-0.50 [-6.16, 5.16]
MELCHART 2005	9.9	8.7	118	10.8	8.3	57	21.3%	-0.90 [-3.57, 1.77]
Total (95% CI)			**351**			**284**	**100.0%**	**-1.92 [-3.15, -0.69]**

Heterogeneity: Chi² = 1.07, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 3.05 (P = 0.002)

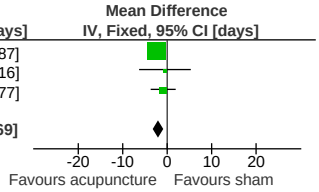


Figure 121: Patient reported headache intensity (0-10)

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Fixed, 95% CI
KARST 2001	4	1.9	34	4.6	1.7	35	100.0%	-0.60 [-1.45, 0.25]
Total (95% CI)			**34**			**35**	**100.0%**	**-0.60 [-1.45, 0.25]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

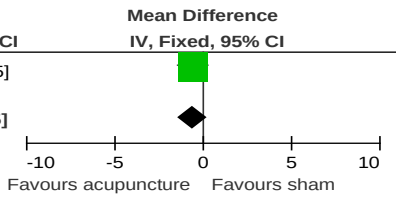


Figure 122: Responder rate (50% reduction in headache days)

Study or Subgroup	Acupuncture Events	Acupuncture Total	Sham Events	Sham Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ENDRES 2007	119	199	91	192	75.7%	1.26 [1.05, 1.52]
MELCHART 2005	61	132	22	63	24.3%	1.32 [0.90, 1.94]
Total (95% CI)		**331**		**255**	**100.0%**	**1.28 [1.08, 1.51]**
Total events	180		113			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.81 (P = 0.005)

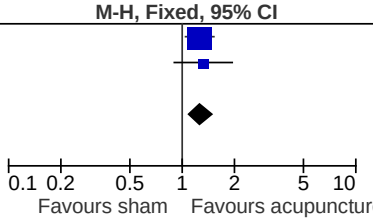


Figure 123: Acute medication use (days / amount per month)

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Sham Mean	Sham SD	Sham Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
KARST 2001	5.3	9	34	26	74	35	30.8%	-0.39 [-0.86, 0.09]
MELCHART 2005	1.9	2.9	117	2.6	2.6	57	69.2%	-0.25 [-0.57, 0.07]
Total (95% CI)			**151**			**92**	**100.0%**	**-0.29 [-0.55, -0.03]**

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)

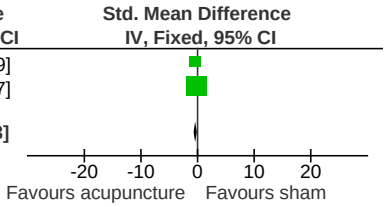


Figure 124: SF-12 physical health

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Fixed, 95% CI
ENDRES 2007	46.8	8.1	199	46.5	8.3	188	100.0%	0.30 [-1.34, 1.94]
Total (95% CI)			**199**			**188**	**100.0%**	**0.30 [-1.34, 1.94]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

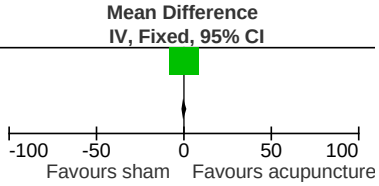


Figure 125: SF-12 mental health

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Fixed, 95% CI
ENDRES 2007	50	9.1	199	50.2	9	188	100.0%	-0.20 [-2.00, 1.60]
Total (95% CI)			**199**			**188**	**100.0%**	**-0.20 [-2.00, 1.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)

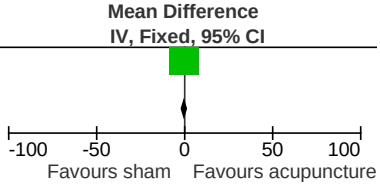


Figure 126: SF-36 physical health

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Fixed, 95% CI
MELCHART 2005	48.2	7.5	119	49	6.1	57	100.0%	-0.80 [-2.88, 1.28]
Total (95% CI)			**119**			**57**	**100.0%**	**-0.80 [-2.88, 1.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)

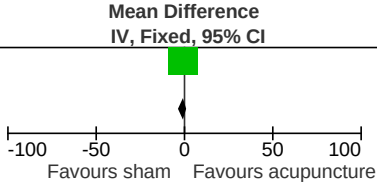


Figure 127: SF-36 mental health

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
MELCHART 2005	47.4	9.8	119	46.1	11.8	57	100.0%	1.30 [-2.23, 4.83]
Total (95% CI)			**119**			**57**	**100.0%**	**1.30 [-2.23, 4.83]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

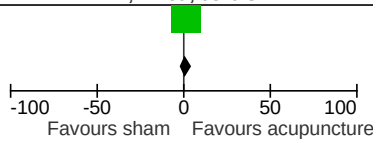
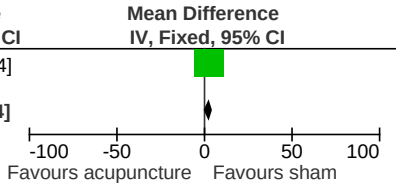


Figure 128: Nottingham health profile

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
KARST 2001	34.1	4.5	34	31.4	5.4	35	100.0%	2.70 [0.36, 5.04]
Total (95% CI)			**34**			**35**	**100.0%**	**2.70 [0.36, 5.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.26 (P = 0.02)



Migraine

Verum acupuncture vs sham

Figure 129: Change in patient reported migraine days

Study or Subgroup	Acupuncture Mean [days]	Acupuncture SD [days]	Acupuncture Total	Sham Mean [days]	Sham SD [days]	Sham Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
DIENER2006	-2.2	3.1	290	-1.9	3.6	317	45.6%	-0.30 [-0.83, 0.23]
LI2012	2.23	2.76	358	3.3	2.74	118	39.8%	-1.07 [-1.64, -0.50]
LINDE 2005	4.9	3.4	138	4.7	3.4	78	14.6%	0.20 [-0.74, 1.14]
Total (95% CI)			**786**			**513**	**100.0%**	**-0.53 [-0.89, -0.17]**

Heterogeneity: Chi² = 6.45, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 2.90 (P = 0.004)

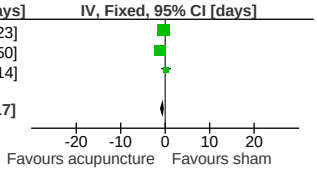


Figure 130: Responder rate (50% reduction in migraine days)

Study or Subgroup	Acupuncture Events	Acupuncture Total	Sham Events	Sham Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DIENER2006	128	290	128	317	69.0%	1.09 [0.91, 1.32]
LINDE 2005	78	138	43	78	31.0%	1.03 [0.80, 1.31]
Total (95% CI)		**428**		**395**	**100.0%**	**1.07 [0.92, 1.25]**
Total events	206		171			

Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)

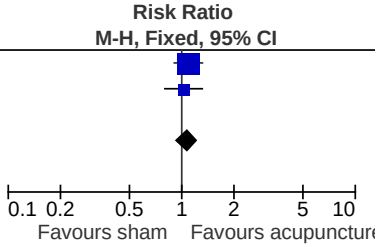


Figure 131: Patient reported migraine intensity (0-10)

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Sham Mean	Sham SD	Sham Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
DIENER2006	63.5	19.1	290	62.6	18.9	317	52.3%	0.05 [-0.11, 0.21]
LI2012	1.23	1.12	358	1.5	1.37	118	30.5%	-0.23 [-0.44, -0.02]
LINDE 2005	3.7	2	138	3.6	2.1	78	17.2%	0.05 [-0.23, 0.33]
Total (95% CI)			**786**			**513**	**100.0%**	**-0.04 [-0.15, 0.08]**

Heterogeneity: Chi² = 4.64, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 0.61 (P = 0.54)

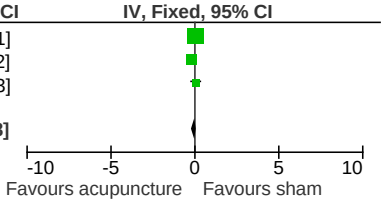


Figure 132: Patient reported migraine frequency

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Fixed, 95% CI
LI2012	1.73	1.66	358	2.4	1.65	118	100.0%	-0.67 [-1.01, -0.33]
Total (95% CI)			**358**			**118**	**100.0%**	**-0.67 [-1.01, -0.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.82 (P = 0.0001)

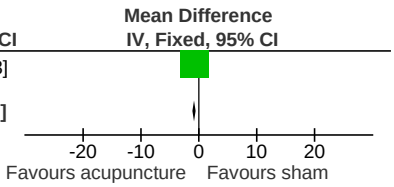


Figure 133: SF-12 physical health

Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Fixed, 95% CI
DIENER2006	47.6	7.3	290	46	8.2	317	100.0%	1.60 [0.37, 2.83]
Total (95% CI)			**290**			**317**	**100.0%**	**1.60 [0.37, 2.83]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.54 (P = 0.01)

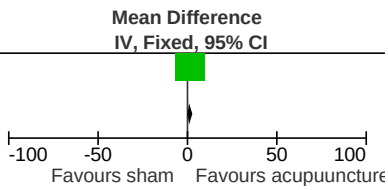


Figure 134: SF-12 mental health

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
DIENER2006	51.5	8.4	290	50.9	8.8	317	100.0%	0.60 [-0.77, 1.97]
Total (95% CI)			**290**			**317**	**100.0%**	**0.60 [-0.77, 1.97]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)

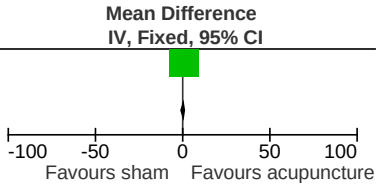


Figure 135: SF-36 physical health

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
LINDE 2005	46.7	7.5	138	47.5	7	78	100.0%	-0.80 [-2.79, 1.19]
Total (95% CI)			**138**			**78**	**100.0%**	**-0.80 [-2.79, 1.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

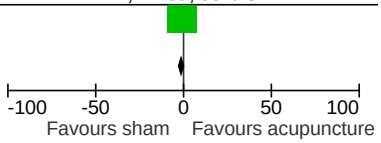


Figure 136: SF-36 mental health

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
LINDE 2005	48.6	8.8	138	47.6	9.6	78	100.0%	1.00 [-1.59, 3.59]
Total (95% CI)			**138**			**78**	**100.0%**	**1.00 [-1.59, 3.59]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)

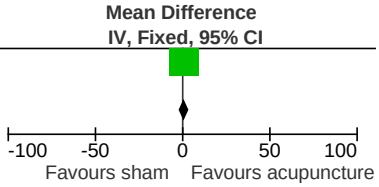


Figure 137: MIDAS

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 Ritualized Sham								
FACCO 2008	2.1	1.5	32	5	1.5	31	100.0%	-2.90 [-3.64, -2.16]
Subtotal (95% CI)			**32**			**31**	**100.0%**	**-2.90 [-3.64, -2.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 7.67 (P < 0.00001)

1.7.2 Western sham (standard mock)								
FACCO 2008	2.1	1.5	32	7.5	3.3	30	100.0%	-5.40 [-6.69, -4.11]
Subtotal (95% CI)			**32**			**30**	**100.0%**	**-5.40 [-6.69, -4.11]**

Heterogeneity: Not applicable
Test for overall effect: Z = 8.20 (P < 0.00001)

Test for subgroup differences: Chi² = 10.85, df = 1 (P = 0.0010), I² = 90.8%

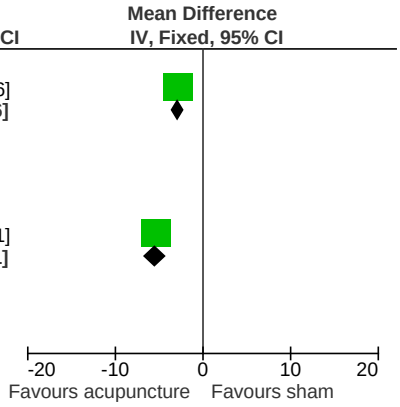


Figure 138: MSQ role restrictive subscale

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
LI2012	79.02	15.6	358	72.7	7.7	118	100.0%	6.32 [4.19, 8.45]
Total (95% CI)			**358**			**118**	**100.0%**	**6.32 [4.19, 8.45]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.81 (P < 0.00001)

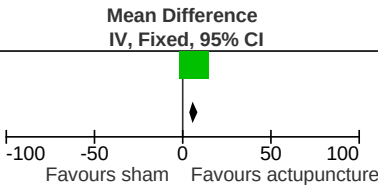


Figure 139: MSQ role preventive subscale

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
LI2012	84.42	17.22	358	79.5	13.44	118	100.0%	4.92 [1.91, 7.93]
Total (95% CI)			**358**			**118**	**100.0%**	**4.92 [1.91, 7.93]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.20 (P = 0.001)

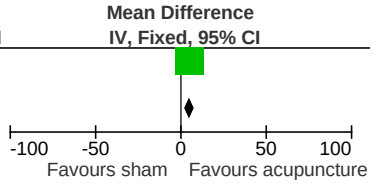


Figure 140: MSQ emotional functioning subscale

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
LI2012	84.76	15.54	358	82.6	15.08	118	100.0%	2.16 [-1.00, 5.32]
Total (95% CI)			**358**			**118**	**100.0%**	**2.16 [-1.00, 5.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)

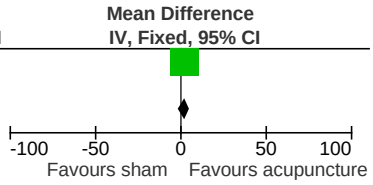


Figure 141: Use of acute pharmacological treatment

Study or Subgroup	Acupuncture Mean	SD	Total	Sham Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.4.1 Sham (ritualised mock Facco)								
FACCO 2008	10	5	32	17	5	30	19.9%	-1.38 [-1.94, -0.82]
LINDE 2005	3.2	3	138	3.4	2.9	78	80.1%	-0.07 [-0.34, 0.21]
Subtotal (95% CI)			**170**			**108**	**100.0%**	**-0.33 [-0.58, -0.08]**

Heterogeneity: Chi² = 17.11, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 2.59 (P = 0.010)

1.4.2 Western sham (standard mock Facco)								
FACCO 2008	10	5	32	17.2	5.4	31	20.2%	-1.37 [-1.92, -0.82]
LINDE 2005	3.2	3	138	3.4	2.9	78	79.8%	-0.07 [-0.34, 0.21]
Subtotal (95% CI)			**170**			**109**	**100.0%**	**-0.33 [-0.58, -0.08]**

Heterogeneity: Chi² = 17.00, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 2.61 (P = 0.009)

Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%

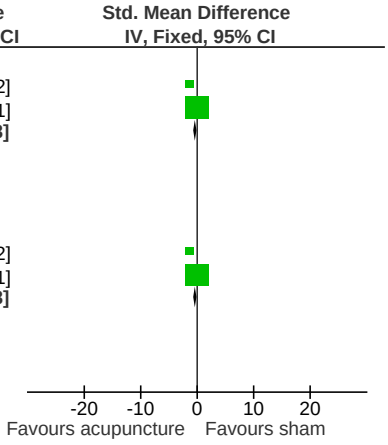
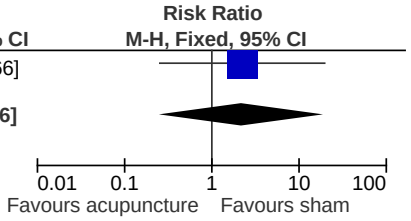


Figure 142: Incidence of serious adverse events

Study or Subgroup	Acupuncture Events	Total	Sham Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
LINDE 2005	4	145	1	81	100.0%	2.23 [0.25, 19.66]
Total (95% CI)		**145**		**81**	**100.0%**	**2.23 [0.25, 19.66]**
Total events	4		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

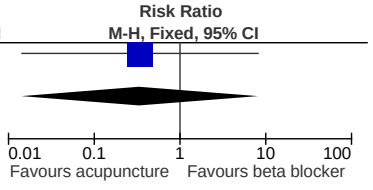


Verum acupuncture plus placebo vs sham acupuncture plus beta-blocker (metoprolol)

Figure 143: Incidence of serious adverse events

Study or Subgroup	Acupuncture + Placebo Events	Total	Beta blocker + Sham Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
HESSE 1994	0	38	1	39	100.0%	0.34 [0.01, 8.14]
Total (95% CI)		**38**		**39**	**100.0%**	**0.34 [0.01, 8.14]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



G.2.9 Prophylactic non-pharmacological management of primary headaches with manual therapies

Tension type headache

G.2.9.1 Manual therapy vs placebo

Figure 144: Change in headache intensity (final values on 0-100 VAS scale)

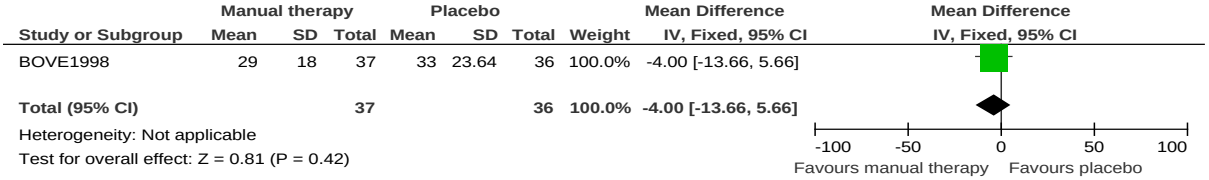
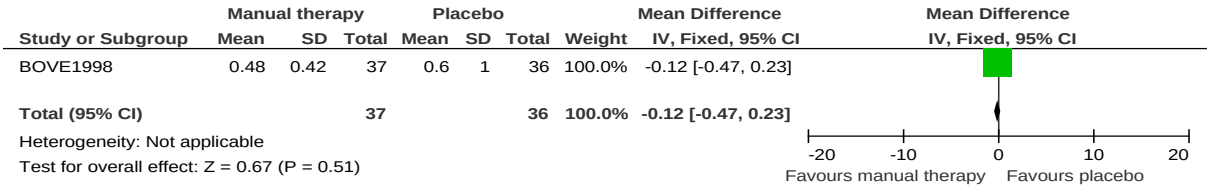
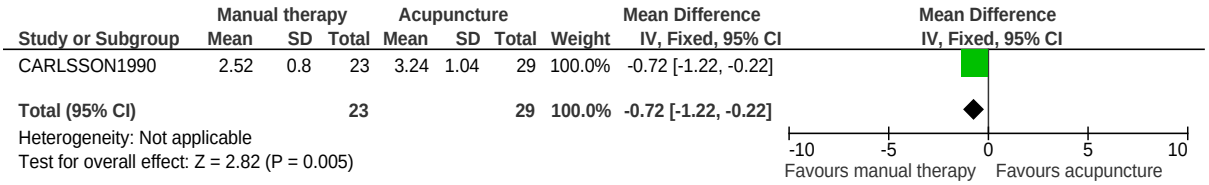


Figure 145: Mean number of analgesics per day (final values)



G.2.9.2 Manual therapy vs acupuncture

Figure 146: Change in headache intensity (final values on a 5 point scale)



G.2.9.3 Manual therapy vs usual care

Figure 147: Change in headache days (change scores from headache diary, 14 days)

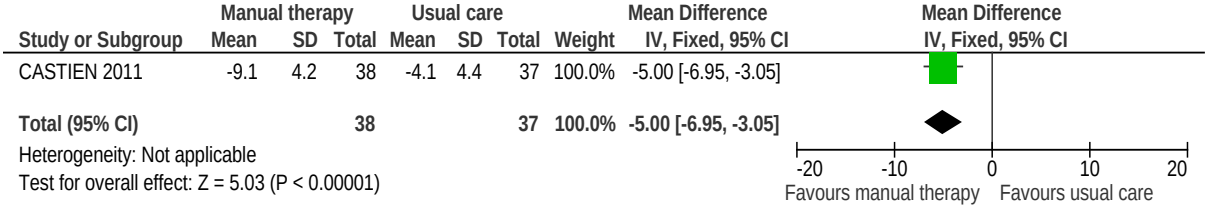


Figure 148: Responder rate

Study or Subgroup	Manual therapy Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CASTIEN 2011	31	38	15	37	100.0%	2.01 [1.32, 3.06]
Total (95% CI)		**38**		**37**	**100.0%**	**2.01 [1.32, 3.06]**
Total events	31		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.28 (P = 0.001)

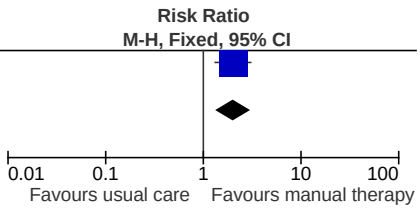


Figure 149: Change in headache intensity (change scores, reported on 0-10 numeric rating scale)

Study or Subgroup	Manual therapy Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
CASTIEN 2011	-3.1	2.8	38	-1.7	2.5	37	100.0%	-1.40 [-2.60, -0.20]
Total (95% CI)			**38**			**37**	**100.0%**	**-1.40 [-2.60, -0.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.29 (P = 0.02)

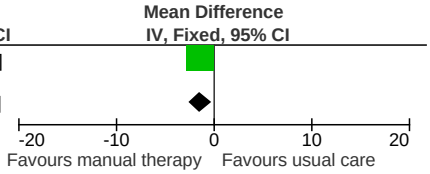


Figure 150: Change in headache specific QoL (HIT-6 change scores)

Study or Subgroup	Manual therapy Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
CASTIEN 2011	-10	8.4	38	-5.5	8.6	37	100.0%	-4.50 [-8.35, -0.65]
Total (95% CI)			**38**			**37**	**100.0%**	**-4.50 [-8.35, -0.65]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.29 (P = 0.02)

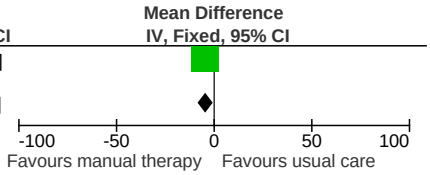


Figure 151: Resource use (Use of additional medical specialists)

Study or Subgroup	Manual therapy Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CASTIEN 2011	1	38	6	37	100.0%	0.16 [0.02, 1.28]
Total (95% CI)		**38**		**37**	**100.0%**	**0.16 [0.02, 1.28]**
Total events	1		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.08)

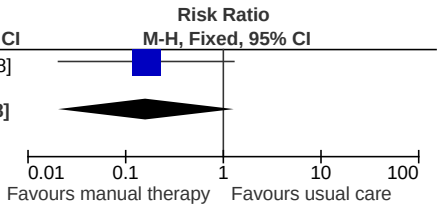
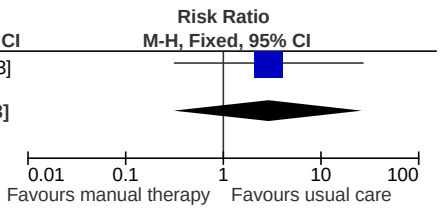


Figure 152: Resource use (Use of additional healthcare, other than hospital attendance/medical specialists)

Study or Subgroup	Manual therapy Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CASTIEN 2011	3	38	1	37	100.0%	2.92 [0.32, 26.83]
Total (95% CI)		**38**		**37**	**100.0%**	**2.92 [0.32, 26.83]**
Total events	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)



Migraine

G.2.9.4 Manual therapy vs placebo

Figure 153: Change in headache days

Study or Subgroup	Spinal manipulation Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
TUCHIN 2000	4.1	6.55	83	6.9	6.6	40	100.0%	-2.80 [-5.28, -0.32]
Total (95% CI)			**83**			**40**	**100.0%**	**-2.80 [-5.28, -0.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.21 (P = 0.03)

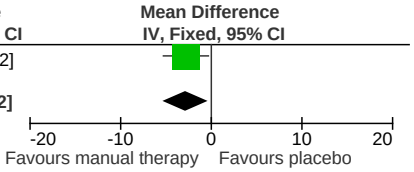


Figure 154: Change in headache intensity

Study or Subgroup	Spinal manipulation Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
TUCHIN 2000	6.9	1.8	83	6.2	1.7	40	100.0%	0.70 [0.05, 1.35]
Total (95% CI)			**83**			**40**	**100.0%**	**0.70 [0.05, 1.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.10 (P = 0.04)

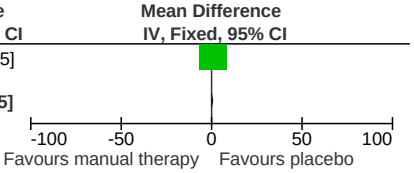
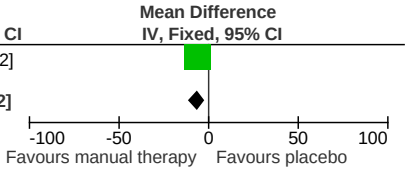


Figure 155: Acute medication use (average number of medications per month)

Study or Subgroup	Spinal manipulation Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
TUCHIN 2000	9.8	12.4	83	16.2	12.4	40	100.0%	-6.40 [-11.08, -1.72]
Total (95% CI)			**83**			**40**	**100.0%**	**-6.40 [-11.08, -1.72]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.68 (P = 0.007)



G.2.9.5 Manual therapy vs pharmacological treatment

Figure 156: Change in headache days-final values

Study or Subgroup	Spinal manipulation Mean	SD	Total	Amitryptiline Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	36.9	29.3	58	40.5	23.3	47	100.0%	-3.60 [-13.66, 6.46]
Total (95% CI)			**58**			**47**	**100.0%**	**-3.60 [-13.66, 6.46]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)

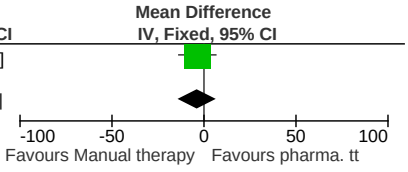


Figure 157: Change in headache intensity-final values

Study or Subgroup	Spinal manipulation Mean	SD	Total	Amitryptiline Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	4.4	1.7	56	4.5	1.3	44	100.0%	-0.10 [-0.69, 0.49]
Total (95% CI)			**56**			**44**	**100.0%**	**-0.10 [-0.69, 0.49]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

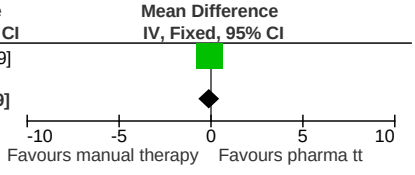


Figure 158: Functional health status -SF-36- final values

Study or Subgroup	Spinal manipulation Mean	SD	Total	Amitryptiline Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	74.4	15.1	58	71.5	12.4	50	100.0%	2.90 [-2.29, 8.09]
Total (95% CI)			**58**			**50**	**100.0%**	**2.90 [-2.29, 8.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)

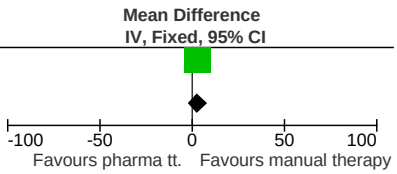
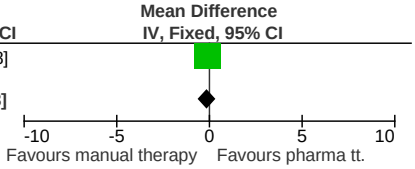


Figure 159: Acute medication use (Over the counter medication (pills/day)-final values)

Study or Subgroup	Spinal manipulation Mean	SD	Total	Amitryptiline Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	1.2	1.2	58	1.3	1.3	47	100.0%	-0.10 [-0.58, 0.38]
Total (95% CI)			**58**			**47**	**100.0%**	**-0.10 [-0.58, 0.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.69)



G.2.9.6 Manual therapy vs manual therapy + tricyclic antidepressants

Figure 160: Change in migraine days-final values

Study or Subgroup	Manual therapy Mean	SD	Total	Combined treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	36.9	29.3	58	39.9	26.6	54	100.0%	-3.00 [-13.35, 7.35]
Total (95% CI)			**58**			**54**	**100.0%**	**-3.00 [-13.35, 7.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

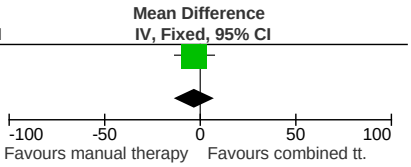


Figure 161: Change in migraine intensity-final values

Study or Subgroup	Manual therapy Mean	SD	Total	Combined treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	4.4	1.7	56	4.3	1.4	50	100.0%	0.10 [-0.49, 0.69]
Total (95% CI)			**56**			**50**	**100.0%**	**0.10 [-0.49, 0.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

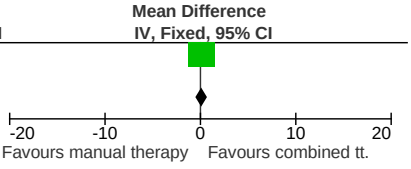


Figure 162: Functional health status -SF-36- final values

Study or Subgroup	Manual therapy Mean	SD	Total	Combined treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	74.4	15.1	58	71.9	14.1	55	100.0%	2.50 [-2.88, 7.88]
Total (95% CI)			**58**			**55**	**100.0%**	**2.50 [-2.88, 7.88]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)

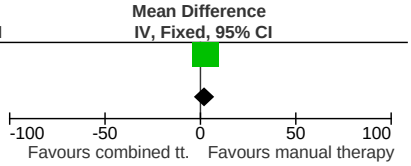
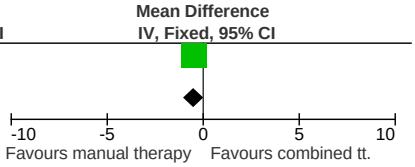


Figure 163: Acute medication use (Over the counter medication (pills/day)-final values)

Study or Subgroup	Manual therapy Mean	SD	Total	Combined treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	1.2	1.2	58	1.7	1.5	54	100.0%	-0.50 [-1.01, 0.01]
Total (95% CI)			**58**			**54**	**100.0%**	**-0.50 [-1.01, 0.01]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)



G.2.9.7 Pharmacological treatment vs combined treatment (Manual therapy + tricyclic antidepressants)

Figure 164: Change in headache days-final values

Study or Subgroup	Amitriptyline Mean	SD	Total	Combined treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	40.5	23.3	47	39.9	26.6	54	100.0%	0.60 [-9.13, 10.33]
Total (95% CI)			**47**			**54**	**100.0%**	**0.60 [-9.13, 10.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.12 (P = 0.90)

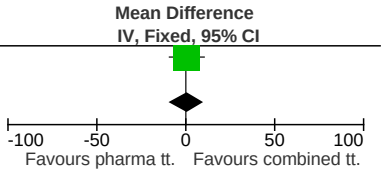


Figure 165: Change in headache intensity-final values

Study or Subgroup	Amitriptyline Mean	SD	Total	Combined treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	4.5	1.3	44	4.3	1.4	50	100.0%	0.20 [-0.35, 0.75]
Total (95% CI)			**44**			**50**	**100.0%**	**0.20 [-0.35, 0.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

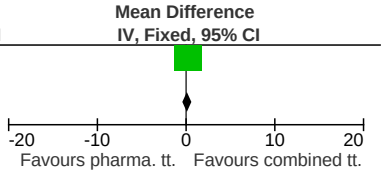


Figure 166: Functional health status -SF-36- final values

Study or Subgroup	Amitriptyline Mean	SD	Total	Combined treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	71.5	12.4	50	71.9	14.1	55	100.0%	-0.40 [-5.47, 4.67]
Total (95% CI)			**50**			**55**	**100.0%**	**-0.40 [-5.47, 4.67]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)

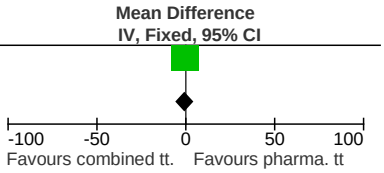
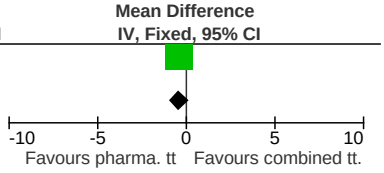


Figure 167: Acute medication use (Over the counter medication (pills/day)-final values)

Study or Subgroup	Amitriptyline Mean	SD	Total	Combined treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
NELSON 1998	1.3	1.3	47	1.7	1.5	54	100.0%	-0.40 [-0.95, 0.15]
Total (95% CI)			**47**			**54**	**100.0%**	**-0.40 [-0.95, 0.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)



G.2.10 Prophylactic non-pharmacological management of primary headaches with psychological therapies

Tension type headache

G.2.10.1 Psychological therapy (written emotional disclosure) vs active control

Figure 168: Change in headache frequency

Study or Subgroup	Psychological therapies Mean	SD	Total	Active control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
D'Souza	12.24	7.9	17	11.24	9.01	17	100.0%	1.00 [-4.70, 6.70]
Total (95% CI)			**17**			**17**	**100.0%**	**1.00 [-4.70, 6.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

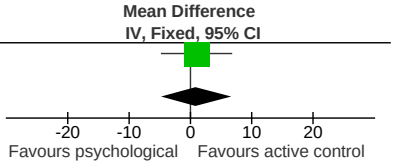


Figure 169: Change in headache intensity

Study or Subgroup	Psychological therapies Mean	SD	Total	Active control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
D'Souza	5	1.62	17	4.71	1.8	17	100.0%	0.29 [-0.86, 1.44]
Total (95% CI)			**17**			**17**	**100.0%**	**0.29 [-0.86, 1.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)

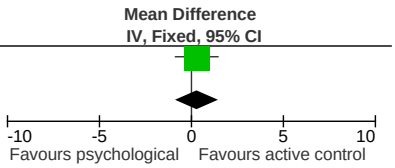
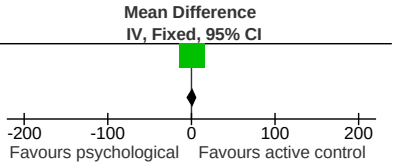


Figure 170: Change in headache-specific QoL

Study or Subgroup	Psychological therapies Mean	SD	Total	Active control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
D'Souza	8.35	8.89	17	7.29	7.82	17	100.0%	1.06 [-4.57, 6.69]
Total (95% CI)			**17**			**17**	**100.0%**	**1.06 [-4.57, 6.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)



Migraine

G.2.10.2 Psychological therapy vs active control

Figure 171: Change in headache frequency

Study or Subgroup	Psychological therapy Mean	SD	Total	Active Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Written emotional disclosure								
D'Souza 2008	9	5.81	29	8.97	6.14	27	40.6%	0.03 [-3.11, 3.17]
Subtotal (95% CI)			**29**			**27**	**40.6%**	**0.03 [-3.11, 3.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.02 (P = 0.99)								
1.1.2 Relaxation training								
Richter 1986	2.91	3.4	15	4.68	5.83	12	28.9%	-1.77 [-5.49, 1.95]
Subtotal (95% CI)			**15**			**12**	**28.9%**	**-1.77 [-5.49, 1.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.93 (P = 0.35)								
1.1.3 Cognitive coping								
Richter 1986	2.52	2.94	15	4.68	5.83	12	30.5%	-2.16 [-5.78, 1.46]
Subtotal (95% CI)			**15**			**12**	**30.5%**	**-2.16 [-5.78, 1.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.17 (P = 0.24)								
Total (95% CI)			**59**			**51**	**100.0%**	**-1.16 [-3.16, 0.84]**

Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)
Test for subgroup differences: Chi² = 0.95, df = 2 (P = 0.62), I² = 0%

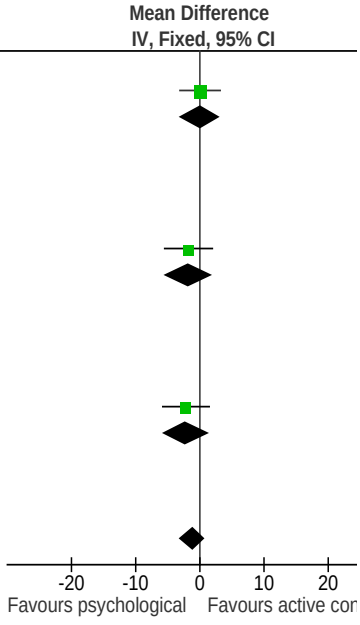


Figure 172: Change in headache intensity

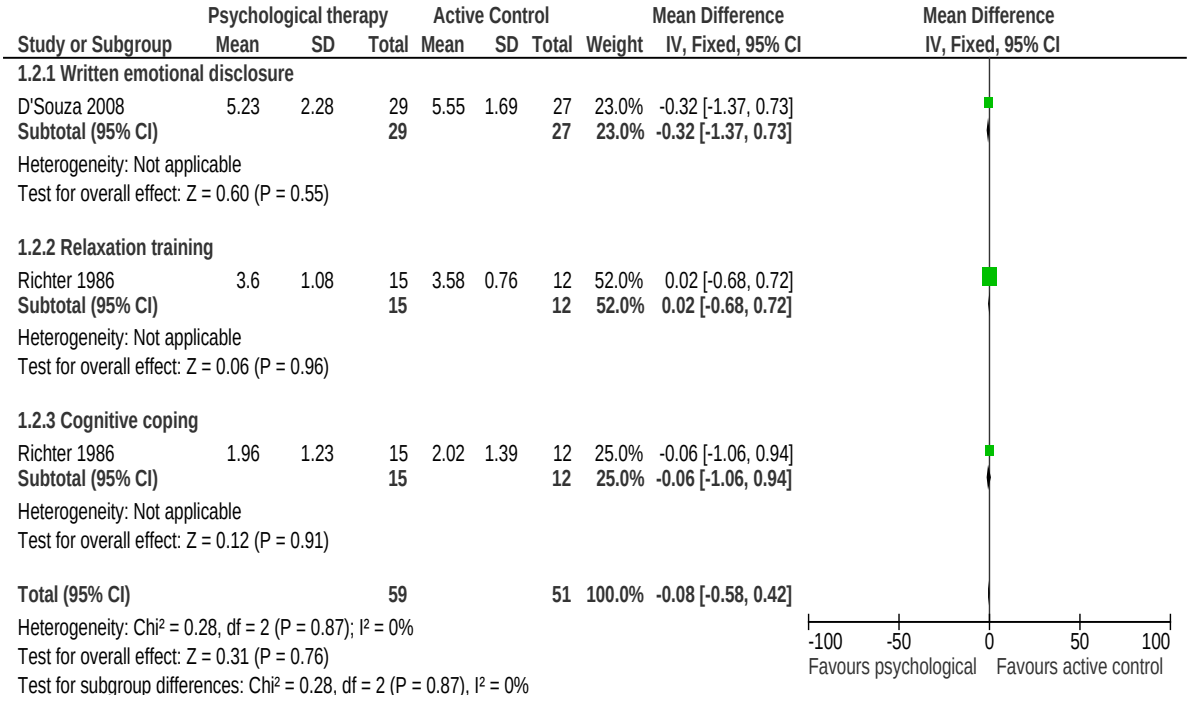
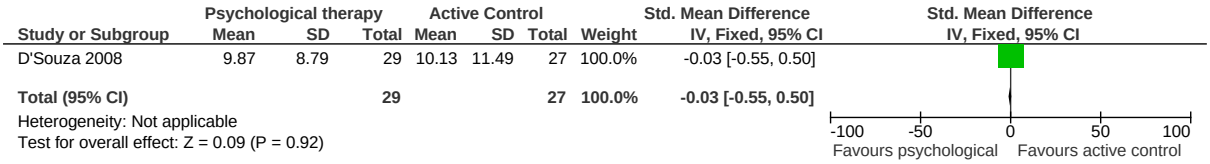


Figure 173: Change in headache specific QoL (MIDAS)



G.2.10.3 Psychological therapy vs topiramate

Figure 174: Responder rate (50% reduction in migraine attack frequency)

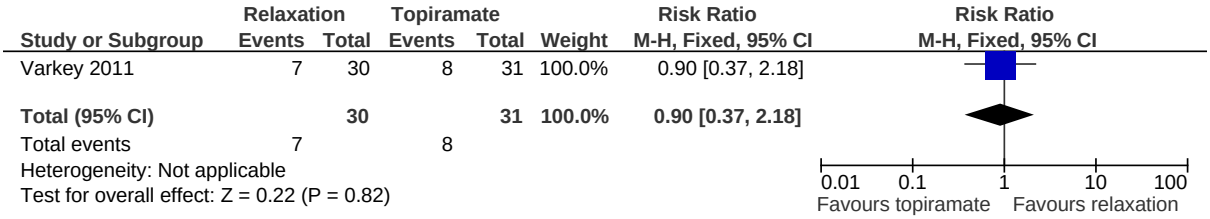


Figure 175: Change in patient reported migraine days

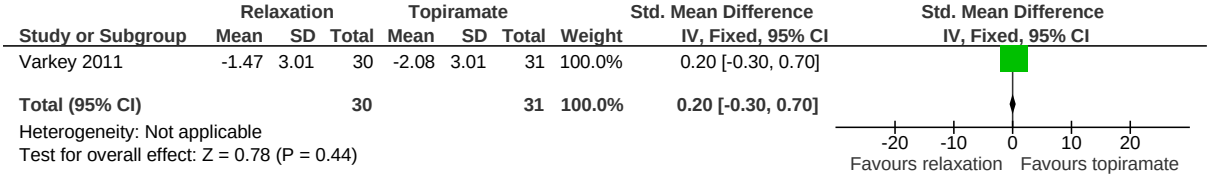


Figure 176: Change in patient reported migraine frequency (attacks / month)

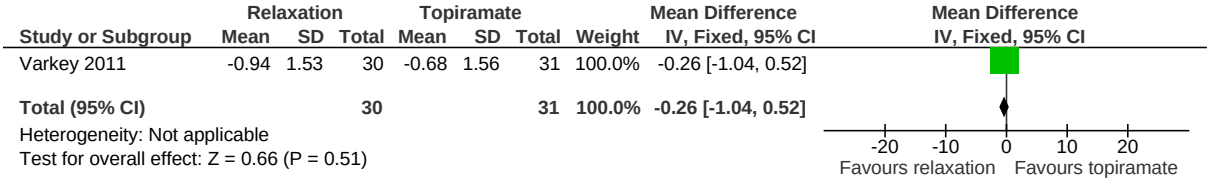


Figure 177: Change in patient reported migraine intensity (0-100 VAS)

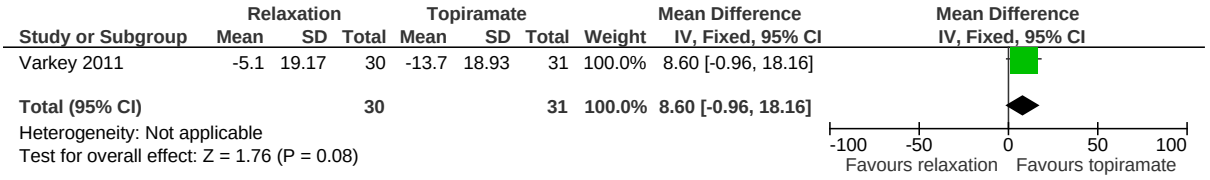


Figure 178: Migraine specific quality of life (0-100)

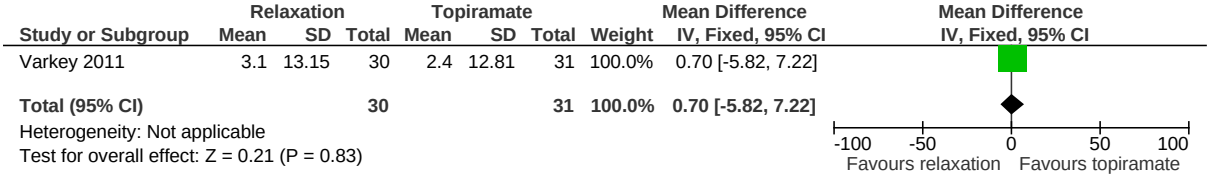
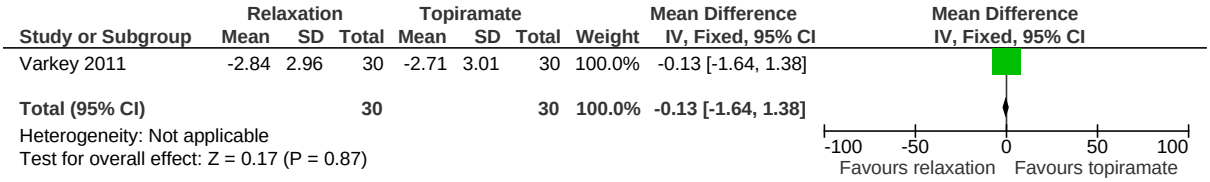


Figure 179: Change in acute pharmacological medication use (doses/month)



G.2.11 Prophylactic non-pharmacological management of primary headaches with dietary supplements

G.2.11.1 Magnesium vs placebo

Figure 180: Responder rate

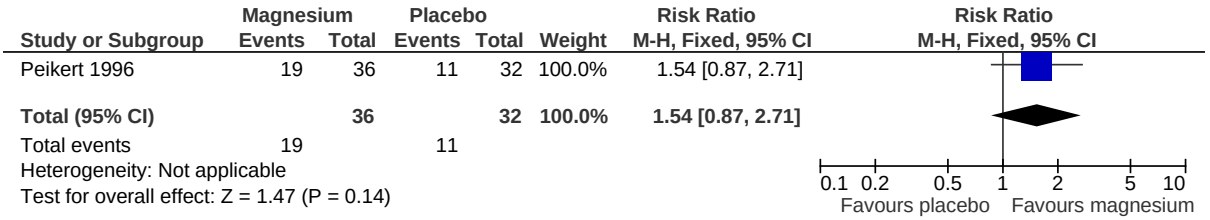


Figure 181: Change in patient reported migraine days

Study or Subgroup	Magnesium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Peikert 1996	-2.49	0.05	43	-1.16	3.89	38	100.0%	-1.33 [-2.57, -0.09]
Total (95% CI)			**43**			**38**	**100.0%**	**-1.33 [-2.57, -0.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.11 (P = 0.04)

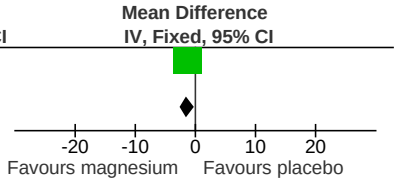


Figure 182: Change in patient reported migraine intensity

Study or Subgroup	Magnesium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Peikert 1996	-2.06	2.77	43	-1.25	2.29	38	100.0%	-0.81 [-1.91, 0.29]
Total (95% CI)			**43**			**38**	**100.0%**	**-0.81 [-1.91, 0.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)

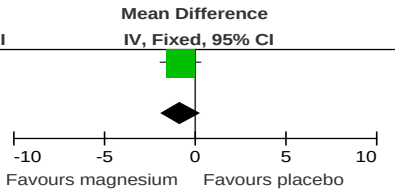


Figure 183: Change in patient reported migraine frequency

Study or Subgroup	Magnesium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Peikert 1996	-1.51	2.07	43	-0.58	2.3	38	100.0%	-0.93 [-1.89, 0.03]
Total (95% CI)			**43**			**38**	**100.0%**	**-0.93 [-1.89, 0.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.90 (P = 0.06)

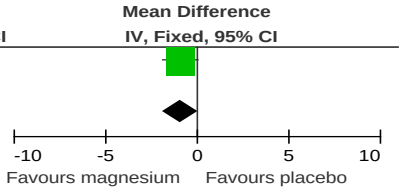


Figure 184: Use of acute pharmacological treatment

Study or Subgroup	Magnesium Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Peikert 1996	-5.07	6.58	43	-2.4	6.59	38	100.0%	-2.67 [-5.54, 0.20]
Total (95% CI)			**43**			**38**	**100.0%**	**-2.67 [-5.54, 0.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)

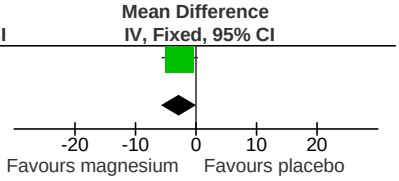
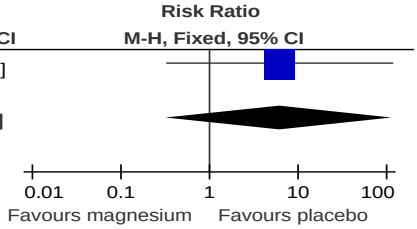


Figure 185: Incidence of serious adverse events

Study or Subgroup	Magnesium Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Peikert 1996	3	43	0	38	100.0%	6.20 [0.33, 116.39]
Total (95% CI)		**43**		**38**	**100.0%**	**6.20 [0.33, 116.39]**
Total events	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

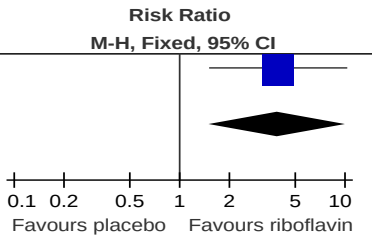


G.2.11.2 Riboflavin vs placebo

Figure 186: Responder rate

Study or Subgroup	Riboflavin Events	Riboflavin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schoenen 1998	17	28	4	26	100.0%	3.95 [1.53, 10.20]
Total (95% CI)		**28**		**26**	**100.0%**	**3.95 [1.53, 10.20]**
Total events	17		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.83 (P = 0.005)



G.2.12 Prophylactic non-pharmacological management of primary headaches with herbal remedies

G.2.12.1 Butterbur vs placebo

Figure 187: Responder rate (>50% reduction)

Study or Subgroup	Butterbur Events	Butterbur Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Grossman2000/ Diener2004C	16	33	4	27	38.4%	3.27 [1.24, 8.64]
Lipton 2004	100	154	39	75	61.6%	1.25 [0.98, 1.60]
Total (95% CI)		**187**		**102**	**100.0%**	**1.81 [0.70, 4.67]**
Total events	116		43			

Heterogeneity: Tau² = 0.37; Chi² = 3.80, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 1.22 (P = 0.22)

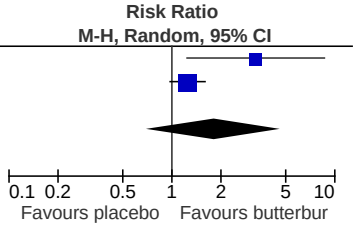


Figure 188: Change in patient reported migraine intensity

Study or Subgroup	Butterbur Mean	Butterbur SD	Butterbur Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Grossman2000/ Diener2004C	3.1	1.73	33	3.4	1.08	27	100.0%	-0.20 [-0.71, 0.31]
Total (95% CI)			**33**			**27**	**100.0%**	**-0.20 [-0.71, 0.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)

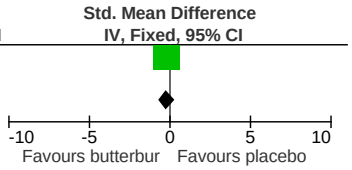


Figure 189: Change in patient reported migraine frequency

Study or Subgroup	Butterbur Mean	Butterbur SD	Butterbur Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Grossman2000/ Diener2004C	1.8	0.95	33	2.6	1.15	27	100.0%	-0.80 [-1.34, -0.26]
Total (95% CI)			**33**			**27**	**100.0%**	**-0.80 [-1.34, -0.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.90 (P = 0.004)

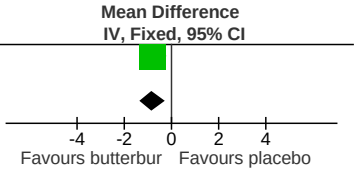


Figure 190: Use of acute pharmacological treatment (% of patients using medication)

Study or Subgroup	Butterbur Events	Butterbur Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Grossman2000/ Diener2004C	6	33	7	27	100.0%	0.70 [0.27, 1.84]
Total (95% CI)		**33**		**27**	**100.0%**	**0.70 [0.27, 1.84]**
Total events	6		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

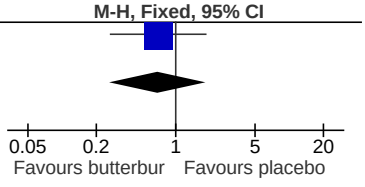
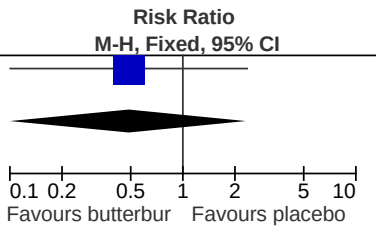


Figure 191: Serious adverse events

Study or Subgroup	Butterbur Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lipton 2004	3	154	3	75	100.0%	0.49 [0.10, 2.36]
Total (95% CI)		**154**		**75**	**100.0%**	**0.49 [0.10, 2.36]**
Total events	3		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)



G.2.12.2 Feverfew vs placebo

Figure 192: Responder rate (>50% reduction)

Study or Subgroup	Feverfew Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Diener 2005A	27	89	14	81	50.5%	1.76 [0.99, 3.11]
Pfaffenrath 2002	25	112	11	35	49.5%	0.71 [0.39, 1.29]
Total (95% CI)		**201**		**116**	**100.0%**	**1.12 [0.46, 2.74]**
Total events	52		25			

Heterogeneity: Tau² = 0.32; Chi² = 4.64, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 0.25 (P = 0.80)

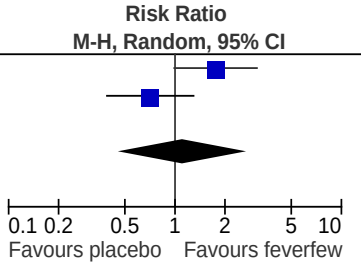


Figure 193: Change in patient reported migraine days

Study or Subgroup	Feverfew Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Diener 2005A	4.74	2.83	89	5.33	2.79	81	100.0%	-0.59 [-1.44, 0.26]
Total (95% CI)			**89**			**81**	**100.0%**	**-0.59 [-1.44, 0.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.37 (P = 0.17)

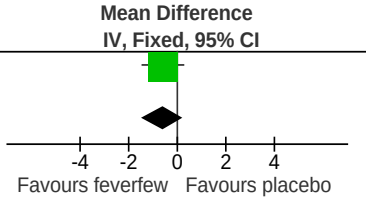


Figure 194: Change in patient reported migraine frequency

Study or Subgroup	Feverfew Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pfaffenrath 2002	-0.46	1.64	85	-0.7	1.9	25	100.0%	0.24 [-0.58, 1.06]
Total (95% CI)			**85**			**25**	**100.0%**	**0.24 [-0.58, 1.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

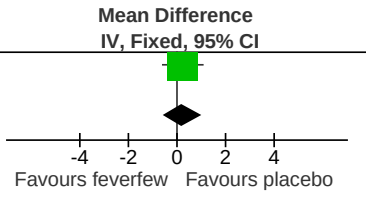
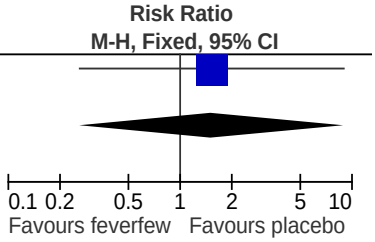


Figure 195: Serious adverse events

Study or Subgroup	Feverfew Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Diener 2005A	3	108	2	110	100.0%	1.53 [0.26, 8.96]
Total (95% CI)		**108**		**110**	**100.0%**	**1.53 [0.26, 8.96]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)



G.2.13 Prophylactic non-pharmacological management of primary headaches with exercise

G.2.13.1 Yoga vs self care

Figure 196: Migraine intensity

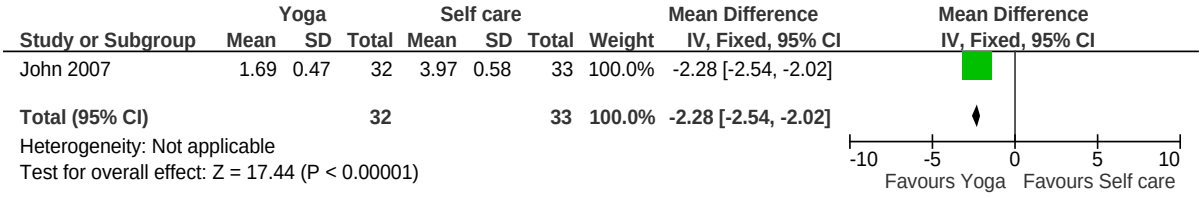


Figure 197: Migraine frequency

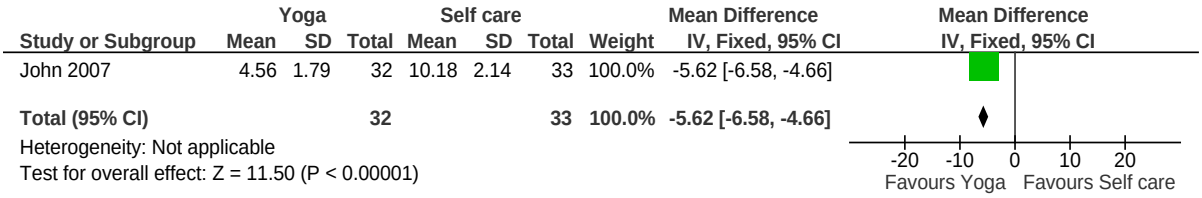
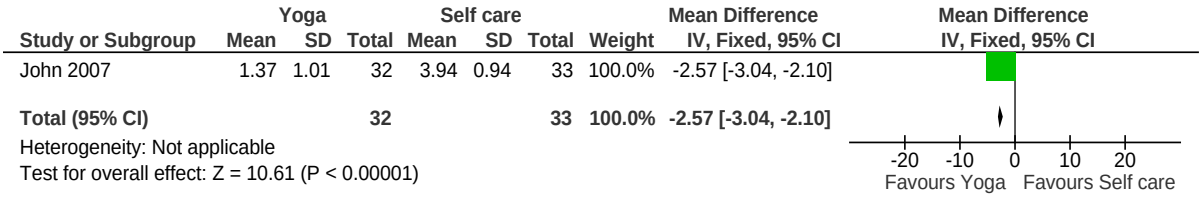


Figure 198: Acute pharmacological treatment



G.2.13.2 Exercise vs Topiramate

Figure 199: Responder rate

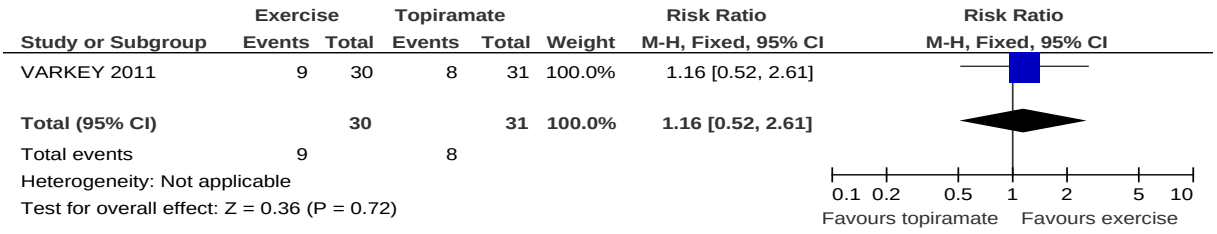


Figure 200: Change in patient reported migraine days

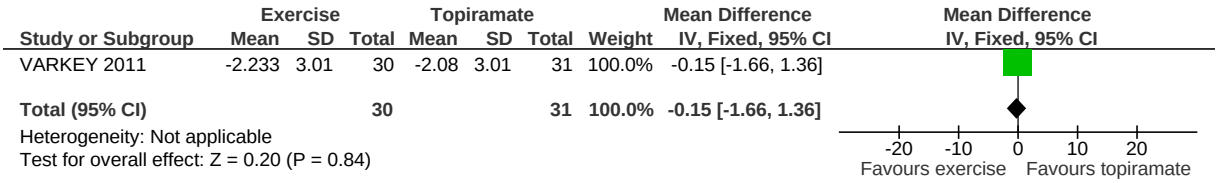


Figure 201: Change in patient reported migraine frequency

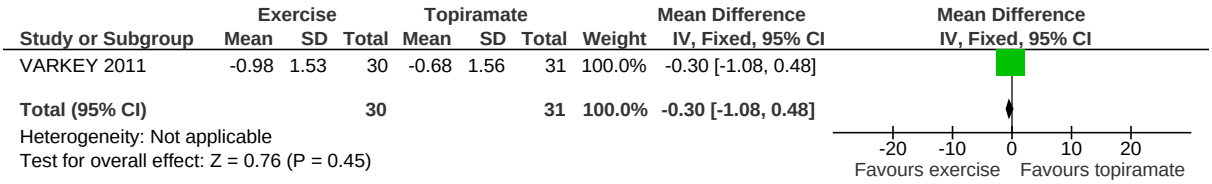


Figure 202: Change in patient reported migraine intensity

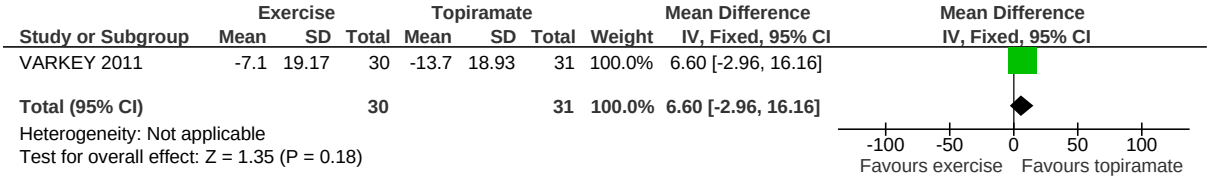


Figure 203: Migraine specific Quality of Life

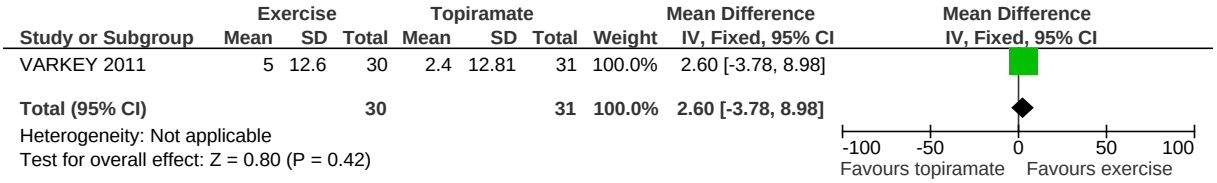
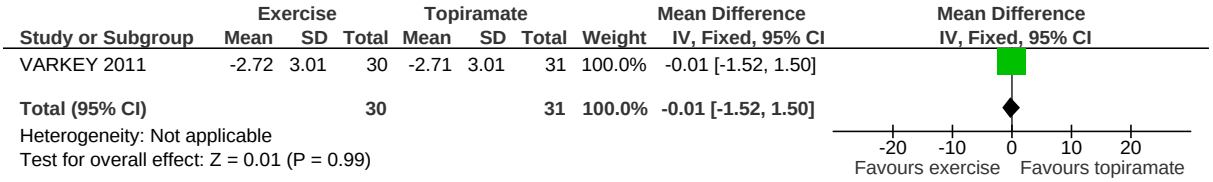


Figure 204: Use of acute pharmacological treatment



G.2.13.3 Exercise vs relaxation

Figure 205: Responder rate (50% reduction in migraine attack frequency)

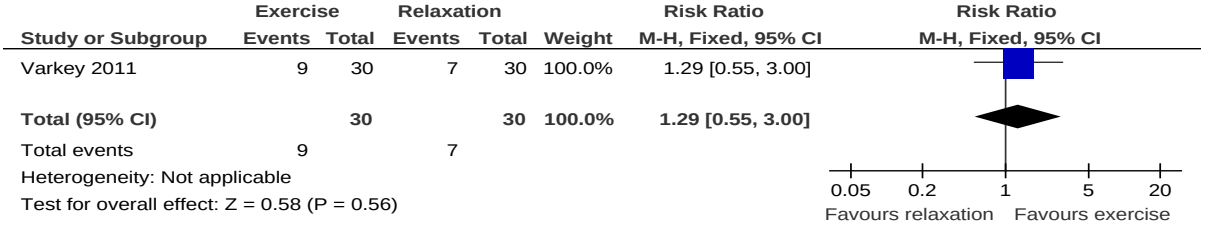


Figure 206: Change in patient reported migraine days

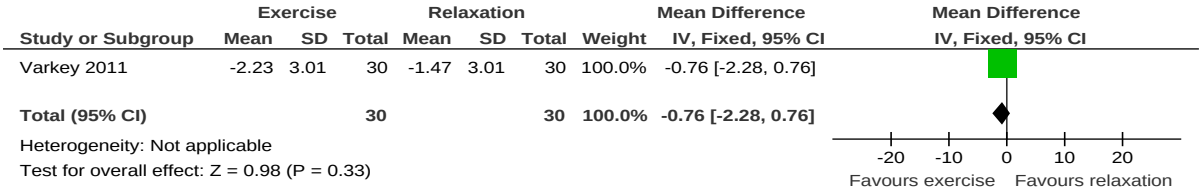


Figure 207: Change in patient reported migraine frequency (attacks / month)

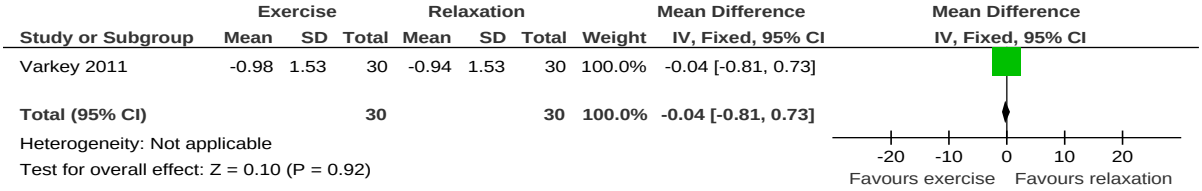


Figure 208: Change in patient reported migraine intensity (0-100 VAS)

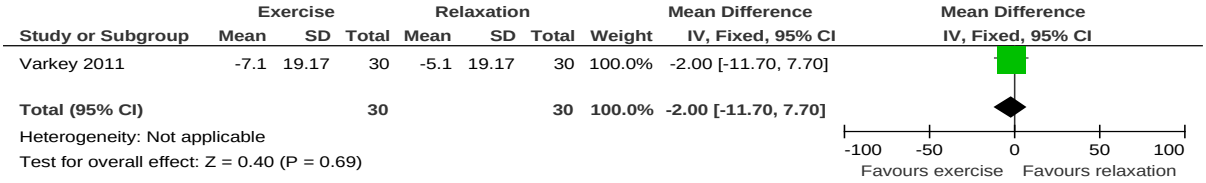


Figure 209: Migraine specific quality of life (0-100)

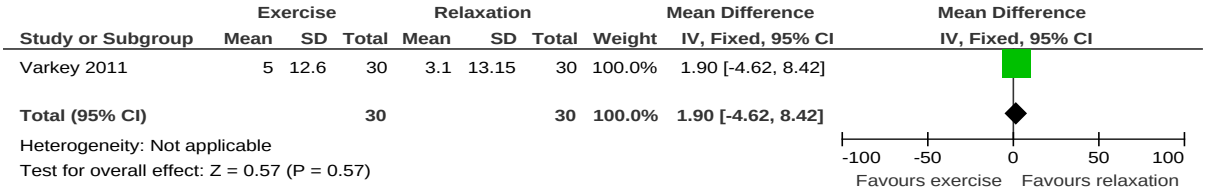
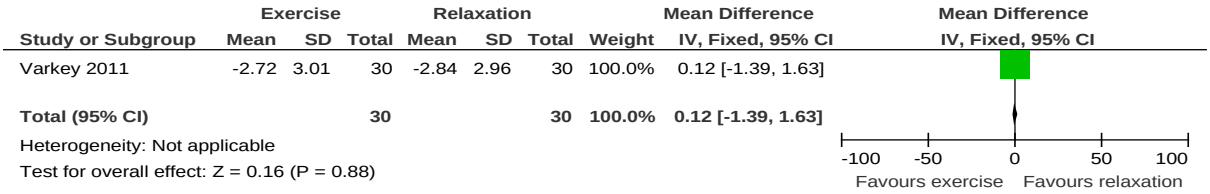


Figure 210: Change in acute pharmacological medication use (doses/month)



G.2.14 Prophylactic non-pharmacological management of primary headaches with education and self-management

Mixed headache

G.2.14.1 Self help vs therapist assisted relaxation

Figure 211: Responder rate

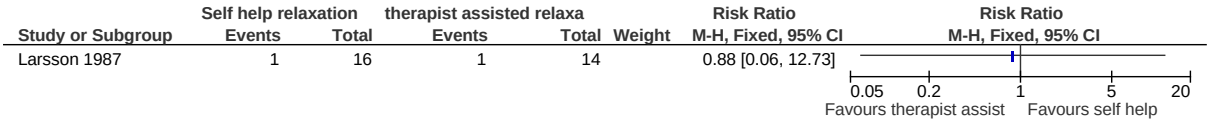
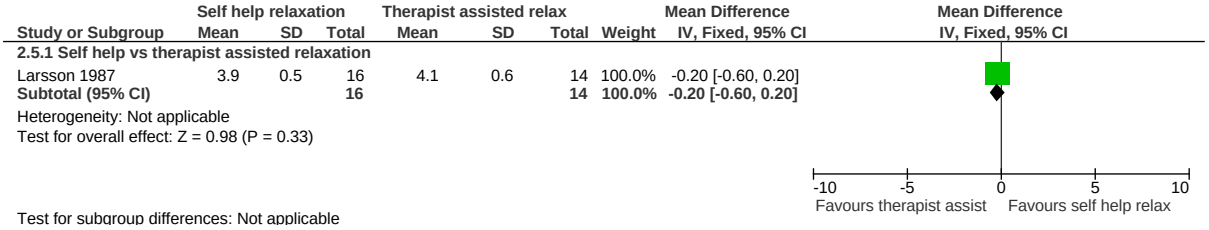
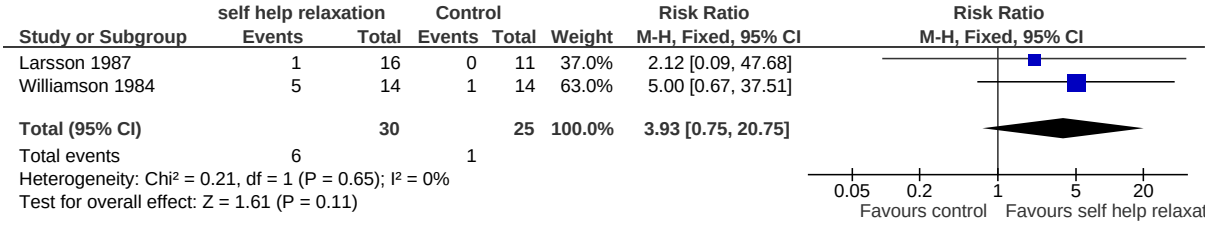


Figure 212: Patient's perception of the usefulness of the programme



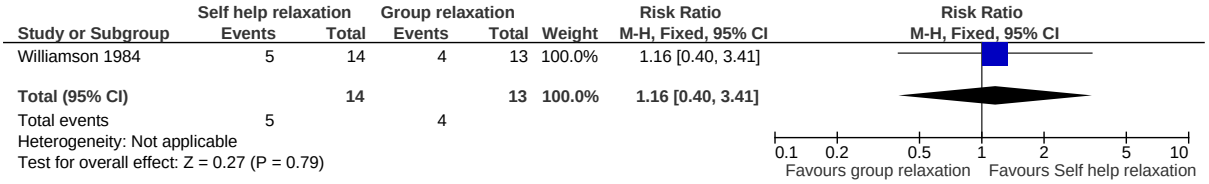
G.2.14.2 Self help vs control

Figure 213: Responder rate



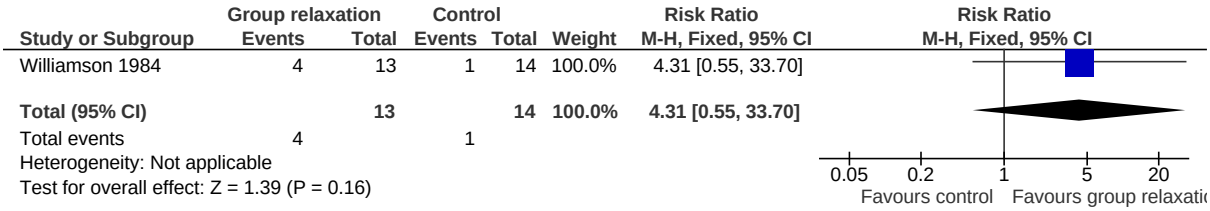
G.2.14.3 Self help relaxation vs group relaxation

Figure 214: Responder rate



G.2.14.4 Group relaxation vs control

Figure 215: Responder rate



G.3 Management of medication overuse headache

G.3.1.1 Withdrawal treatment vs prophylactic treatment

Figure 216: Change in headache days at 3 months

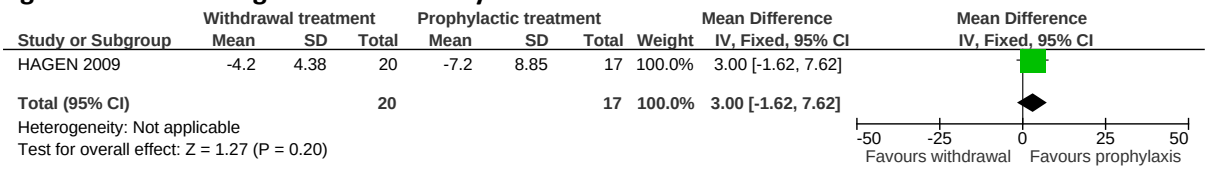


Figure 217: Change in headache days 12 months

Study or Subgroup	Withdrawal treatment Mean	SD	Total	Prophylactic treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HAGEN 2009	-5.1	10.9	20	-10.3	8.75	17	100.0%	5.20 [-1.13, 11.53]
Total (95% CI)			**20**			**17**	**100.0%**	**5.20 [-1.13, 11.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)

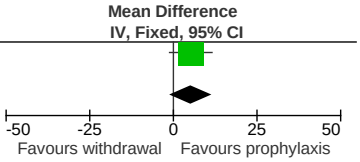


Figure 218: Responder rate 12 months

Study or Subgroup	Withdrawal treatment Events	Total	Prophylactic treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
HAGEN 2009	4	14	9	16	100.0%	0.51 [0.20, 1.29]
Total (95% CI)		**14**		**16**	**100.0%**	**0.51 [0.20, 1.29]**
Total events	4		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)

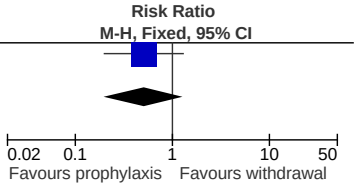


Figure 219: Change in mental health component score of SF12 [MCS 12]at 12 months

Study or Subgroup	Withdrawal treatment Mean	SD	Total	Prophylactic treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HAGEN 2009	14.6	18.27	20	13.9	23.14	17	100.0%	0.70 [-12.91, 14.31]
Total (95% CI)			**20**			**17**	**100.0%**	**0.70 [-12.91, 14.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)

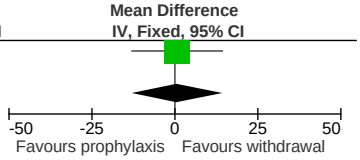


Figure 220: Change in physical health component score of SF12 [MCS 12]at 12 months

Study or Subgroup	Withdrawal treatment Mean	SD	Total	Prophylactic treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HAGEN 2009	6.5	19.23	20	20.2	27.33	17	100.0%	-13.70 [-29.19, 1.79]
Total (95% CI)			**20**			**17**	**100.0%**	**-13.70 [-29.19, 1.79]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)

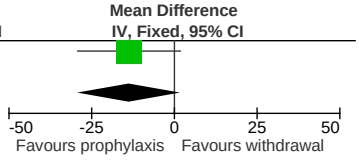


Figure 221: Change in days with acute medication per month at 3 months

Study or Subgroup	Withdrawal treatment Mean	SD	Total	Prophylactic treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HAGEN 2009	-19.1	8.97	20	-13.2	10.89	17	100.0%	-5.90 [-12.40, 0.60]
Total (95% CI)			**20**			**17**	**100.0%**	**-5.90 [-12.40, 0.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.78 (P = 0.08)

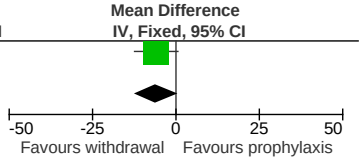
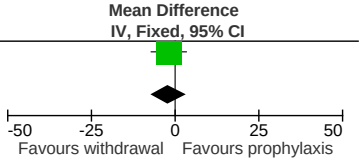


Figure 222: Change in days with acute medication per month at 12 months

Study or Subgroup	Withdrawal treatment Mean	SD	Total	Prophylactic treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HAGEN 2009	-16.1	10.68	20	-14.2	4.77	17	100.0%	-1.90 [-7.10, 3.30]
Total (95% CI)			**20**			**17**	**100.0%**	**-1.90 [-7.10, 3.30]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



G.3.1.2 Outpatient vs inpatient withdrawal of medication

Figure 223: Responder rate

Study or Subgroup	Outpatient tt. Events	Total	Inpatient tt. Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CREACH2011	16	34	14	32	32.5%	1.08 [0.63, 1.83]
ROSSI2006	28	39	30	39	67.5%	0.93 [0.72, 1.21]
Total (95% CI)		**73**		**71**	**100.0%**	**0.98 [0.76, 1.26]**
Total events	44		44			

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)

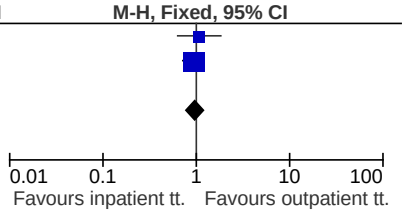


Figure 224: Change in headache days per month

Study or Subgroup	Outpatient tt. Mean	SD	Total	Inpatient tt. Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
SUHR 1999	9.6	10.1	41	12.6	11.3	60	100.0%	-3.00 [-7.21, 1.21]
Total (95% CI)			**41**			**60**	**100.0%**	**-3.00 [-7.21, 1.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)

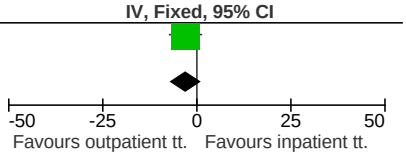


Figure 225: Relapse to MOH within 1 year

Study or Subgroup	Outpatient tt. Events	Total	Inpatient tt. Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ROSSI2006	6	26	7	28	100.0%	0.92 [0.36, 2.39]
Total (95% CI)		**26**		**28**	**100.0%**	**0.92 [0.36, 2.39]**
Total events	6		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)

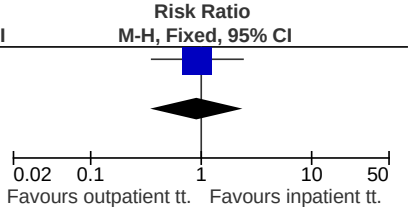


Figure 226: Relapse to MOH within 5 years

Study or Subgroup	Outpatient tt. Events	Total	Inpatient tt. Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SUHR 1999	6	41	15	60	100.0%	0.59 [0.25, 1.38]
Total (95% CI)		**41**		**60**	**100.0%**	**0.59 [0.25, 1.38]**
Total events	6		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

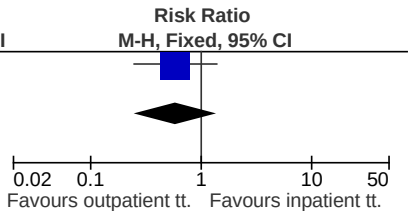
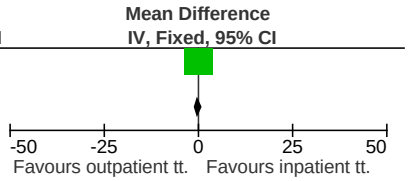


Figure 227: Change in mean headache intensity

Study or Subgroup	Outpatient tt. Mean	SD	Total	Inpatient tt. Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
SUHR 1999	6.4	2.6	41	6.5	2.2	60	100.0%	-0.10 [-1.07, 0.87]
Total (95% CI)			**41**			**60**	**100.0%**	**-0.10 [-1.07, 0.87]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)



G.4 Management during pregnancy and contraceptive use

G.4.1 Management of primary headaches during pregnancy

G.4.1.1 Adverse events in pregnant girls and women with primary headache taking triptans

Figure 228: Spontaneous abortion

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
SCHUHAIBER 1998	11	96	6	96	1.94 [0.69, 5.48]

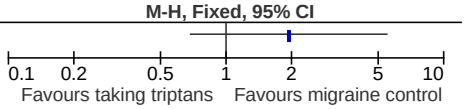


Figure 229: Therapeutic abortion

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
SCHUHAIBER 1998	4	96	2	96	2.04 [0.37, 11.43]

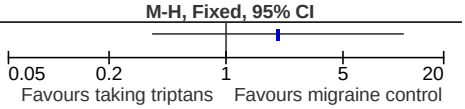


Figure 230: Gestational age <37 weeks

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
NEZVALOVA 2010	86	1535	30	373	0.68 [0.44, 1.05]
OLESON 2000	5	34	3	89	4.94 [1.11, 21.97]
SCHUHAIBER 1998	8	96	16	96	0.45 [0.18, 1.12]

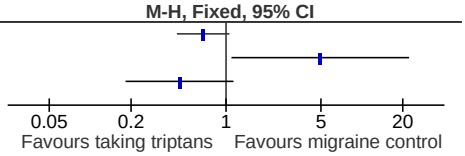


Figure 231: Major birth defects

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
NEZVALOVA 2010	46	1535	11	373	1.02 [0.52, 1.98]
SCHUHAIBER 1998	1	82	1	90	1.10 [0.07, 17.86]

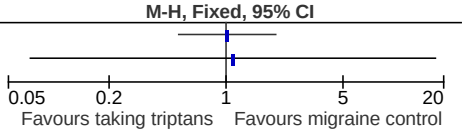


Figure 232: Any malformations

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
NEZVALOVA 2010	75	1535	22	373	0.82 [0.50, 1.34]

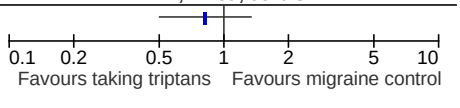


Figure 233: Stillbirth

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
NEZVALOVA 2010	0	1535	2	373	0.05 [0.00, 1.01]

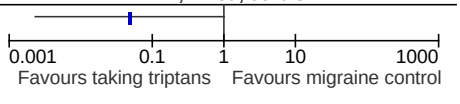


Figure 234: Perinatal death

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
NEZVALOVA 2010	6	1535	3	373	0.48 [0.12, 1.94]

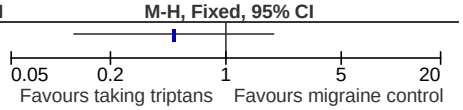


Figure 235: Death during first 12 months of life

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
NEZVALOVA 2010	5	1535	0	373	2.68 [0.15, 48.65]

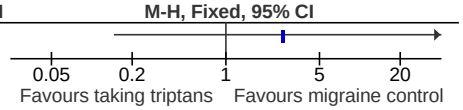


Figure 236: Low birth weight (<2500g)

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
NEZVALOVA 2010	65	1535	19	373	0.82 [0.49, 1.39]
OLESON 2000	1	34	5	89	0.51 [0.06, 4.52]

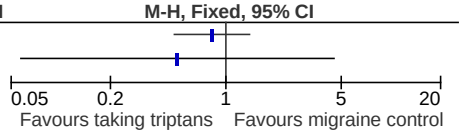


Figure 237: APGAR score <7 at 1 minute

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
NEZVALOVA 2010	88	1535	18	373	1.20 [0.71, 2.02]

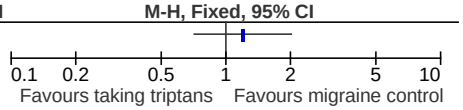
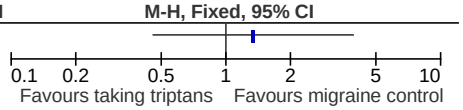


Figure 238: APGAR score <7 at 5 minutes

Study or Subgroup	Taking triptans Events	Total	Migraine control Events	Total	Odds Ratio M-H, Fixed, 95% CI
NEZVALOVA 2010	22	1535	4	373	1.34 [0.46, 3.92]



G.4.1.2 Adverse events in pregnant girls and women taking verapamil

Figure 239: Miscarriage

Study or Subgroup	Verapamil Events	Total	No CCB Events	Total	Odds Ratio M-H, Fixed, 95% CI
WEBER 2008	4	62	59	806	0.87 [0.31, 2.49]

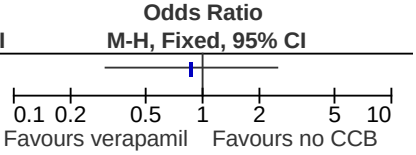


Figure 240: Still births (excluding elective termination of pregnancy)

Study or Subgroup	Verapamil Events	Total	No CCB Events	Total	Odds Ratio M-H, Fixed, 95% CI
WEBER 2008	1	62	6	806	2.19 [0.26, 18.45]

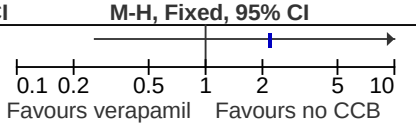


Figure 241: Elective termination of pregnancy (ETOP)

Study or Subgroup	Verapamil Events	Total	No CCB Events	Total	Odds Ratio M-H, Fixed, 95% CI
WEBER 2008	4	62	30	806	1.78 [0.61, 5.24]

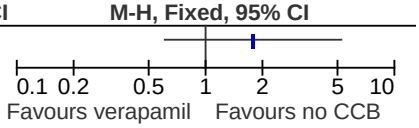


Figure 242: Preterm children

Study or Subgroup	Verapamil Events	Total	No CCB Events	Total	Odds Ratio M-H, Fixed, 95% CI
WEBER 2008	12	62	47	806	3.88 [1.93, 7.77]

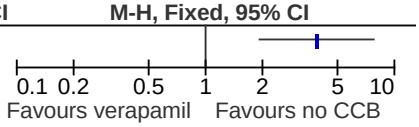


Figure 243: All birth defects

Study or Subgroup	Verapamil Events	Total	No CCB Events	Total	Odds Ratio M-H, Fixed, 95% CI
WEBER 2008	6	62	33	806	2.51 [1.01, 6.24]

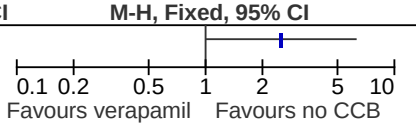
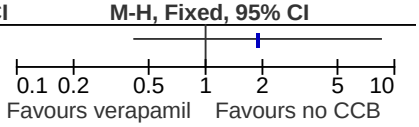


Figure 244: Major birth defects

Study or Subgroup	Verapamil Events	Total	No CCB Events	Total	Odds Ratio M-H, Fixed, 95% CI
WEBER 2008	2	62	14	806	1.89 [0.42, 8.49]



G.4.2 Combined hormonal contraceptive use in girls and women with migraine

G.4.2.1 Migraine with oral contraceptive use vs No migraine or oral contraceptive use

Figure 245: Ischaemic stroke

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
CHANG 1999	2.8273	0.932	16.90 [2.72, 105.00]

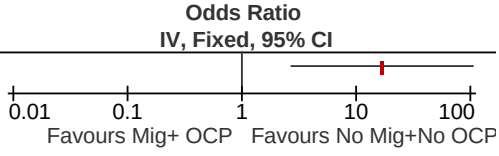
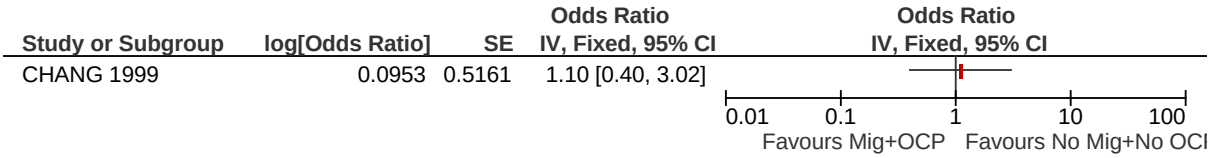


Figure 246: Haemorrhagic stroke



G.4.2.2 Migraine without oral contraceptive vs No migraine or oral contraceptive use

Figure 247: Ischaemic stroke

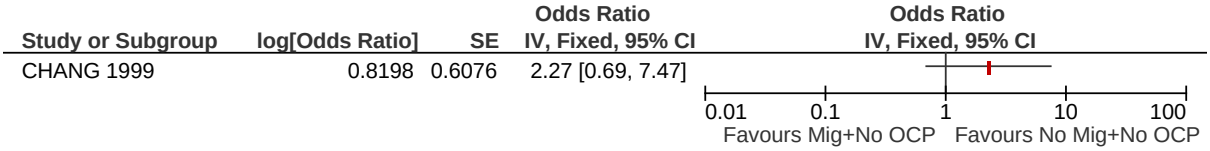
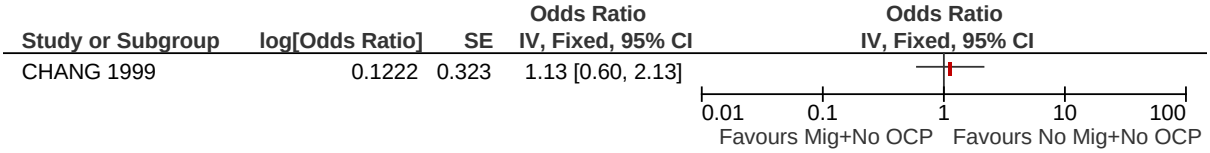
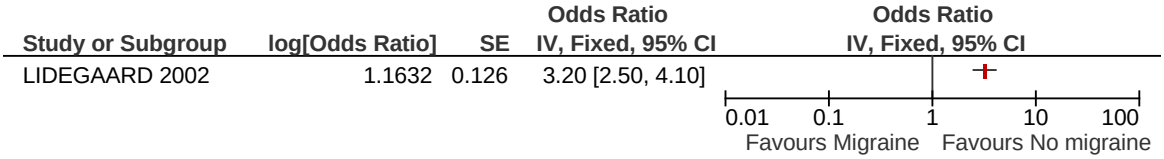


Figure 248: Haemorrhagic stroke



G.4.2.3 Migraine vs No migraine (adjusted for oral contraceptive use)

Figure 249: Stroke



Appendix H: 2x2 tables for diagnostic reviews

H.1 Identifying people with primary headaches

Reference test: Clinician diagnosis according to ICHD criteria

New diagnostic test: Questionnaire, as stated in figure heading

H.1.1 Migraine

Figure 250: ID Migraine vs clinician diagnosis – Headache centres

		Reference test		
		+ test result	- test result	Totals
New diagnostic test	+ test result	**143**	**20**	163
	- test result	**7**	**52**	59
	Totals	150	72	222

Source: Brighina 2007

Figure 251: ID Migraine vs clinician diagnosis - Neurology

		Reference test		
		+ test result	- test result	Totals
New diagnostic test	+ test result	**297**	**50**	347
	- test result	**41**	**142**	183
	Totals	338	192	530

Source: Ertas 2003

Figure 252: ID Migraine vs clinician diagnosis – Ear Nose and Throat outpatients

		Reference test		
		+ test result	**- test result**	**Totals**
New diagnostic test	**+ test result**	**123**	**31**	154
	- test result	**123**	**31**	154
	Totals	246	62	308

Source: Ertas 2003

Figure 253: ID Migraine vs clinician diagnosis - Opthalmology clinic

		Reference test		
		+ test result	**- test result**	**Totals**
New diagnostic test	**+ test result**	**119**	**19**	138
	- test result	**30**	**60**	90
	Totals	149	79	228

Source: Ertas 2003

Figure 254: ID Migraine vs clinician diagnosis – Headache clinics

		Reference test		
		+ test result	**- test result**	**Totals**
New diagnostic test	**+ test result**	**78**	**19**	97
	- test result	**5**	**29**	34
	Totals	83	48	131

Source: GilGouveia 2010

Figure 255: ID Migraine vs clinician diagnosis – Neurology

		Reference test		
		+ test result	**- test result**	**Totals**
New diagnostic test	**+ test result**	**842**	**329**	1171
	- test result	**75**	**570**	645
	Totals	917	899	1816

Source: Karli 2007

Figure 256: ID Migraine vs clinician diagnosis – GP clinics

		Reference test		
		+ test result	**- test result**	**Totals**
New diagnostic test	**+ test result**	**189**	**34**	223
	- test result	**173**	**188**	361
	Totals	362	222	584

Source: Khu 2008

Figure 257: ID Migraine vs clinician diagnosis – TMJ and orofacial pain clinics

		Reference test		
		+ test result	**- test result**	**Totals**
New diagnostic test	**+ test result**	**19**	**3**	22
	- test result	**14**	**140**	154
	Totals	33	143	176

Source: Kim 2006

Figure 258: ID Migraine vs clinician diagnosis – Primary care

		Reference test		
		+ test result	- test result	Totals
New diagnostic test	+ test result	**289**	**23**	312
	- test result	**68**	**71**	139
	Totals	357	94	451

Source: Lipton 2003B

Figure 259: ID Migraine vs clinician diagnosis – Headache clinic post emergency department discharge

		Reference test		
		+ test result	- test result	Totals
New diagnostic test	+ test result	**172**	**3**	175
	- test result	**11**	**13**	24
	Totals	183	16	199

Source: Mostardini 2009

Figure 260: Structured migraine interview vs clinician diagnosis – specialist headache clinic

		Reference test		
		+ test result	- test result	Totals
New diagnostic test	+ test result	**138**	**5**	143
	- test result	**20**	**7**	27
	Totals	158	12	170

Source: Samaan 2010

H.1.2 Cluster headache

Figure 261: Cluster headache screening questionnaire vs clinician diagnosis – headache clinic

		Reference test		
		+ test result	- test result	Totals
New diagnostic test	+ test result	**29**	**0**	29
	- test result	**8**	**59**	67
	Totals	37	59	96

Source: Dousset 2009

H.2 Headache diaries as an aid to diagnosis

Reference test: Clinician diagnosis according to ICHD criteria

New diagnostic test: Headache diary

H.2.1 Migraine

Figure 262: Diary vs clinician diagnosis - Migraine

		Reference test		
		+ test result	- test result	Totals
New diagnostic test	+ test result	**28**	**3**	31
	- test result	**5**	**9**	14
	Totals	33	12	45

Source: Phillip et al. 2007[628]

Figure 263: Diary vs clinician diagnosis – migraine without aura

		Reference test		
		+ test	- test	Totals
New diagnostic test	+ test result	**50**	**4**	54
	- test result	**3**	**4**	7
	Totals	53	8	61

Source: Russell et. al 1992[679]

Figure 264: Diary vs clinician diagnosis – Migraine with aura

		Reference test		
		+ test	- test	Totals
New diagnostic test	+ test result	**8**	**14**	22
	- test result	**3**	**36**	39
	Totals	11	50	61

Source: Russell et al. 1992[679]

Figure 265: Diary vs clinician diagnosis - Migraine

		Reference test		
		+ test	- test	Totals
New diagnostic test	+ test result	**59**	**5**	64
	- test result	**5**	**7**	12
	Totals	64	12	76

Source: Tassorelli et al. 2008[772]

H.2.2 Tension type headache

Figure 266: Diary vs clinician diagnosis - TTH

		Reference test		
		+ test	- test	Totals
New diagnostic test	+ test result	**37**	**1**	38
	- test result	**5**	**2**	7
	Totals	42	3	45

Source: Phillip et al. 2007[628]

Figure 267: Diary vs clinician diagnosis – Chronic TTH

		Reference test		
		+ test	**- test**	**Totals**
New diagnostic test	**+ test result**	**37**	**1**	38
	- test result	**5**	**2**	7
	Totals	42	3	45

Source: Phillip et al. 2007[628]

Figure 268: Diary vs clinician diagnosis – Episodic TTH

		Reference test		
		+ test	**- test**	**Totals**
New diagnostic test	**+ test result**	**16**	**23**	39
	- test result	**3**	**19**	22
	Totals	19	42	61

Source: Russell et al. 1992[679]

Figure 269: Diary vs clinician diagnosis – Chronic TTH

		Reference test		
		+ test	**- test**	**Totals**
New diagnostic test	**+ test result**	**4**	**0**	4
	- test result	**15**	**42**	57
	Totals	19	42	61

Source: Russell et al. 1992[679]

Figure 270: Diary vs clinician diagnosis - TTH

		Reference test		
		+ test	**- test**	**Totals**
New diagnostic test	**+ test result**	**21**	**20**	41
	- test result	**7**	**28**	35
	Totals	28	48	76

Source: Tassorelli et al. 2008[772]

H.2.3 Medication overuse headache

Figure 271: Diary vs clinician diagnosis – medication overuse headache

		Reference test		
		+ test	**- test**	**Totals**
New diagnostic test	**+ test result**	**12**	**8**	20
	- test result	**4**	**52**	56
	Totals	16	60	76

Source: Tassorelli et al. 2008[772]

Appendix I: Network meta-analysis of pharmacological interventions for the acute treatment of migraine

I.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in chapter 11 and forest plots in appendix G.2.2) does not help inform which intervention is most effective in the treatment of acute migraine. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different acute treatment, in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial (for example, NSAID vs ergot).
- There are frequently multiple overlapping comparisons (for example, triptan vs NSAID, triptan vs triptan and NSAID and NSAID vs triptan and NSAID), that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions. In this case, in order of efficacy, defined as:

- the proportion of people achieving headache response at up to 2 hours
- the proportion of people achieving freedom from pain at up to 2 hours
- the proportion of people achieving sustained headache response at 24 hours
- the proportion of people achieving sustained freedom from pain at 24 hours.

The analysis also provided estimates of effect (with 95% credible intervals) for each intervention compared to one another and compared to a single baseline risk (in this case the baseline treatment was triptan). These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling presented in appendix K.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term “network” better describes the data structure, whereas “mixed treatments” could easily be misinterpreted as referring to combinations of treatments.

I.2 Methods

I.2.1 Study selection and data collection

To estimate the relative risks, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

From the outset, we sought to minimise any clinical or methodological heterogeneity by focusing the analysis on RCTs with comparable routes of administration of treatments, identifying equivalent outcomes and including only RCTs that presented data for each headache attack treated (in cases where people treated multiple headache attacks with each intervention). All of the dosages of drugs in the included RCTs were within the therapeutic range as indicated by the BNF. In consultation with the GDG we chose to perform an NMA for acute treatment of migraine by oral, subcutaneous or nasal administration. The evidence on acute treatment by these routes included multiple comparisons and an NMA would allow us to synthesize the evidence in a more comprehensive way. Treatments administered by intravenous or intramuscular routes were excluded from this analysis as it was agreed these clinician administered treatments were not comparable with the other treatments which could be self-administered by participants.

As such, four networks of evidence were identified, defined by outcome measure:

- Network 1: Proportion of people achieving headache response at up to 2 hours
- Network 2: Proportion of people achieving freedom from pain at up to 2 hours
- Network 3: Proportion of people maintaining sustained headache response at 24 hours
- Network 4: Proportion of people maintaining sustained freedom from pain at 24 hours.

I.2.2 Outcome measures

The NMA evidence reviews for interventions considered four clinical efficacy outcomes identified from the clinical evidence review; headache response at 2 hours, pain free at up to 2 hours, sustained headache response at 24 hours and sustained pain free at 24 hours. Time to freedom from pain, percentage reporting serious adverse events and functional health status were not included in the list of outcome measures as they were infrequently reported across the studies. The GDG considered that headache response and pain freedom at 2 and 24 hours were the most important clinical outcomes for testing acute migraine treatment efficacy.

Outcome measures were calculated on an available case basis (i.e. the analysis was based on the number of analysed headache attacks), regardless of how the original study investigators analysed their data. Using available case analysis was most appropriate for these studies due to the numbers of people randomised who then did not suffer from a headache attack during the study period, and therefore would count as missing data had intention to treat analysis been used.

I.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical evidence review already presented in chapter 11 of the full guideline and in appendix E. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in each network are shown in Table 1.

Table 1: Treatments included in network meta-analysis

Network 1: Headache response at up to 2 hours	Network 2: Pain free at up to 2 hours	Network 3: Sustained headache response at 24 hours	Network 4: Sustained freedom from pain at 24 hours
Triptans	Triptans	Triptans	Triptans
NSAIDs	NSAIDs	NSAIDs	NSAIDs
Paracetamol	Paracetamol	Paracetamol	Paracetamol
Ergots	Ergots	Ergots	Ergots
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	-	-	-

The details of these interventions can be found in the clinical evidence review in chapter 11 of the full guideline and evidence tables in appendix E.

I.2.4 Baseline risk

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.

Baseline odds were derived by the logistic regression in WinBUGS. This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of baseline and relative effects is accounted for in the model. This method produced baseline odds [mean (SD)] of 0.36 (0.17) for headache response at up to two hours, -0.89 (0.12) for freedom from pain at up to 2 hours, -0.37 (0.23) for sustained headache response at 24 hours and -1.42 (0.16) for sustained freedom from pain at 24 hours.

I.2.5 Statistical analysis

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.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome subgroup, a diagram of the evidence network was produced in Figure 272 - Figure 275 and presented in section I.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For the analyses, a series of 50,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 11, and Appendix G.2.2).

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:

$$\tilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$\boldsymbol{p} = \frac{\boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}{\mathbf{1} + \boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability ($\boldsymbol{p_b}$) to get treatment specific relative risks ($\boldsymbol{rr_b}$):

$$\boldsymbol{p_b} = \frac{\boldsymbol{e}^{\boldsymbol{BO}}}{\mathbf{1} + \boldsymbol{e}^{\boldsymbol{BO}}}$$

$$\boldsymbol{rr_b} = \frac{\boldsymbol{p}}{\boldsymbol{p_b}}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

We also calculated the overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

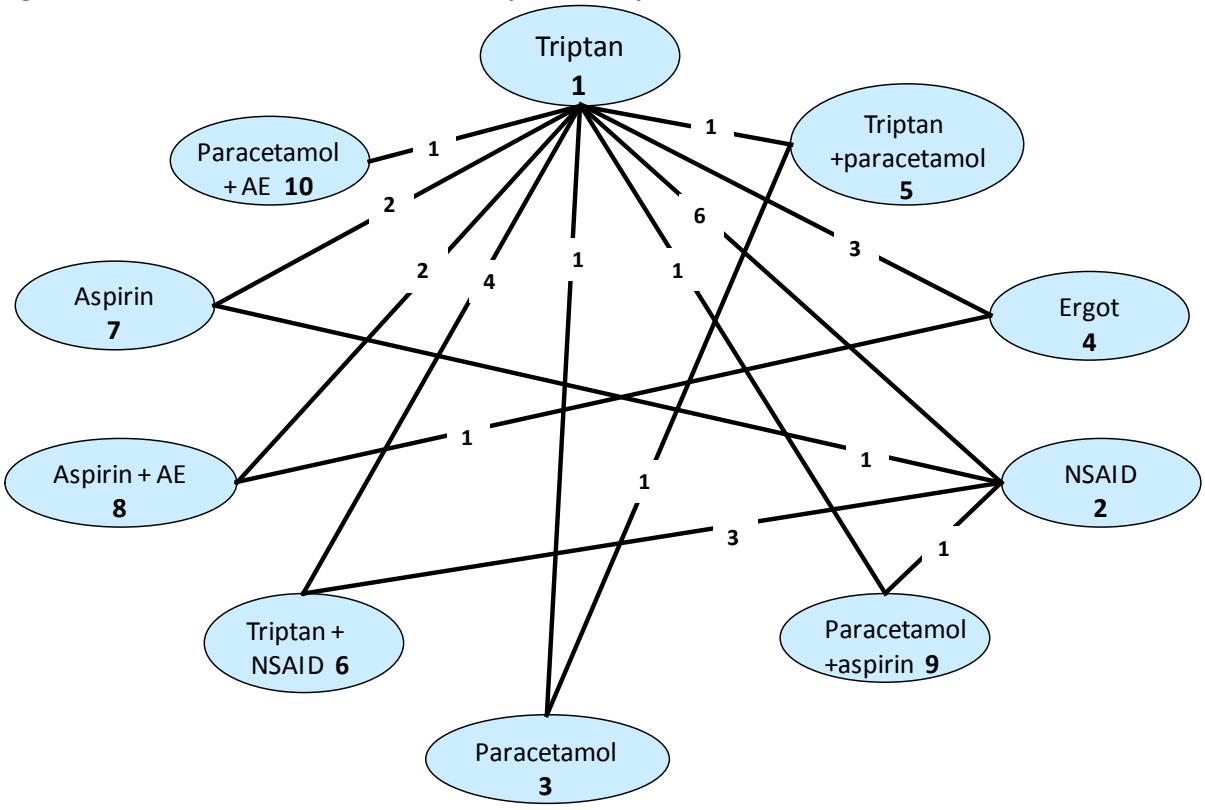
- Different populations (e.g. gender, age)
- Different interventions (doses)
- Different routes of administration.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the relative risks from the direct evidence (from pair-wise meta-analysis) to the relative risks from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the relative risk from the NMA did not fit within the confidence interval of the relative risk from the direct comparison. No inconsistency was identified.

I.3 Results

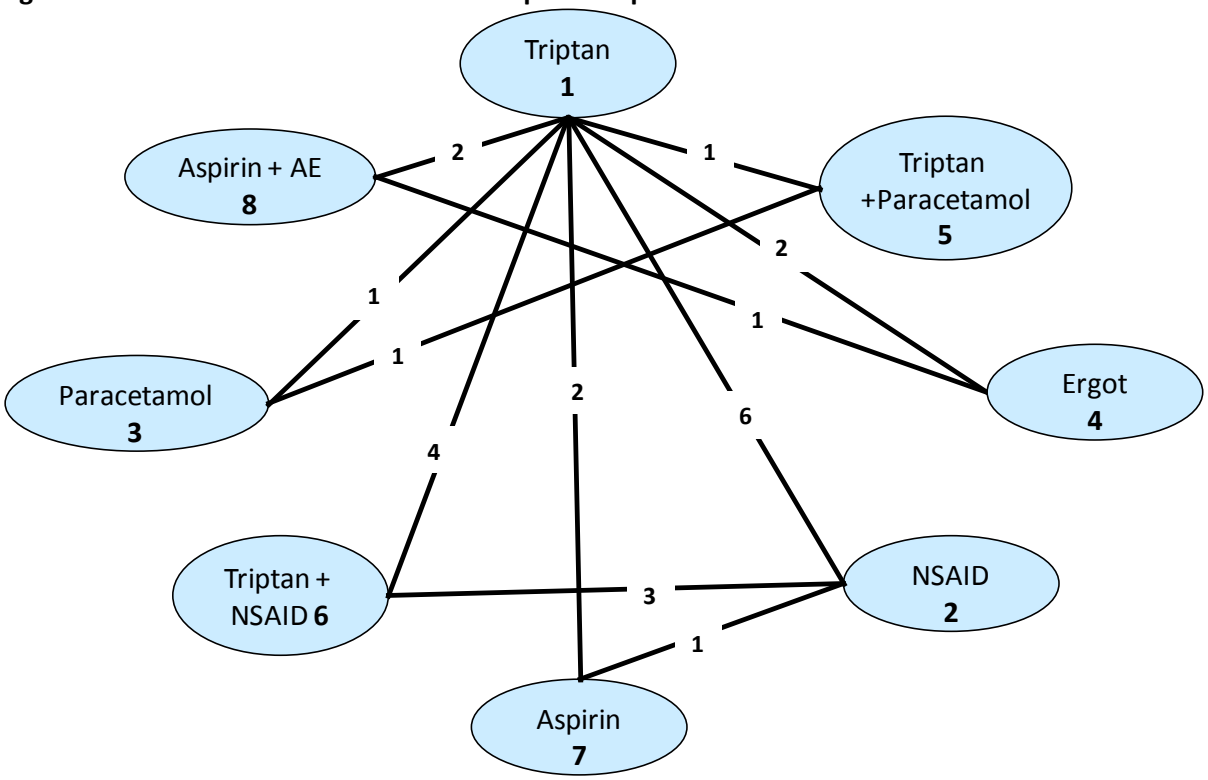
A total of 19 studies from the original evidence review met the inclusion criteria for at least one network. Figure 272 - Figure 275 show the four networks created by eligible comparisons for each NMA. The number on the line linking two treatments indicates the number of studies included that assessed that direct comparison.

Figure 272: Network for headache response at up to 2 hours



AE=Antiemetic

Figure 273: Network for freedom from pain at up to 2 hours



AE=Antiemetic

Figure 274: Network for sustained headache response at 24 hours

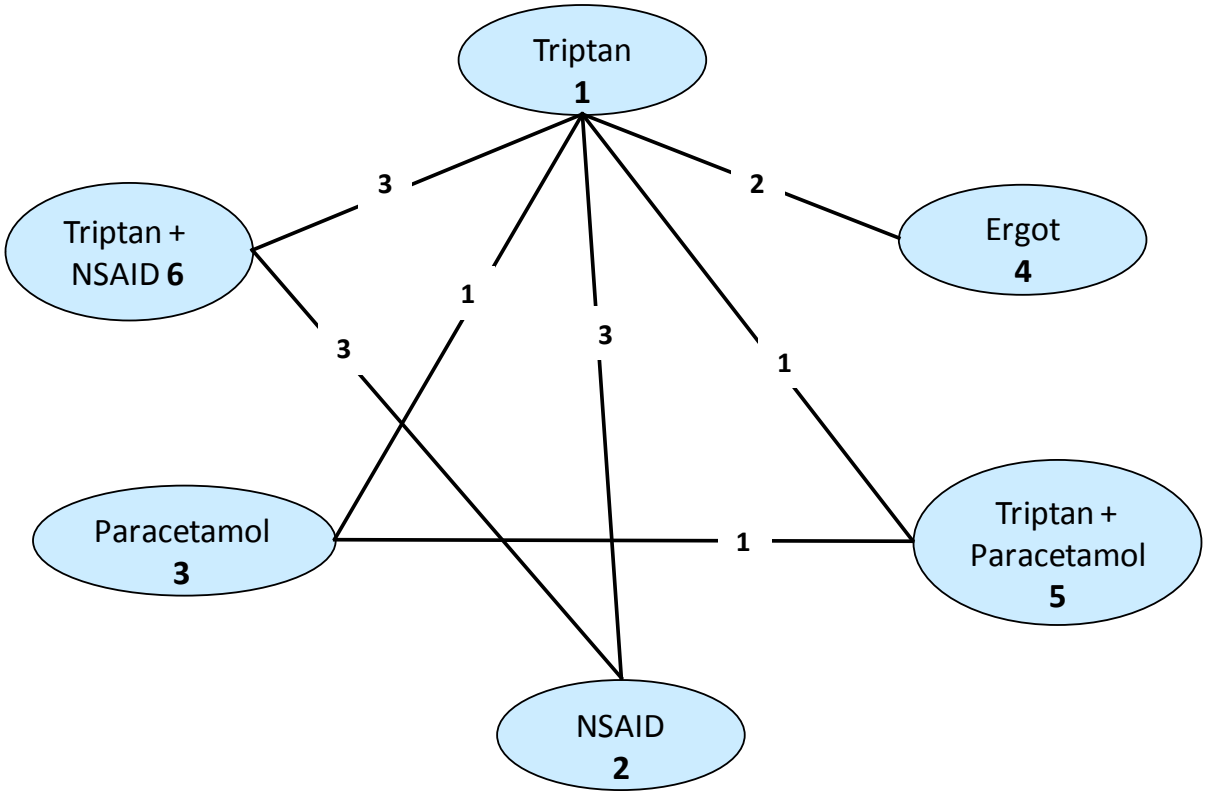
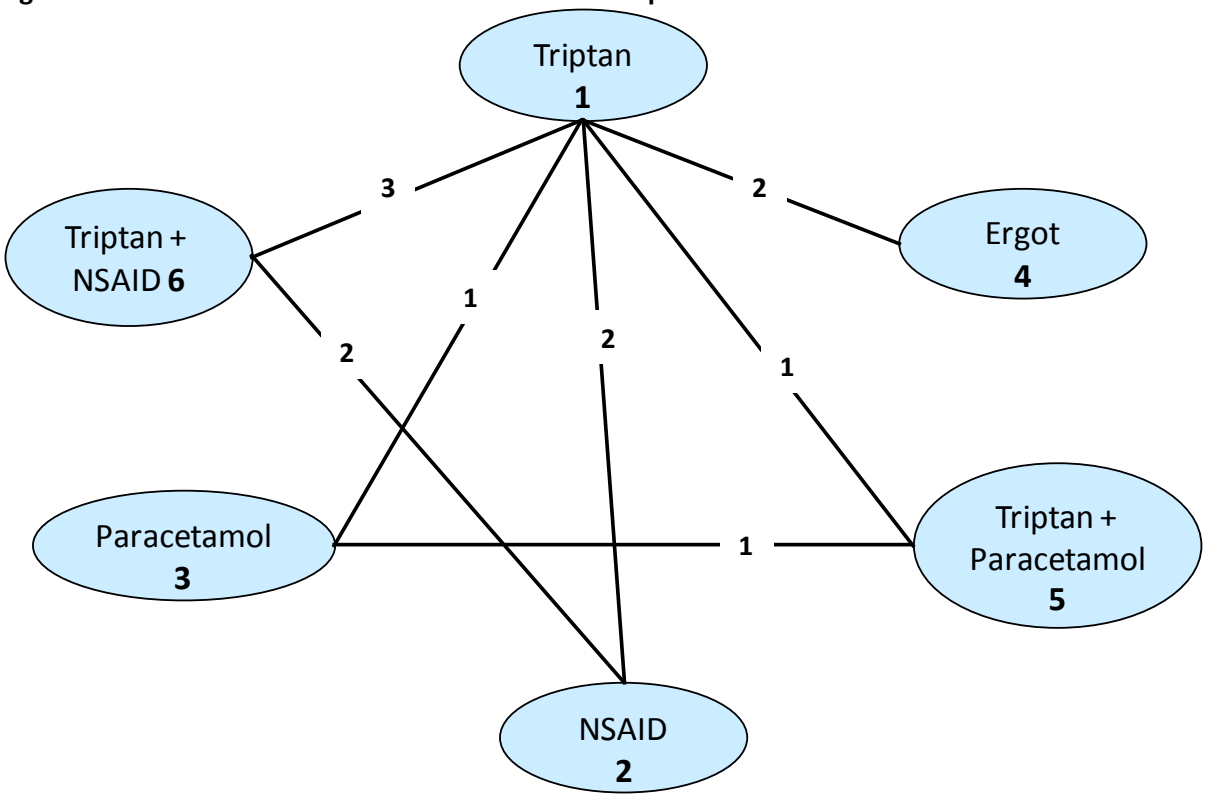


Figure 275: Network for sustained freedom from pain at 24 hours



The trial data from the 18 studies included in the NMA for headache response at up to 2 hours are shown in Table 2. The trial data from the 13 studies included in the NMA for pain free at up to 2 hours are presented in Table 3. The trial data from the six studies included in the NMA for sustained headache response at 24 hours are presented in Table 4. Data from the six studies for the NMA for sustained pain free at 24 hours are presented in Table 5.

Table 2: Study data for headache response at up to 2 hours

Study	Active Treatment	Comparator1	Comparator2	Active treatment		Comparator 1		Comparator 2	
				N	NR	N	NR	N	NR
Brandes 2007A i [105,106]	Triptan	NSAID	Triptan + NSAID	200	361	157	356	237	364
Brandes 2007A ii [105,106]	Triptan	NSAID	Triptan + NSAID	182	362	158	364	207	362
Diener 2002A [217,219]	Triptan	Ergot	-	253	415	65	197	-	-
Diener 2004 [213,217]	Triptan	NSAID	Aspirin	125	224	127	221	116	221
Diener 2004B [216,217]	Triptan	Aspirin	-	66	135	72	146	-	-
Dowson 2000 [233,236]	Triptan	Paracetamol + antiemetic	-	39	117	43	118	-	-
Freitag 2008A [287,291]	Triptan	Paracetamol	Triptan + paracetamol	33	43	30	43	43	48

Study	Active Treatment	Comparator1	Comparator2	Active treatment		Comparator 1		Comparator 2	
Goldstein 2005 [329,330]	Triptan	Paracetamol + aspirin	-	30	46	42	50	-	-
Goldstein 2006 [329,331]	NSAID	Paracetamol + aspirin	-	413	666	448	669	-	-
Lainez 2007 [463,464]	Triptan	Ergot	-	105	182	85	182	-	-
LeJeunne 1999 [484]	Ergot	Aspirin + antiemetic	-	48	132	73	134	-	-
Misra 2007 [561,562]	Triptan	NSAID	-	39	53	28	53	-	-
Myllyla 1998 [577]	Triptan	NSAID	-	33	42	33	43	-	-
Osamscs 1992 [785]	Triptan	Aspirin + antiemetic	-	74	133	62	138	-	-
Schoenen 2008 [705,706]	Triptan	Triptan + NSAID	-	34	90	32	90	-	-
Smith 2005 [742,743]	Triptan	NSAID	Triptan + NSAID	111	226	114	248	163	250
Tfelthansen 1995 [780]	Triptan	Aspirin + antiemetic	-	63	119	76	133	-	-
Winner 1996 [855,857]	Triptan	Ergot	-	128	150	106	145	-	-

N; number of events, NR; number randomised

Eighteen studies were included for headache response at up to 2 hours (Table 2). The minimum age of participants in all studies was 18 years with the exception of Misra (2007) [561,562] which included children aged 12 years and older, but had a mean age of 30.5, range 16 – 58).

The majority of treatments were oral administration, with the exception of Winner (1996) [855,857] in which both triptan and ergot were administered by subcutaneous injection into the thigh. All treatments, whether oral or subcutaneous, were self-administered by the participants themselves and were given in accordance with the usual therapeutic dosages as recommended by the British National Formulary (BNF)[402].

Table 3: Study data for freedom from pain at up to 2 hours

Study	Active Treatment	Comparator 1	Comparator 2	Active treatment		Comparator 1		Comparator 2	
				N	NR	N	NR	N	NR
Brandes 2007A i [105,106]	Triptan	NSAID	Triptan + NSAID	90	362	53	356	125	364
Brandes 2007A ii [105,106]	Triptan	NSAID	Triptan + NSAID	82	362	57	364	107	362
Diener 2002A [217,219]	Triptan	Ergot	-	137	415	20	197	-	-
Diener 2004 [213,217]	Triptan	NSAID	Aspirin	83	224	79	221	60	221
Diener 2004B [216,217]	Triptan	Aspirin	-	33	135	37	146	-	-

Study	Active Treatment	Comparator 1	Comparator 2	Active treatment		Comparator 1		Comparator 2	
Freitag 2008A [287,291]	Triptan	Paracetamol	Triptan + paracetamol	17	43	11	43	23	48
Lainez 2007 [463,464]	Triptan	Ergot	-	38	182	25	182	-	-
LeJeunne 1999 [484]	Ergot	Aspirin + antiemetic	-	11	132	27	134	-	-
Misra 2007 [561,562]	Triptan	NSAID	-	20	53	16	53	-	-
Myllyla 1998 [577]	Triptan	NSAID	-	21	53	16	53	-	-
Osamscs 1992 [785]	Triptan	Aspirin + antiemetic	-	35	133	19	138	-	-
Schoenen 2008 [705,706]	Triptan	Triptan + NSAID	-	26	90	37	90	-	-
Smith 2005 [742,743]	Triptan	NSAID	Triptan + NSAID	46	226	45	248	85	250
Tfelthansen 1995 [780]	Triptan	Aspirin + antiemetic	-	36	122	29	135	-	-

N; number of events, NR; number randomised

Fourteen studies were included for pain free at up to 2 hours (Table 3). The minimum age of participants in all studies was 18 years with the exception of Misra (2007) [561,562] which included children aged 12 years and older, but had a mean age of 30.5, range 16 – 58).

All treatments were administered orally and were given in accordance with the usual therapeutic dosages as recommended by the BNF[402].

Table 4: Study data for sustained headache response at 24 hours

Study	Active Treatment	Comparator 1	Comparator 2	Active treatment		Comparator 1		Comparator 2	
				N	NR	N	NR	N	NR
Brandes 2007A i [105,106]	Triptan	NSAID	Triptan + NSAID	127	362	107	356	174	364
Brandes 2007A ii [105,106]	Triptan	NSAID	Triptan + NSAID	121	362	102	264	158	362
Diener 2002A [217,219]	Triptan	Ergot	-	191	419	55	201	-	-
Freitag 2008A [287,291]	Triptan	Paracetamol	Triptan + Paracetamol	23	43	18	43	30	48
Smith 2005 [742,743]	Triptan	NSAID	Triptan + NSAID	66	226	62	248	115	250
[798]	Triptan	Ergot	-	144	266	104	266	-	-

N; number of events, NR; number randomised

Six studies were included for sustained headache response at 24 hours (Table 4). The minimum age of participants in all studies was 18 years.

The majority of treatments were oral administration, with the exception of Touchon (1996) [855,857] in which the triptan was administered as a subcutaneous injection into the thigh and ergot was in the

form of a nasal spray. All treatments, whether oral, nasal or subcutaneous, were self-administered by the participants themselves and were given in accordance with the usual therapeutic dosages as recommended by the BNF[402].

Table 5: Study data for sustained freedom from pain at 24 hours

Study	Active Treatment	Comparator 1	Comparator 2	Active treatment		Comparator 1		Comparator 2	
				N	NR	N	NR	N	NR
Brandes 2007A i [105,106]	Triptan	NSAID	Triptan + NSAID	59	362	37	356	90	364
Brandes 2007A ii [105,106]	Triptan	NSAID	Triptan + NSAID	51	362	37	364	83	362
Diener 2002A [217,219]	Triptan	Ergot	-	108	419	17	201	-	-
Freitag 2008A [287,291]	Triptan	Paracetamol	Triptan + Paracetamol	10	43	7	43	15	48
Lainez 2007 [463,464]	Triptan	Ergot	-	37	182	21	182	-	-
Schoenen 2008 [705,706]	Triptan	Triptan + NSAID	-	19	90	28	90	-	-

N; number of participants, NR; number randomised

Six studies were included for sustained pain free at 24 hours (Table 5). The minimum age of participants in all studies was 18 years.

All treatments were administered orally and were given in accordance with the usual therapeutic dosages as recommended by the BNF[402].

I.3.1 Network 1: Headache response at up to 2 hours for acute treatment of migraine

Table 6 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

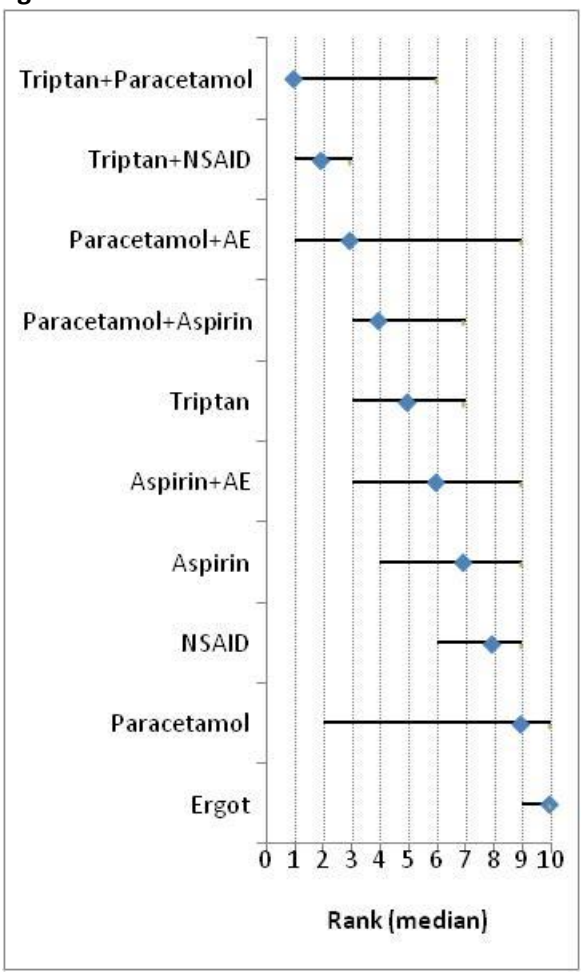
Table 6: Risk ratios for headache response at up to 2 hours

Comparison		Risk ratio	
		Direct (mean)	NMA (median)
Versus triptan	NSAID vs triptan	0.88 (0.82,0.95)	0.90 (0.83,0.96)
	Paracetamol vs triptan	0.91 (0.70,1.17)	0.84 (0.46,1.23)
	Ergot vs triptan	0.73 (0.54,0.98)	0.65 (0.55,0.75)
	Triptan + paracetamol vs triptan	1.17 (0.96,1.41)	1.34 (0.94,1.65)
	Triptan + NSAID vs triptan	1.18 (1.09,1.28)	1.16 (1.09,1.24)
	Aspirin vs triptan	0.97 (0.84,1.11)	0.92 (0.80,1.03)
	Aspirin + antiemetic vs triptan	0.94 (0.70,1.24)	0.95 (0.82,1.06)
	Paracetamol + aspirin vs triptan	1.29 (1.01,1.64)	1.01 (0.90,1.12)
	Paracetamol + antiemetic vs triptan	1.09 (0.77,1.55)	1.05 (0.83,1.26)
Versus	Paracetamol vs NSAID	-	0.94 (0.50,1.38)

Comparison		Risk ratio	
NSAID	Ergot vs NSAID	-	0.72 (0.60,0.84)
	Triptan + paracetamol vs NSAID	-	1.48 (1.04,1.88)
	Triptan + NSAID vs NSAID	1.25 (1.15,1.36)	1.29 (1.19,1.42)
	Aspirin vs NSAID	0.91 (0.77,1.08)	1.02 (0.89,1.16)
	Aspirin + antiemetic vs NSAID	-	1.05 (0.90,1.21)
	Paracetamol + aspirin vs NSAID	1.08 (1.00,1.17)	1.13 (1.03,1.24)
	Paracetamol + antiemetic vs NSAID	-	1.17 (0.91,1.43)
Versus paracetamol	Ergot vs paracetamol	-	0.77 (0.50,1.43)
	Triptan + paracetamol vs paracetamol	1.28 (1.03,1.60)	1.57 (1.09,2.72)
	Triptan + NSAID vs paracetamol	-	1.38 (0.94,2.57)
	Aspirin vs paracetamol	-	1.09 (0.73,2.04)
	Aspirin + antiemetic vs paracetamol	-	1.12 (0.74,2.09)
	Paracetamol + aspirin vs paracetamol	-	1.20 (0.81,2.24)
	Paracetamol + antiemetic vs paracetamol	-	1.25 (0.80,2.36)
Versus ergot	Triptan + paracetamol vs ergot	-	2.06 (1.42,2.78)
	Triptan + NSAID vs ergot	-	1.80 (1.53,2.18)
	Aspirin vs ergot	-	1.43 (1.18,1.75)
	Aspirin + antiemetic vs ergot	1.50 (1.14,1.97)	1.46 (1.24,1.75)
	Paracetamol + aspirin vs ergot	-	1.57 (1.31,1.91)
	Paracetamol + aspirin vs ergot	-	1.63 (1.25,2.11)
Versus triptan + paracetamol	Triptan + NSAID vs triptan + paracetamol	-	0.87 (0.71,1.24)
	Aspirin vs triptan + paracetamol	-	0.69 (0.53,0.99)
	Aspirin + antiemetic vs triptan + paracetamol	-	0.71 (0.54,1.02)
	Paracetamol + aspirin vs triptan + paracetamol	-	0.76 (0.60,1.09)
	Paracetamol + antiemetic vs triptan + paracetamol	-	0.79 (0.57,1.16)
Versus triptan + NSAID	Aspirin vs triptan + NSAID	-	0.79 (0.68,0.90)
	Aspirin + antiemetic vs triptan + NSAID	-	0.81 (0.69,0.93)
	Paracetamol + aspirin vs triptan + NSAID	-	0.87 (0.77,0.96)
	Paracetamol + antiemetic vs triptan + NSAID	-	0.91 (0.71,1.09)
Versus aspirin	Aspirin + antiemetic vs aspirin	-	1.03 (0.85,1.23)
	Paracetamol + aspirin vs aspirin	-	1.10 (0.94,1.30)
	Paracetamol + antiemetic vs aspirin	-	1.14 (0.88,1.44)
Versus aspirin + antiemetic	Paracetamol + aspirin vs aspirin + antiemetic	-	1.07 (0.91,1.28)
	Paracetamol + antiemetic vs aspirin + antiemetic	-	1.12 (0.86,1.41)
Versus Paracetamol + antiemetic	Paracetamol + aspirin vs paracetamol + antiemetic	-	1.04 (0.80,1.29)

Figure **276** shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 10 different interventions being evaluated.

Figure 276: Rank order for treatments based on headache response at up to 2 hours



Mean (SD)

1.44 (1.25)
2.06 (0.60)
4.05 (1.99)
4.49 (1.32)
4.75 (0.97)
6.37 (1.60)
6.96 (1.41)
7.64 (0.95)
7.42 (2.54)
9.82 (0.38)

AE=Antiemetic

Based on the direct comparisons (first results column Table 6), efficacy as assessed by headache response at up to 2 hours favours triptan over NSAID or ergot, triptan in combination with an NSAID over triptan or NSAID, paracetamol in combination with aspirin over triptan alone, triptan in combination with paracetamol over paracetamol alone and aspirin in combination with an antiemetic over ergot. No other treatment effects reached statistical significance. The random effects model used for the NMA is a relatively good fit, with a residual deviance of 55.55 reported. This corresponds fairly well to the total number of trial arms, 41.

The deviance information criteria (DIC) statistics are as follows in Table 7:

Table 7: DIC for headache response at 2 hours – random effects

	Dbar	Dhat	pD	DIC
r	261.969	227.185	34.783	269.752
total	261.969	227.185	34.783	269.752

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

No inconsistency was identified between the direct and NMA results for any comparison. All the median risk ratios from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

I.3.1.1 Evidence statements

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 comination with an NSAID is ranked second, paracetamol in combination with an anti-emetic third, paracetamol in combination with aspsirin 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.

I.3.2 Network 2: Freedom from pain at up to 2 hours for the acute treatment of migraine

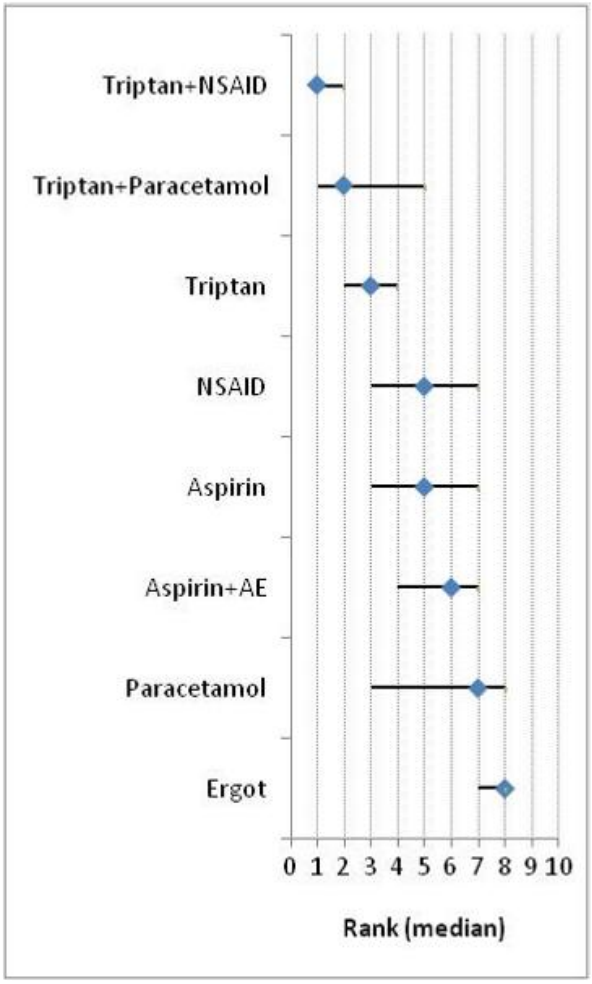
Table 8: Risk ratios for freedom from pain at up to 2 hours

Comparison		Risk ratio	
		Direct (mean)	NMA (median)
Versus triptan	NSAID vs triptan	0.77 (0.67,0.88)	0.78 (0.68,0.90)
	Paracetamol vs triptan	0.65 (0.34,1.21)	0.60 (0.26,1.19)
	Ergot vs triptan	0.45 (0.21,0.95)	0.39 (0.29,0.52)
	Triptan + paracetamol vs triptan	1.21 (0.76,1.94)	1.27 (0.70,2.00)
	Triptan + NSAID vs triptan	1.42 (1.23,1.63)	1.42 (1.27,1.58)
	Aspirin vs triptan	0.84 (0.60,1.18)	0.74 (0.58,0.93)
	Aspirin + antiemetic vs triptan	0.79 (0.51,1.21)	0.69 (0.51,0.91)
Versus NSAID	Paracetamol vs NSAID	-	0.77 (0.33,1.56)
	Ergot vs NSAID	-	0.50 (0.35,0.69)
	Triptan + paracetamol vs NSAID	-	1.62 (0.88,2.62)
	Triptan + NSAID vs NSAID	2.03 (1.71,2.40)	1.81 (1.57,2.10)
	Aspirin vs NSAID	0.76 (0.57,1.00)	0.94 (0.73,1.21)
	Aspirin + antiemetic vs NSAID	-	0.88 (0.63,1.21)
Versus	Ergot vs paracetamol	-	0.64 (0.30,1.55)

Comparison		Risk ratio	
paracetamol	Triptan + paracetamol vs paracetamol	1.87 (1.04,3.38)	2.07 (1.10,4.35)
	Triptan + NSAID vs paracetamol	-	2.34 (1.17,5.40)
	Aspirin vs paracetamol	-	1.22 (0.59,2.88)
	Aspirin + antiemetic vs paracetamol	-	1.14 (0.54,2.72)
Versus ergot	Triptan + paracetamol vs ergot	-	3.25 (1.68,5.68)
	Triptan + NSAID vs ergot	-	3.63 (2.66,5.07)
	Aspirin vs ergot	-	1.90 (1. 03,2.78)
	Aspirin + antiemetic vs ergot	2.42 (1.25,4.67)	1.77 (1.23,2.56)
Versus triptan + paracetamol	Triptan + NSAID vs triptan + paracetamol	-	1.11 (0.70,2.05)
	Aspirin vs triptan + paracetamol	-	0.58 (0.35,1.10)
	Aspirin + antiemetic vs triptan + paracetamol	-	0.54 (0.31,1.05)
	Paracetamol + aspirin vs triptan + paracetamol	-	-
	Paracetamol + antiemetic vs triptan + paracetamol	-	-
Versus triptan + NSAID	Aspirin vs triptan + NSAID	-	0.52 (0.40,0.67)
	Aspirin + antiemetic vs triptan + NSAID	-	0.49 (0.35,0.66)
Versus aspirin	Aspirin + antiemetic vs aspirin	-	0.93 (0.63,1.35)

Figure 277 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 8 different interventions being evaluated.

Figure 277: Rank order for treatments based on freedom from pain at up to 2 hours



AE=Antiemetic

Based on the direct comparisons (first results column Table 8), efficacy as assessed by pain free at up to 2 hours favours triptan over NSAID or ergot, triptan in combination with an NSAID over triptan or NSAID alone, triptan in combination with paracetamol over paracetamol alone and aspirin in combination with an antiemetic over ergot. No other treatment effects reached statistical significance. The random effects model used for the NMA is a good fit, with a residual deviance of 40.22 reported. This corresponds well to the total number of trial arms, 33.

The DIC statistics were as follows in Table 9:

Table 9: DIC for freedom from pain at 2 hours – random effects

	Dbar	Dhat	pD	DIC
r	203.167	176.532	26.635	229.802
total	203.167	176.532	26.635	229.802

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

No inconsistency was identified between the direct and NMA results for any comparison. All the median risk ratios from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

I.3.2.1 Evidence statements

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 anstiemetic 6th, paracetamol 7th, and ergots were ranked as least effectiveat 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.

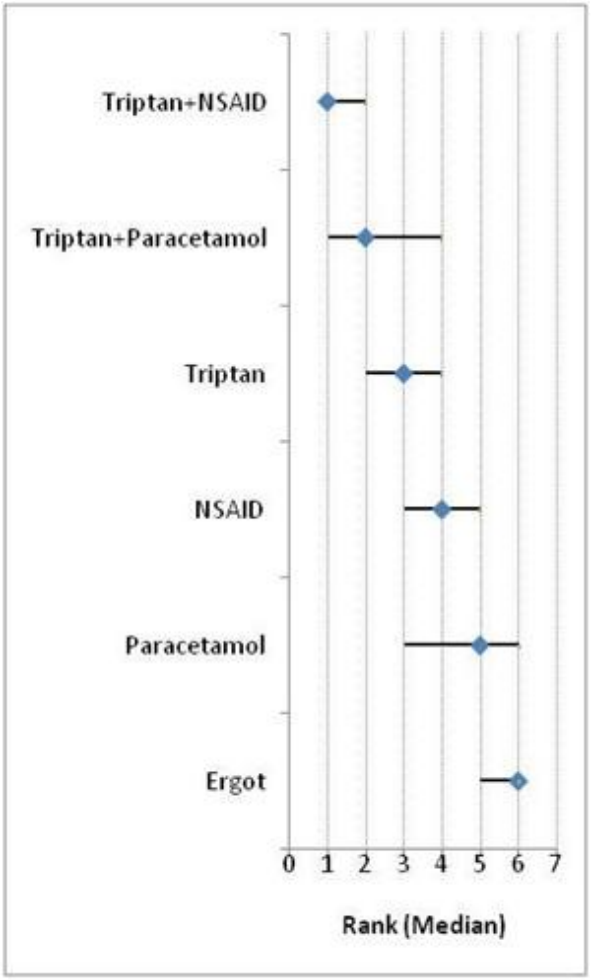
I.3.3 Network 3: Sustained headache response at 24 hours for the acute treatment of migraine

Table 10: Relative risk for sustained headache response at 24 hours

Comparison		Risk ratio	
		Direct (mean)	NMA (median)
Versus triptan	NSAID vs triptan	0.85 (0.74,0.97)	0.87 (0.75,0.98)
	Paracetamol vs triptan	0.78 (0.50,1.23)	0.74 (0.37,1.23)
	Ergot vs triptan	0.67 (0.56,0.80)	0.63 (0.51,0.75)
	Triptan + paracetamol vs triptan	1.17 (0.82,1.67)	1.23 (0.74,1.75)
	Triptan + NSAID vs triptan	1.39 (1.24,1.55)	1.32 (1.20,1.48)
Versus NSAID	Paracetamol vs NSAID	-	0.85 (0.43,1.45)
	Ergot vs NSAID	-	0.73 (0.57,0.90)
	Triptan + paracetamol vs NSAID	-	1.42 (0.85,2.08)
	Triptan + NSAID vs NSAID	1.64 (1.45,1.85)	1.53 (1.35,1.78)
Versus paracetamol	Ergot vs paracetamol	-	0.85 (0.49,1.72)
	Triptan + paracetamol vs paracetamol	1.49 (0.99,2.26)	1.64 (1.01,2.99)
	Triptan + NSAID vs paracetamol	-	1.79 (1.07,3.64)
Versus ergot	Triptan + paracetamol vs ergot	-	1.95 (1.15,3.02)
	Triptan + NSAID vs ergot	-	2.11 (1.69,2.74)
Versus triptan + paracetamol	Triptan + NSAID vs triptan + paracetamol	-	1.08 (0.76,1.81)

Figure 278 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the eight different interventions being evaluated.

Figure 278: Rank order for treatments based on sustained headache response at 24 hours



Based on the direct comparisons (first results column Table 10), efficacy as assessed by sustained headache response at 24 hours favours triptan over NSAID or ergot and triptan in combination with an NSAID over triptan or NSAID alone. No other treatment effects reached statistical significance. The random effects model used for the NMA is a very good fit, with a residual deviance of 13.3 reported. This corresponds very well to the total number of trial arms, 16.

The DIC statistics were as follows in Table 11:

Table 11: DIC for sustained headache response at 24 hours – random effects

	Dbar	Dhat	pD	DIC
r	105.162	92.766	12.396	117.557
total	105.162	92.766	12.396	117.557

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

No inconsistency was identified between the direct and NMA results for any comparison. All the median risk ratios from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

I.3.3.1 Evidence statements

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-analsysis 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-analsysis 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-analsysis 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-analsysis of six studies comparing six treatments suggested that triptan in combnation with paracetamol and triptan in combination with an NSAID are more effective than paracetamol in producing sustained headache response at 24 hours.

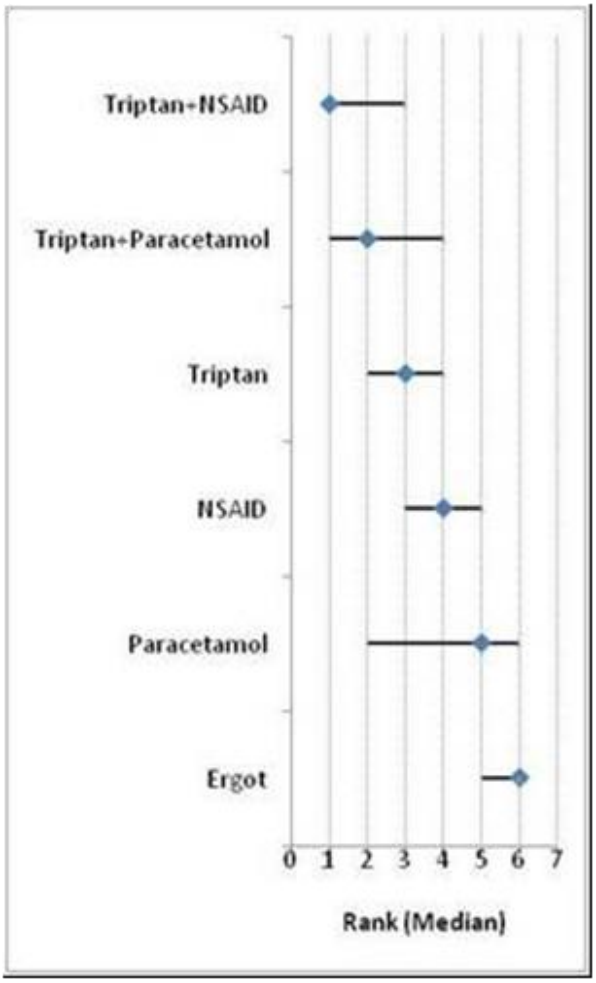
I.3.4 Network 4: Sustained freedom from pain at 24 hours for the acute treatment of migraine

Table 12: Relative risks for sustained freedom from pain at 24 hours

Comparison		Risk ratio	
		Direct (mean)	NMA (median)
Versus triptan	NSAID vs triptan	0.68 (0.51,0.89)	0.68 (0.52,0.89)
	Paracetamol vs triptan	0.70 (0.29,1.67)	0.68 (0.24,1.58)
	Ergot vs triptan	0.43 (0.25,0.74)	0.40 (0.27,0.57)
	Triptan + paracetamol vs triptan	1.34 (0.68,2.67)	1.38 (0.65,2.51)
	Triptan + NSAID vs triptan	1.55 (1.27,1.89)	1.52 (1.27,1.81)
Versus NSAID	Paracetamol vs NSAID	-	0.99 (0.34,2.45)
	Ergot vs NSAID	-	0.59 (0.37,0.91)
	Triptan + paracetamol vs NSAID	-	2.01 (0.91,3.92)
	Triptan + NSAID vs NSAID	2.32 (1.80,2.98)	2.22 (1.74,2.87)
Versus paracetamol	Ergot vs paracetamol	-	0.59 (0.23,1.75)
	Triptan + paracetamol vs paracetamol	1.92 (0.86,4.26)	2.00 (0.91,5.05)
	Triptan + NSAID vs paracetamol	-	2.24 (0.94,6.39)
Versus ergot	Triptan + paracetamol vs ergot	-	3.42 (1.50,7.03)
	Triptan + NSAID vs ergot	-	3.78 (2.55,5.75)
Versus triptan + paracetamol	Triptan + NSAID vs triptan + paracetamol	-	1.10 (0.59,2.39)

Figure 279 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 8 different interventions being evaluated.

Figure 279: Median rank for sustained pain free at 24 hours



Based on the direct comparisons (first results column Table 12), efficacy as assessed by sustained headache response at 24 hours favours triptan over NSAID or ergot and triptan in combination with an NSAID over triptan or NSAID alone. No other treatment effects reached statistical significance. The random effects model used for the NMA is a very good fit, with a residual deviance of 13.91 reported. This corresponds very well to the total number of trial arms, 15.

The DIC statistics were as follows in Table 13:

Table 13: DIC for sustained freedom from pain at 24 hours – random effects

	Dbar	Dhat	pD	DIC
r	90.12	77.371	12.749	102.869
total	90.12	77.371	12.749	102.869

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

No inconsistency was identified between the direct and NMA results for any comparison. All the median risk ratios from the NMA lie within the 95% confidence interval from the direct comparison of the same comparisons.

I.3.4.1 Evidence statements

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.

I.3.5 Sensitivity analysis

The GDG were concerned that the effectiveness of subcutaneously administered treatments could be significantly greater than oral or nasal preparations and were concerned that inclusion of these studies could skew the results. Therefore, sensitivity analysis was conducted to test the robustness of including studies investigating sub-cutaneous administered treatments in the NMA. The following scenarios were tested in a sensitivity analysis:

1. Including all studies of patient administered treatments (as reported above)
2. Excluding studies of treatments administered via a subcutaneous route.

This only affected headache response at up to two hours and sustained headache response at 24 hours. There were no studies with subcutaneous treatments reporting pain free outcomes. Using 50,000 burn-in and 100,000 simulations, we found no important difference in the results between all the scenarios in goodness of fit and discrepancy or consistency of result. As the evidence mainly applied to oral treatments rather than subcutaneous, and the inclusion or exclusion does not affect the results, it was agreed that the economic model should be based on the analysis without subcutaneous treatment to reflect the available clinical evidence.

I.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in chapter 11 and appendix G, deciding upon the most effective intervention for the acute treatment of migraine is difficult. In order to overcome the difficulty of interpreting the conclusions from these numerous separate comparisons, NMA of the direct evidence were performed.

Our analyses were based on a total of 19 studies of 10 different interventions (five monotherapy and five different combinations of two agents). The studies formed four networks of evidence each for a different outcome.

The findings from the NMA were used to facilitate the GDG in decision making when developing recommendations for the acute treatment of migraine.

In the first network of headache response at two hours all treatments were found to be superior to ergots; NSAID in combination with a triptan was superior to triptan alone, NSAID alone, aspirin, aspirin in combination with an antiemetic and paracetamol in combination with aspirin; triptan in combination with paracetamol was superior to NSAID, paracetamol and aspirin; triptan was found to be superior to NSAID and paracetamol in combination with aspirin was superior to NSAID.

In the ranking of treatments triptan in combination with paracetamol was ranked first although there is considerable uncertainty about this estimate as the credible intervals are quite wide. Triptan in combination with NSAID was ranked second, with much smaller credible intervals only spanning three ranking positions. The first four ranked treatments are all dual therapy combination.

In the second network of freedom from pain at two hours all treatments except paracetamol were found to be superior to ergots; NSAID in combination with a triptan was superior to triptan alone, NSAID alone, paracetamol, aspirin and aspirin in combination with an antiemetic; triptan in combination with paracetamol was superior to paracetamol alone and triptan was found to be superior to NSAID, aspirin and aspirin in combination with an antiemetic.

In the ranking of treatments triptan in combination with NSAID was ranked first. Triptan in combination with paracetamol was ranked second, however the credible intervals ranged from first to fifth so there is uncertainty in this estimate. Triptan was ranked third.

In the third network of sustained headache response at 24 hours all treatments except paracetamol were found to be superior to ergot; NSAID in combination with a triptan was superior to all other treatments included except triptan in combination with paracetamol in which case both were similarly effective; triptan in combination with paracetamol was superior to paracetamol alone and triptan was found to be superior to NSAID.

In the ranking of treatments triptan in combination with NSAID was ranked first. Triptan in combination with paracetamol was ranked second, however the credible intervals ranged from first to fourth so there is uncertainty in this estimate. Triptan was ranked third.

In the fourth network of sustained freedom from pain at 24 hours all treatments except paracetamol were found to be superior to ergot; NSAID in combination with a triptan was superior to all other treatments included except paracetamol alone and triptan in combination with paracetamol in which case both were similarly effective; triptan was found to be superior to NSAID.

In the ranking of treatments triptan in combination with NSAID was ranked first, however the credible intervals ranged from first to third and triptan in combination with paracetamol was ranked second with credible intervals ranging from first to fourth so there is uncertainty in both estimates. Triptan was ranked third.

The analysis compared all treatments to triptan, therefore this does not provide evidence of treatments that are not effective for acute treatment of migraine, but does provide a hierarchy of treatments that may be used.

All four networks seem to fit well, as demonstrated by residual deviance and no inconsistencies in the networks were found.

In summary, the four outcomes chosen for this analysis were considered to be the most important for assessing efficacy of acute treatments for migraine. Two of these outcomes (freedom from pain at 2 hours and sustained freedom from pain at 24 hours) also fed into the cost effectiveness analysis (see Appendix J:).

I.5 Conclusion

This analysis allowed us to combine the findings from many different comparisons presented in the reviews for acute treatment of migraine even when direct comparative data was lacking.

Overall, the results of all four networks showed that combination treatments, particularly triptan in combination with NSAID or triptan in combination with paracetamol are likely to be the most effective for the treatment of acute migraine.

It should be noted that this 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.

I.6 WinBUGS codes

```
#Random effects model for multi-arm trials (any number of arms)

model{

for(i in 1:NS){

      w[i,1] <-0

            mu[i] ~ dnorm(0,.0001)                                  # vague priors for 24 trial baselines

            for (k in 1:na[i])  {

                r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])                                  # binomial likelihood

                              logit(p[i,t[i,k]])<-mu[i] + d[t[i,k]] - d[t[i,1]]
# model


#Deviance residuals for data i

    rhat[i,k] <- p[i,t[i,k]] * n[i,k]

    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))  +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))

                    }

          sdev[i]<- sum(dev[i,1:na[i]])

 }

d[1]<-0

for (k in 2:NT){d[k] ~ dnorm(0,.0001) }                 #  vague priors for basic parameters

sd~dunif(0,2)                                 #  vague prior for random effects standard deviation

tau<-1/pow(sd,2)

sumdev <- sum(sdev[])                                          # Calculate residual deviance


#Calculation of absolute probabilities of success#


BR~dnorm(meanBR,precBR)

for (k in 1:NT){

                                                                  logit(T[k])<-BR + d[k]
```

```
                                                    }

#Calculation of relative risks#

for (k in 1:NT){
                                                                    rr[k]<-T[k]/T[1]
                                                }
# pairwise ORs
for (c in 1:(NT-1))
        {  for (k in (c+1):NT)
             {  lor[c,k] <- d[k] - d[c]
               log(or[c,k]) <- lor[c,k]
                                                lrr[c,k] <- log(rr[k]) - log(rr[c])
                                                log(rrisk[c,k]) <- lrr[c,k]
             }
         }

# Ranking and prob[164,164]
 for (k in 1:NT) {
            rk[k]<-NT+1-rank(d[],k)
best[k]<-equals(NT+1-rank(d[],k),1)}

}

# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#        per trial in the dataset. In this dataset M is 3.

Treatment code
1          Triptan
2          NSAID
3          Paracetamol
```

4 Ergot

5 Triptan+Paracetamol

6 Triptan+NSAID

7 Aspirin

8 Aspirin+AE

9 Paracetamol+Aspirin

10 Paracetamol+AE

###Analysis one- Sustained pain free at 2 hours###

###Data###

list(NS=13,NT=8,meanBR=-0.8928,precBR=68.64129)

r[,1] r[,2] r[,3] n[,1] n[,2] n[,3] t[,1] t[,2] t[,3] na[]

90 53 125 362 356 364 1 2 6 3

82 57 107 362 364 362 1 2 6 3

137 20 NA 415 197 1 1 4 NA 2

83 79 60 224 221 221 1 2 7 3

33 37 NA 135 146 1 1 7 NA 2

17 11 23 43 43 48 1 3 5 3

38 25 NA 182 182 1 1 4 NA 2

11 27 NA 132 134 1 4 8 NA 2

20 16 NA 53 53 1 1 2 NA 2

21 16 NA 42 43 1 1 2 NA 2

26 37 NA 90 90 1 1 6 NA 2

46 45 85 226 248 250 1 2 6 3

36 29 NA 122 135 1 1 8 NA 2

END

###Inits###

list(

```
d=c(NA,0,0,0,0,0,0,0),

sd=.2,

mu=c(3,-2,-2,0,-3,-2,1,1,-1,1,3,-3,-3))
```

Appendix J: Cost-effectiveness analysis: Acute pharmacological treatment of migraine

J.1 Introduction

This economic analysis explores the cost effectiveness of different acute treatments for resolution of migraine. The topic of 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 patients at some point. Original economic analysis was initially planned for migraine, tension type headache and cluster headache; however no quality of life data was identified for tension type or cluster headache. The GDG discussed whether the results of the model for acute treatment of migraine could be applicable to other types of headache. However given the difference in both choice of treatments and quality of life, the GDG believe the results cannot be extrapolated to other types of headache.

No economic studies comparing oral treatments for acute migraine attacks were included in our systematic review of economic literature (see chapter 11 of the full guideline). One study[613] 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[265,872], 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[265] were in agreement with our findings (triptans more cost-effective than ergots) while the USA study[872] 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 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.

Other economic evaluations[133,134,515,790] 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.

J.2 Methods

J.2.1 Model overview

A cost-utility analysis was undertaken where costs and QALYs were considered from a UK NHS and personal social services perspective.

J.2.1.1 Comparators

The comparators considered in the model are: NSAIDs, paracetamol, ergots, triptans, triptan in combination with NSAID, and triptan in combination with paracetamol. A 'no treatment' strategy was not considered an option since the GDG believed that patients presenting with migraine should always be prescribed some form of acute treatment. It was decided by the GDG to only compare oral treatments since they are more representative of common clinical practice than other formulations, which are considered only when oral treatment is not an option.

J.2.1.2 Population

The population entering the model comprises patients experiencing an acute migraine attack, indicated for oral treatment, and population characteristics were as in the clinical review: patients aged 12 or over, diagnosed with migraine.

J.2.1.3 Time horizon

The time horizon considered in the model was 24 hours; we chose this time horizon to reflect the short term nature of the treatment and the duration of the trials; outcomes in the trials were reported at 24 hours and no further costs or health consequences were assessed. Since we did not do any extrapolation to any long term outcome, this short time horizon was deemed appropriate. Choosing a 24 hour time horizon maps directly to two of our main clinical outcomes, namely sustained pain free (SPF) at 24 hours and sustained headache response (SHR) at 24 hours. In view of the short time horizon, it was not necessary to discount costs or outcomes.

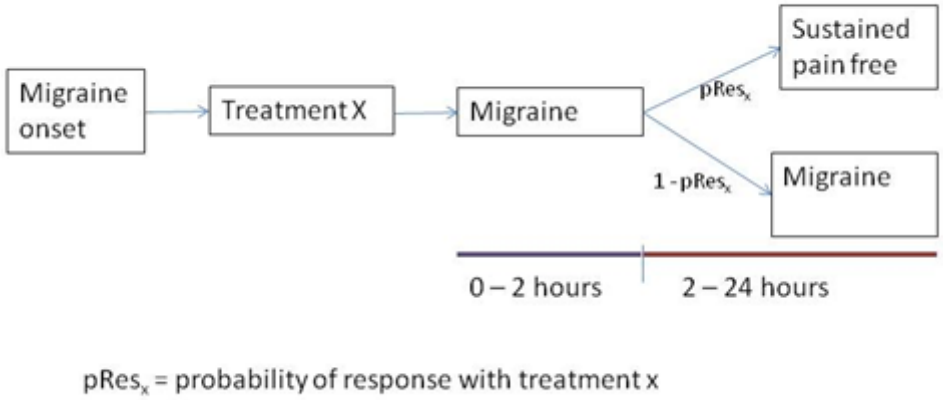
J.2.2 Approach to modelling

J.2.2.1 Model structure

A decision tree was constructed whereby the QALY gain is driven by the proportion of people who respond to treatment in terms of either SPF at 24 hours, the primary outcome chosen for the analysis, or sustained headache response SHR in a sensitivity analysis. It was agreed with the GDG not to make use of the equivalent outcomes (SPF and SHR) at 2 hours in the model when calculating QALYs, since it would be impossible to discern the exact time at which treatment response occurred. In addition, the effectiveness results at 2 hours presented in paragraphs I.3.1 and I.3.2 suggest that the calculation of QALYs at 2 hours is unlikely to modify the results as there is no significant change in the ranking of the treatments. Therefore we assume that the QALY gain occurs in the 2-24 hour time window only; this is a conservative estimate, since, by omitting the first 2 hours, we may underestimate the total QALY gain for people who responded at 2 hours and sustained the response at 24 hours. The GDG decided that, in the base case, the SPF outcome should be used, since this maps directly to our quality of life data, and that the SHR outcome should be explored in sensitivity analysis.

Adverse events of treatments were not included in the model as no useful data on this outcome was available from the RCTs included in our systematic review. Furthermore, the limited time-horizon of the model would limit the analysis in terms of capturing the long-term costs and disutilities due to adverse events.

Figure 280- Model structure



pRes$_x$ = probability of response with treatment x

J.2.2.2 Uncertainty

We conducted a probabilistic sensitivity analysis in order to explore the uncertainty in model results. In a probabilistic sensitivity analysis, each parameter is assigned a distribution reflecting its uncertainty; random draws are then taken from this distribution and propagated through the model, to calculate costs and QALYs. This process is repeated 10,000 times and a model result which represents an average of the simulations is computed. One way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters.

J.2.3 Model inputs

J.2.3.1 Summary table of model inputs

Model inputs were based on the clinical evidence identified in the systematic review and network meta-analysis (NMA) undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 14 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 14: Summary of base-case model inputs

Input	Data	Source
Probability of SPF with triptan (baseline)	19.4%	Logistic regression carried out on arms of trials that contained triptans – see J.2.3.2
Probability of SPF with NSAID	13.3%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SPF with paracetamol	13.1%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SPF with ergots	7.8%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SPF with triptan + paracetamol	26.8%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SPF with triptan + NSAID	29.5%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SHR with triptan	38.0%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SHR with NSAID	32.6%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SHR with paracetamol	27.5%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SHR with ergots	21.6%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SHR with triptan + paracetamol	47.3%	NMA conducted as part of clinical review – see J.2.3.3
Probability of SHR with triptan + NSAID	51.3%	NMA conducted as part of clinical review – see J.2.3.3
Cost of one dose of triptan	£2.17	See J.2.3.5
Cost of one dose of NSAID 500mg	£0.06	BNF 61[403] dose: 500mg - See J.2.3.5
Cost of one dose of paracetamol 1000mg	£0.03	BNF 61[403] – dose: 1000mg - See J.2.3.5
Cost of one dose of ergot 200mg	£0.34	BNF 61[403] – dose: 200mg - See J.2.3.5
Cost of one dose of triptan + paracetamol	£2.20	Sum of cost of triptan and cost of

Input	Data	Source
		paracetamol - See J.2.3.5
Cost of one dose of triptan + NSAID	£2.23	Sum of cost of triptan and cost of NSAID - See J.2.3.5
Utility weight for a patient experiencing a migraine attack	-0.3	Evans et al (1997)[265] – see J.2.3.4
Utility weight following successful migraine treatment	0.81	Kind et al (1998)[437] – see J.2.3.4

SPF=Sustained pain free at 24 hours
SHR=Sustained headache response at 24 hours (sensitivity analysis only)
NMA = network meta-analysis

J.2.3.2 Baseline events

We considered triptans to be our baseline treatment in the model, since the clinical review was not designed to explore 'no treatment' as a comparator. Baseline events were modelled using a logistic regression in Winbugs, the code for which can be found in the NMA section (I.6). The aim of the logistic regression was to calculate baseline odds on the log scale for sustained pain free and sustained headache response at 24 hours by pooling response rates for triptans taken from the RCTs.

J.2.3.3 Relative treatment effects

To calculate relative treatment effects, a NMA was conducted in Winbugs (see 0I.6). The aim of the NMA was to calculate treatment specific log odds ratios for response, which can be combined with the baseline log odds to produce absolute probabilities on the natural scale as follows.

Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:

$$\tilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$\boldsymbol{p} = \frac{\boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}{\mathbf{1} + \boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

J.2.3.4 Utilities

For economic evaluation, a specific measure of health-related quality of life (HRQoL) known as utility is required to calculate QALYs. Utilities indicate the preference for health states on a scale from 0 (death) to 1 (perfect health). The NICE reference case specifies that the preferred way for this to be assessed is by the EQ-5D instrument.

A systematic search identified only one study[265] with a utility measure that corresponded directly to our clinical outcomes (SPF and SHR) . This study used a Canadian prevalence study[643] and the Quality of Wellbeing (QWB) measure to derive a utility weight of -0.3 (see Table 14) for an "average migraine attack". This utility weight was therefore used to calculate the QALYs associated with non responders; to calculate the QALYs, the SPF and SHR outcomes were used in the base case and sensitivity analysis respectively. This is explained in J.2.4.1. For responders, we used the utility weight of 0.81 which represents the HRQoL in the general population in the UK[437]. A potential limitation of the utility value used in the analysis is that, though the authors provided a brief explanation of its calculation, we were unable to repeat this calculation ourselves.

J.2.3.5 Resource use and cost

Due to the short time horizon and the paucity of data to inform more complex assumptions, we decided to only consider resource use in terms of one drug administration. Potential downstream costs, such as visits to healthcare professionals in case of no response to treatment, tests and further rescue medication are omitted from the model; therefore the results represent a conservative estimate of cost effectiveness as the most effective treatments might be associated with lower costs.

The cost of drug treatments were calculated based on the most common dose and on the cost described in the BNF61[403]. The cost of one dose was calculated by dividing the cost of a pack by the number of doses available in the pack.

A different approach was used to cost triptans as various preparations with different costs are available. In the base case model, a weighted average cost for triptans was calculated based on the number of patients who received each preparation in the RCT informing the clinical parameters and on their costs. Table 15 shows how this weighted cost was derived. This was varied in a sensitivity analysis where minimum and maximum values were used.

Table 15: Weighted average triptan cost

Study	Triptan/dose	Cost per dose[a] (c)	Number of patients given triptan (n)	Weight (w=n/1684)	Weighted cost (c * w)
Brandes 2007[105]	Sumatriptan 80 mg	£0.41	362	21.5%	£0.09
Brandes 2007[105]	Sumatriptan 80 mg	£0.41	362	21.5%	£0.09
Diener 2002 [219]	Eletriptan 80/40 mg	£5.49	419	24.9%	£1.37
Freitag 2008[287]	Rizatriptan 10 mg	£4.45	43	2.6%	£0.11
Lainez 2007[464]	Almotriptan 12.5 mg	£3.02	182	10.8%	£0.33
Schoenen 2008[705]	Almotriptan 12.5 mg	£3.02	90	5.3%	£0.16
Smith 2005[743]	Sumatriptan 50mg	£0.21	226	13.4%	£0.03
TOTAL	**-**	**-**	**1684**	**100%**	**£2.17**

(a) Source: BNF61[403]

We assume the costs of combination treatments are additive, since no single formulation combining triptans with NSAID or paracetamol is available at present.

J.2.4 Computations

The mean cost and effectiveness and the incremental monetary benefit of the compared strategies were calculated using Microsoft Office Excel 2007.

J.2.4.1 Calculating QALYs

To calculate the quality of life associated with each treatment, we calculated the overall QALYs for responders and non responders, based on treatment specific response rates, and summed the values to get an overall QALY estimate for the cohort. To do this, we took the following steps:

1. Calculate the number of responders and non-responders (at 24 hours) for each treatment using the methods described for relative and baseline treatment effects in J.2.3.2 and J.2.3.3.

   Let c, and p denote the number of patients in the cohort and the treatment specific probability of response, respectively, then:

$$number\ of\ responders = \boldsymbol{res} = \boldsymbol{p} \times \boldsymbol{c}$$
$$number\ of\ non\ responders = \boldsymbol{Nres} = (\boldsymbol{1} - \boldsymbol{p}) \times \boldsymbol{c}$$

2. Calculate QALYs for responders ($\boldsymbol{QALY_{res}}$), based on 2 hours with migraine and 22 hours without migraine (note $util_{well} = 0.81$ and $util_{migraine} = -0.3$):

$$\boldsymbol{QALYres} = \left(\frac{2}{24 \times 365} \times (-0.3)\right) + \left(\frac{22}{24 \times 365} \times 0.81\right) = 0.002$$

3. Calculate QALYs for non-responders ($\boldsymbol{QALY_{Nres}}$) based on 24 hours with no migraine relief:

$$\boldsymbol{QALY_{Nres}} = \left(\frac{1}{365} \times -0.3\right) = -0.000822$$

4. Calculate overall QALYs ($\boldsymbol{Q_{tot}}$) per patient, based on responder rates and QALYs associated with response and no response:

$$\boldsymbol{Q_{tot}} = \frac{(\boldsymbol{res} \times \boldsymbol{QALY_{res}}) + (\boldsymbol{Nres} \times \boldsymbol{QALY_{Nres}})}{\boldsymbol{c}}$$

Thus, $\boldsymbol{Q_{tot}}$ represents the overall, treatment specific QALY gain.

J.2.4.2 Calculating costs

The total cost associated with a strategy is the cost of drugs used in the strategy as described in J.2.3.5.

J.2.4.3 Calculating cost-effectiveness

It is possible, for a particular cost-effectiveness threshold, to express cost-effectiveness results in term of incremental net monetary benefit (INMB) vs baseline comparator. This is calculated by multiplying the incremental QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the incremental costs (see equation VII). The decision rule then applied is that the comparator with the highest INMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation the INMB is used to identify the optimal strategy in the probabilistic analysis simulations.

For a given treatment strategy **X**

$$\boldsymbol{INMB_X} = \boldsymbol{incQALYS_X} \times \boldsymbol{\lambda} - \boldsymbol{incCOST_X}$$

Where:

$incQALYS_X$ = total incremental QALYs of strategy x vs baseline comparator

λ = cost-effectiveness threshold

$incCOST_X$ = incremental cost of strategy x vs baseline comparator

The probabilistic analysis was run for 10,000 simulations. For each simulation, total discounted costs and total discounted QALYs were calculated for each strategy. The INMB was also calculated and the most cost-effective option identified (that is, the one with the highest INMB), at a threshold of £20,000 per QALY gained.

The results of the probabilistic analysis were summarised in terms of mean discounted costs and QALYs with rank-probability plots, where cost effectiveness rankings were calculated for each strategy and the probability of a given treatment attaining a certain rank determined by the number of times the treatment achieved that rank in all the simulations, divided by the number of simulations. For example, suppose treatment 2 achieved rank 1, that is, it had the highest net benefit in 200 simulations, the probability of treatment 2 being ranked 1^{st} is $\frac{200}{10000} = 2\%$

J.2.5 Sensitivity analyses

Uncertainty was explored through deterministic sensitivity analyses and probabilistic sensitivity analysis. All sensitivity analyses were run probabilistically.

J.2.5.1 Deterministic analysis in the model

Deterministic sensitivity analyses were conducted, in order that the sensitivity of model results to changes in key parameters could be tested. The following parameters were varied (see Table 17).

- Primary clinical outcome: all trials reported the outcomes sustained pain free at 24 hours and sustained headache response at 24 hours, hence there was uncertainty as to which should be used as efficacy inputs for the model. The GDG considered both outcomes important but sustained pain free was used in the base cases since corresponds more linearly to our quality of life data. In a sensitivity analysis we ran the model using the sustained headache response outcomes from our clinical review but using the same utility data as the base case model.

- Utility following headache resolution: we changed the utility having just recovered from a migraine, as the GDG believe the quality of life following headache resolution is likely to be lower than that of the general population. As we found no data on the quality of life after headache resolution, an arbitrary value of 0.5 was chosen based on expert opinion.

- Utility during a migraine episode: we changed the utility associated with a migraine episode from -0.3 in the base case to 0.25. This value was identified by the GDG as no other value could be found.

- Triptan cost: since triptans were treated as a class and there are many different variants, there was some uncertainty as to which should be used. In the base case it was decided to use a weighted average cost, based on the products used in the trials (see Table 16). In a series of sensitivity analyses, we used the cost of the lowest and highest doses likely to be used in clinical practice (sumatriptan 50mg and rizatriptan 10mg), and the most expensive dose used in the trials (eletriptan 80mg). See Table 17 for more details.

J.2.5.2 Probabilistic analysis in the model

Due to the information available and the fact that the only costs included were drug costs from the BNF[403], we only assigned distributions to treatment effects in the model for the probabilistic sensitivity analysis. We were unable to assign a distribution to utilities since no estimate of their uncertainty is available.

We assumed that the log odds for triptans followed a lognormal distribution as follows:

$$\ln(\beta) \sim \text{Normal}(-1.42, 0.16)$$

Where:

β=baseline odds

Additionally we assumed that the log odds ratios associated with each treatment were defined by a multivariate lognormal distribution. When simulating from a multivariate lognormal distribution it is important to preserve the correlations between parameters, which can be represented by the variance covariance matrix. We therefore parameterise the treatment specific log odds ratios (δ_i) as follows:

$$\begin{pmatrix} \delta_1 \\ \delta_2 \\ \delta_3 \\ \delta_4 \\ \delta_5 \end{pmatrix} \sim MVLN(\boldsymbol{\mu}, \boldsymbol{\Sigma})$$

Where: $\boldsymbol{\mu} = \begin{pmatrix} d_1 \\ d_2 \\ d_3 \\ d_4 \\ d_5 \end{pmatrix}$

is a vector representing the mean log odds ratios for each treatment

and

$$\boldsymbol{\Sigma} = \begin{pmatrix} \boldsymbol{\sigma}_{1,1}^2 & \boldsymbol{\sigma}_{1,2} & \cdots & \ldots & \boldsymbol{\sigma}_{1,5} \\ \boldsymbol{\sigma}_{2,1} & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ \boldsymbol{\sigma}_{5,1} & \boldsymbol{\sigma}_{5,2} & \ldots & \ldots & \boldsymbol{\sigma}_{5,5}^2 \end{pmatrix}$$

is a matrix representing the variances of the log odds ratios for each treatment and the covariance between them. For example $\boldsymbol{\sigma}_{1,5}$ represents the covariance between treatments 1 and 5. Then the treatment specific log odds ratios are sampled using a cholesky decomposition and then transformed into absolute probabilities of response.

J.2.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of the model formulae and calculations, also by using a series of sensitivity analyses with extreme values. The model parameters and results were also assessed against the content of this appendix.

J.2.7 Interpreting results

The strategy with the highest INMB is the one that should be recommended. However, since we were unable to capture the incidence or disutilities of treatment specific adverse events, caution should be exercised in recommending treatments where there is some concern about side effects. It

should also be noted that this economic analysis applies to migraine only, since, due to the paucity of quality of life data we were unable to conduct an equivalent analysis in tension type or cluster headache.

J.3 Results

J.3.1 Base case

In the base case, model inputs were set as shown in Table 14. The ranking according to mean net benefit is reported in Table 16.

Table 16 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 in combination with NSAID was ranked the most cost effective treatment in the base case. To reflect the uncertainty in model results we produced rank-probability graphs, derived as explained in section J.2.5.2. The y-axis shows the rank and the x-axis shows the probability of a given treatment obtaining that rank.

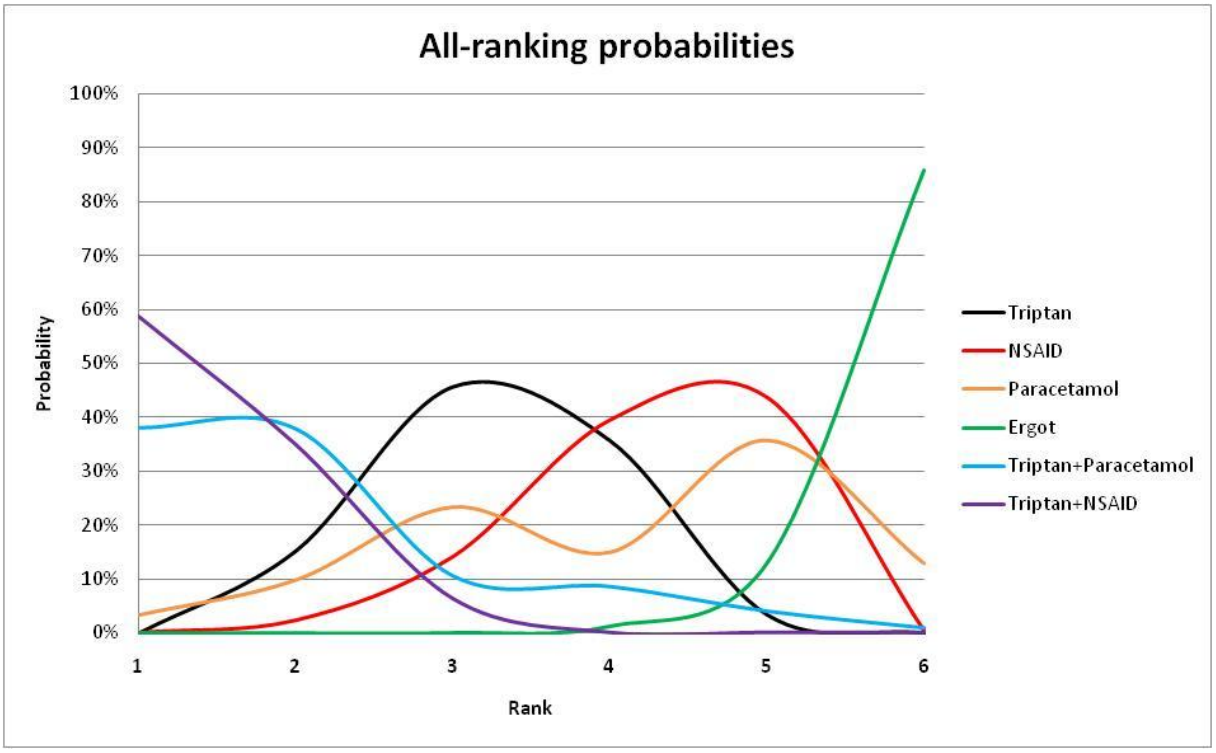


Figure 281 - Rank-probability graph. The y-axis shows the rank and the x-axis shows the probability of a given treatment obtaining that rank.

Figure 281 shows that the two treatments with the highest probability of being cost effective were triptan in combination with NSAID and triptan in combination with paracetamol.

J.3.2 Sensitivity analyses

One way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters. The sensitivity analyses conducted are shown in Table 17.

Table 17 - Sensitivity analyses

Analysis	Primary clinical outcome	Utility weight after migraine relief	Utility weight during migraine episode	Triptan cost
Base case	*Sustained pain free at 24 hours*	*0.81*	*-0.3*	*£2.17*
Sensitivity analysis one (Table 18)	Sustained headache response at 24 hours	0.81	-0.3	£2.17
Sensitivity analysis two (Table 19)	Sustained pain free at 24 hours	0.5	-0.3	£2.17
Sensitivity analysis three (Table 20)	Sustained pain free at 24 hours	0.81	0.25	£2.17
Sensitivity analysis four (Table 21)	Sustained pain free at 24 hours	0.81	-0.3	£0.21 (generic sumatriptan 50 mg)
Sensitivity analysis five (Table 22)	Sustained pain free at 24 hours	0.81	-0.3	£4.45 (Maxalt® 10 mg)
Sensitivity analysis six (Table 23)	Sustained pain free at 24 hours	0.81	-0.3	£7.75 (Relpax® 80 mg)

For each one way sensitivity analysis, the model was run probabilistically and treatments ranked according to their net benefit ranking.

Table 18 - Sensitivity analysis one - results

Rank	Treatment	Average cost	Average QALYs	Net benefit
1	Triptan + NSAID	£2.23	0.00061	9.908
2	Triptan + paracetamol	£2.20	0.00051	8.021
3	Triptan	£2.17	0.00024	2.622
4	NSAID	£0.06	0.00009	1.778
5	Paracetamol	£0.03	-0.00001	-0.287
6	Ergot	£0.34	-0.00021	-4.552

Using sustained response at 24 hours as a clinical outcome meant that NSAID and paracetamol swapped rankings (Table 18).

Table 19- Sensitivity analysis two - results

Rank	Treatment	Average cost	Average QALYs	Net benefit
1	Triptan + NSAID	£2.23	-0.00023	-6.748
2	Triptan + paracetamol	£2.20	-0.00026	-7.482
3	Paracetamol	£0.03	-0.00053	-10.597
4	Triptan	£2.17	-0.00043	-10.758
5	NSAID	£0.06	-0.00055	-11.077
6	Ergot	£0.34	-0.00066	-13.541

Table 19 shows the results of sensitivity analysis two, where 0.5 was used as the utility weight associated with migraine relief, instead of the UK average of 0.81.

Table 20- Sensitivity analysis three - results

Rank	Treatment	Average cost	Average QALYs	Net benefit
1	Triptan+NSAID	£2.23	0.000008	-2.072
2	Triptan+Paracetamol	£2.20	-0.000039	-2.988
3	Triptan	£2.17	-0.000276	-7.684
4	Paracetamol	£0.03	-0.000413	-8.290
5	NSAID	£0.06	-0.000445	-8.951
6	Ergot	£0.34	-0.000599	-12.321

Table 20 shows the results of sensitivity analysis three, where 0.25 was used as the utility weight associated with a migraine episode, instead of the value -0.3 used in the base case. The conclusions are very similar to the base case analysis and the ranking of treatments is the same.

Table 21- Sensitivity analysis four - results

Rank	Treatment	Average cost	Average QALYs	Net benefit
1	Triptan + NSAID	£0.27	0.000011	-0.055
2	Triptan + paracetamol	£0.24	-0.000043	-1.097
3	Triptan	£0.21	-0.000274	-5.694
4	Paracetamol	£0.03	-0.000427	-8.562
5	NSAID	£0.06	-0.000445	-8.956
6	Ergot	£0.34	-0.000597	-12.286

Table 22- Sensitivity analysis five - results

Rank	Treatment	Average cost	Average QALYs	Net benefit
1	Triptan + NSAID	£4.47	0.000008	-4.315
2	Triptan + paracetamol	£4.44	-0.000046	-5.364
3	Paracetamol	£0.03	-0.000419	-8.400
4	NSAID	£0.06	-0.000447	-9.006
5	Triptan	£4.41	-0.000277	-9.954
6	Ergot	£0.34	-0.000603	-12.406

Table 23- Sensitivity analysis six - results

Rank	Treatment	Average cost	Average QALYs	Net benefit
1	Triptan + NSAID	£7.81	0.000010	-7.613
2	Triptan + paracetamol	£7.78	-0.000045	-8.690
3	Paracetamol	£0.03	-0.000414	-8.315
4	NSAID	£0.06	-0.000445	-8.956
5	Triptan	£7.75	-0.000275	-13.246
6	Ergot	£0.34	-0.000601	-12.353

Table 21, Table 22 and Table 23 show the results of sensitivity analyses where the triptan dose with the lowest cost, highest cost for a single dose and highest cost used in the model are explored. The GDG wanted to explore higher and lower costs of triptans due to the wide variety available on the market. Clearly the results show that the cost effectiveness of triptan monotherapy is highly sensitive

to variation in cost, however, the combination of triptan and NSAID remains the most cost effective treatment, irrespective of costs.

J.4 Discussion

J.4.1 Summary of results

Our cost effectiveness analysis shows that, based on a NMA of RCTs and on acquisition costs, triptan in combination with NSAID is the most cost effective treatment for acute treatment of migraine. These results were robust to both one way and probabilistic sensitivity analyses.

J.4.2 Limitations and interpretation

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, 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.

J.4.3 Generalisability to other populations / settings

It should be noted that all of our findings relate mostly to an adult population. The model relates to a “one off” dose of migraine and should not be used to inform decisions regarding sequential and long term treatment.

J.4.4 Comparisons with published studies

There were no other UK specific cost effectiveness analyses that used cost per QALY as a measure of cost effectiveness.

J.4.5 Conclusion = evidence statement

Our analysis suggests that triptan in combination with NSAID is the most cost effective treatment for acute treatment of migraine.

Appendix K: Network meta-analysis of pharmacological interventions for the prophylactic treatment of migraine

K.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in Chapter 14 and the Forest plots in Appendix G.2.5) do not help inform which intervention is most effective in the treatment of prophylactic migraine. The challenge of interpretation has arisen for two reasons:

In isolation, each pair-wise comparison does not inform the choice among the different prophylactic treatment, in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial (for example, acupuncture vs antiepileptic).

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions based on efficacy. In this case efficacy was defined as the change in number of migraine days.

The analysis also provided estimates of effect (with 95% credible intervals) for each intervention compared to placebo. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling presented in Appendix L:.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on participants in trials of intervention A compared to intervention B as it does for participants in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term “network” better describes the data structure, whereas “mixed treatments” could easily be misinterpreted as referring to combinations of treatments.

K.2 Methods

K.2.1 Study selection and data collection

To estimate the effect sizes, we performed a NMA that simultaneously used all the relevant randomised controlled trial evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular

treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

From the outset, we sought to minimise any clinical or methodological heterogeneity by focusing the analysis on RCTs with placebo controls and identifying equivalent outcomes. All of the dosages of drugs in the included RCTs were within the therapeutic range as indicated by the BNF. In consultation with the GDG we chose to perform a NMA for prophylactic treatment of migraine assessed by difference in number of migraine days assessed at 3 or 6 months after initiation of treatment.

K.2.2 Outcome measures

The possible clinical efficacy outcomes identified from the clinical evidence review included; migraine days, migraine frequency and responder rate. Migraine intensity, percentage reporting serious adverse events, use of acute pharmacological medication, headache specific quality of life and functional health status were not included in the list of outcome measures as they were infrequently reported across the studies. The GDG considered that change in migraine days was the most important clinical outcome for assessing prophylactic migraine treatment efficacy. It was agreed that no additional information would be gained by undertaking a NMA of migraine frequency or responder rate.

Outcome measures were calculated on an available case basis (i.e. the analysis was based on the number of participants analysed in each study), regardless of how the original study investigators analysed their data.

K.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical evidence review already presented in chapter 14 and 17 of the full guideline and in appendix G. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in the network for change in migraine days for prophylactic treatment of migraine were:

- Angiotensin receptor blockers (ARB):
  - Telmisartan
- Antiepileptics:
  - Divalproex
  - Topiramate
  - Oxcarbazepine
- Beta-blockers:
  - Propranolol
- Acupuncture
- Placebo.

The details of these interventions can be found in the clinical evidence review in chapter 14 and 17 of the full guideline and appendix E.

K.2.4 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a multi-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.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome, a diagram of the evidence network was produced (see Figure 282) and presented in section K.3.

The model used was based on a random effects logistic regression, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis; for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of zero and standard deviation of 10,000.

For the analyses, a series of 50,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of mean difference, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 14, Appendix G.2.5).

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 compared the placebo by counting the proportion of simulations of the Markov chain in which each intervention had the highest reduction in migraine days.

Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

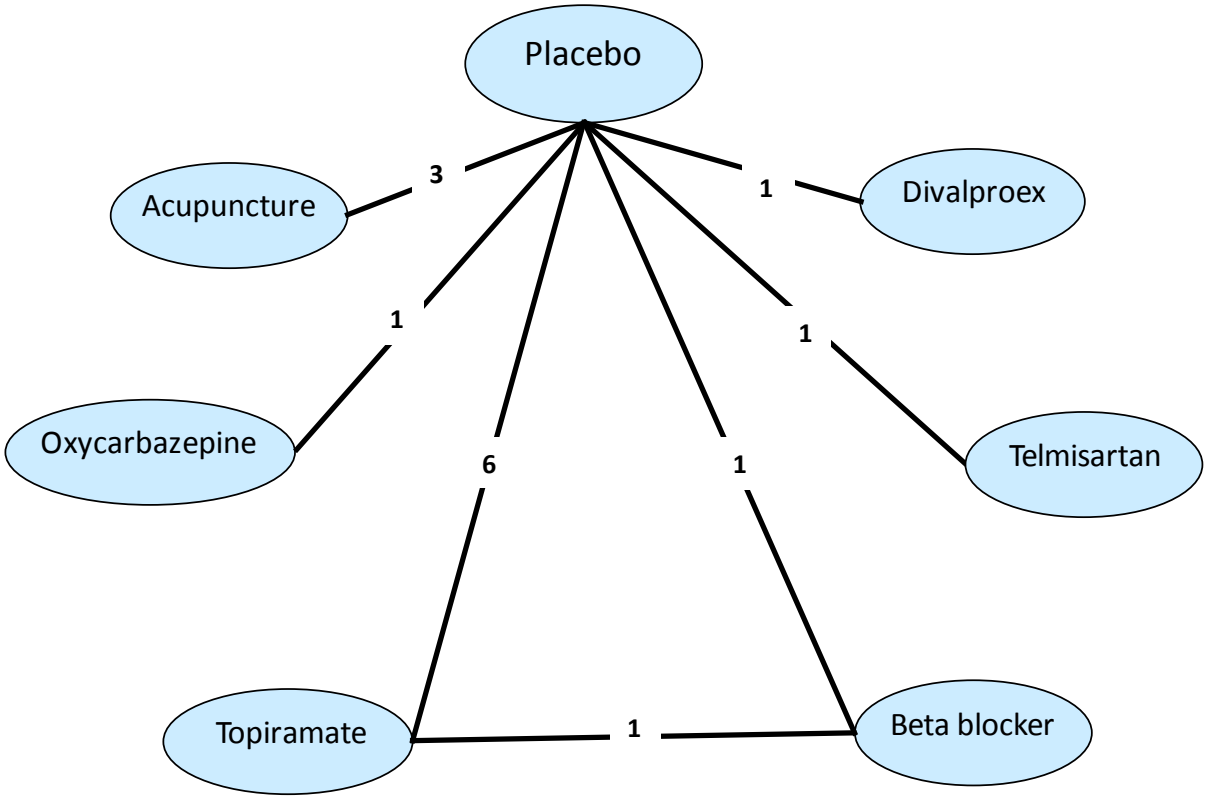
- Different populations (e.g. gender, age)
- Different interventions (doses)
- Different routes of administration.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the change in migraine days from the direct evidence (from pair-wise meta-analysis) to the change in migraine days from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the relative risk from the NMA was not contained within the confidence interval from the direct comparison. No inconsistency was identified.

K.3 Results

A total of 12 studies from the original evidence review met the inclusion criteria for the network. Figure 282 shows the network created by eligible comparisons for the NMA, with numbers on the connecting lines indicating the number of studies for each comparison.

Figure 282: Network for change in migraine days



The trial data from the 12 studies included in the NMA for change in migraine days are shown in Table 24.

Table 24: Study data for change in migraine days

Study	Control	Comparator 1	Comparator 2	Age (range, yrs)	Control		Comparator 1		Comparator 2	
					N	NR	N	NR	N	NR
Apostol et al. 2008[41]	Placebo	Divalproex	-	12-17	71	73	228	232	-	-
Brandes et al. 2004[106]	Placebo	Topiramate	-	≥12	114	120	243	363	-	-
Diener et al. 2004[225]	Placebo	Topiramate	Beta-blocker	12-65	143	146	282	285	143	144
Diener et al. 2006[221]	Placebo	Acupuncture	-	18-65	317	339	290	313	-	-
Diener et al. 2009[218]	Placebo	ARB	-	18-65	44	47	40	48	-	-

Study	Control	Comparator 1	Comparator 2	Age (range,	Control		Comparator 1		Comparator 2	
Lewis et al. 2009[490]	Placebo	Topiramate	-	12-17	33	NR	70	NR	-	-
Li et al. 2012	Placebo	Acupuncture	-	18-65	118	118	358	358	-	-
Linde et al. 2005[501]	Placebo	Acupuncture	-	18-65	78	81	138	145	-	-
Lipton et al. 2011[509]	Placebo	Topiramate	-	18-65	171	197	159	188	-	-
Silberstein et al. 2004[728]	Placebo	Topiramate	-	12-65	115	117	354	370	-	-
Silberstein et al. 2007[727]	Placebo	Topiramate	-	18-74	153	163	153	165	-	-
Silberstein et al. 2008[723]	Placebo	Oxcarbazepine	-	16-65	85	85	85	85	-	-

N; number of participants analysed, NR; number randomised

Two of the included studies were in adolescents only[41,490]. However, three of the other studies included people from age 12 and above[106,225,728] and one from age 16 and over[723]. The GDG did not consider that there was any reason adolescents should be expected to respond differently to adults for the treatments included in the network.

K.3.1 Network meta-analysis results: Change in migraine days

Table 25 summarises the results of the conventional meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA in terms of median difference for each treatment compared to placebo.

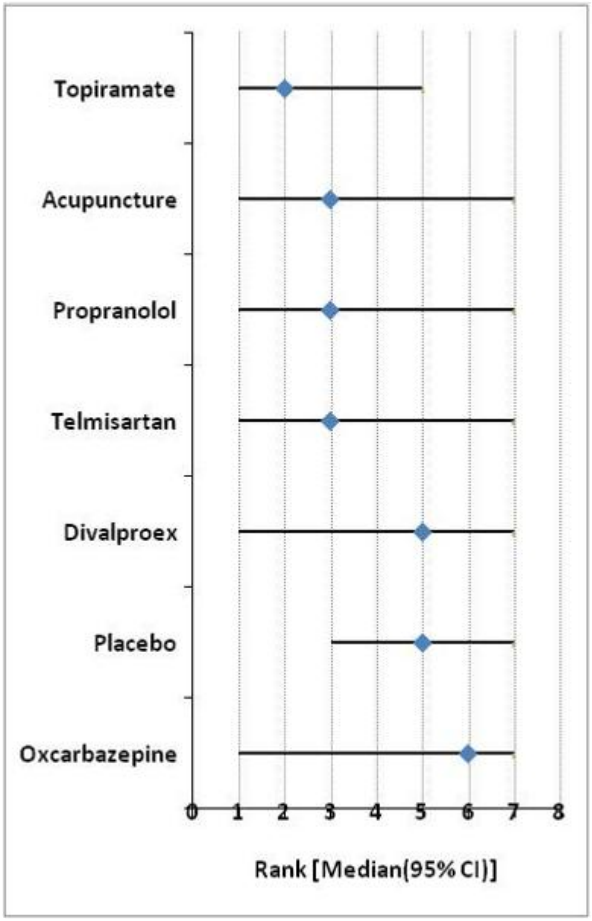
Table 25: Effect size for change in migraine days

Comparison	Effect size	
	Direct comparison (mean difference)	NMA (median difference)
Acupuncture vs placebo	-0.53 (-0.89, 0.17)	-0.58(-1.85, 0.70)
Divalproex vs placebo	0.10 (-0.72, 0.92)	0.10 (-2.13, 2.33)
Oxcarbazepine vs placebo	0.37 (-0.55, 1.29)	0.36 (-1.87, 2.62)
Propranolol vs placebo	-0.80 (-1.48, -0.12)	-0.58 (-2.49, 1.37)
Telmisartan vs placebo	-1.92 (-3.61, -0.23)	-0.53 (-3.07, 2.03)
Topiramate vs placebo	-1.03 (-1.36, -0.70)	-1.02 (-1.90, -0.06)
Topiramate vs propranolol	0.35 (-0.25, 0.95)	--

Effect size reported as: Mean difference (95% confidence interval) or median difference (95% credible interval)

Figure 282 shows the rank of each intervention compared to all other treatments. The rank is based on the median difference compared to placebo and indicates the probability of being the best treatment, second best, third best and so on among the seven different interventions being evaluated.

Figure 283: Rank order for treatments



Mean (SD)

2.16 (1.13)

3.33 (1.50)

3.49 (1.83)

3.62 (2.17)

4.94 (1.91)

5.08 (1.02)

5.43 (1.83)

Based on the direct comparisons (first results column Table 25), efficacy, as assessed by change in migraine days, favours topiramate over placebo. Propranolol (beta blocker), telmisartan (ARB) and acupuncture may be more effective than placebo but there is some uncertainty as the confidence interval crosses the line of minimum important difference. All other interventions are not shown to be more effective than placebo. The random effects model used for the NMA is a very good fit, with a residual deviance of 25.21 reported. This corresponds very well to the total number of trial arms, 25.

The DIC statistics were as follows in Table 26:

Table 26: DIC for migraine days – random effects

	Dbar	Dhat	pD	DIC
R	13.956	-10.048	24.004	37.96
Total	13.956	-10.048	24.004	37.96

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

No inconsistency was identified between the direct and NMA results for any comparison. All the median differences from the NMA lie within the 95% confidence interval from the direct comparison of the same treatments.

K.3.1.1 Evidence statements

A network meta-analysis of twelve studies comparing seven interventions suggested that topiramate is ranked as the 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.

K.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in chapter 14 and appendices G.2.5, deciding upon the most effective intervention for the prophylactic treatment of migraine is difficult. In order to overcome the difficulty of interpreting the conclusions from the numerous separate comparisons, an NMA of the direct evidence was performed.

Our analyses were based on a total of 12 studies of seven different interventions (six pharmacological and one non-pharmacological). The studies formed a network of evidence for change in migraine days.

The findings from the NMA were used to facilitate the GDG in decision making when developing recommendations for the prophylactic treatment of migraine.

Topiramate was the only treatment found to be conclusively superior to placebo in reducing the number of migraine days. Propranolol, telmisartan and acupuncture were all suggested to be more effective than placebo, but there was some uncertainty. In the ranking of treatments topiramate was also ranked first. Propranolol, telmisartan and acupuncture were joint second, but these had very large confidence intervals so there is considerable uncertainty. Oxcarbazepine was ranked lower than placebo.

The analysis compared all treatments to placebo in calculation of the mean differences, however the ranking looks at all treatments relative to each other and thus provides a hierarchy of treatments that may be used.

The network seems to fit well, as demonstrated by residual deviance and the fact that no inconsistencies in the network were found.

K.5 Conclusion

This analysis allowed us to combine the findings from many different comparisons presented in the reviews for prophylactic treatment of migraine even when direct comparative data was lacking.

Overall, the results of the network showed that topiramate is the most effective prophylactic treatment for migraine out of those included in this review.

It should be noted that this 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 (Chapter 14 and Chapter 17).

K.6 WinBUGS codes

```
# Normal likelihood, identity link

# Random effects model for multi-arm trials

model{                          # *** PROGRAM STARTS

for(i in 1:NS){                  #   LOOP THROUGH STUDIES

   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm

   delta[i,1] <- 0           # treatment effect is zero for control arm

   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines

   for (k in 1:na[i]) {           #  LOOP THROUGH ARMS

      var[i,k] <- pow(se[i,k],2)   # calculate variances

      prec[i,k] <- 1/var[i,k]      # set precisions

      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood

      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor

#Deviance contribution

      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]

    }

#  summed residual deviance contribution for this trial

   resdev[i] <- sum(dev[i,1:na[i]])

   for (k in 2:na[i]) {           # LOOP THROUGH ARMS

# trial-specific LOR distributions

      delta[i,k] ~ dnorm(md[i,k],taud[i,k])

# mean of LOR distributions, with multi-arm trial correction

      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]

# precision of LOR distributions (with multi-arm trial correction)

      taud[i,k] <- tau *2*(k-1)/k

# adjustment, multi-arm RCTs

      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
```

```
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
 }
for(k in 1:NT){
                                                                    #rk[k] <- NT+1-rank(d[],k)
                                                                    rk[k] <- rank(d[],k)
                                                                    best[k] <- equals(rk[k],1)
                                                            }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:NT){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
#A ~ dnorm(meanA,precA)
#for (k in 1:nt) { T[k] <- A + d[k]  }
}                              # *** PROGRAM ENDS


 Data
# ns= number of studies; nt=number of treatments
list(NS=12,NT=7)


 t[,1] t[,2] t[,3] y[,1] y[,2] y[,3] se[,1] se[,2] se[,3] na[]
 1 2 NA -2.8 -2.7 NA 0.36 0.22 NA 2
 1 4 NA -1.3 -2.75 NA 0.32 0.31 NA 2
 1 4 5 -1.1 -2.55 -1.9 0.24 0.24 0.25 3
 1 3 NA -1.14 -1.65 NA 0.57 0.55 NA 2
 1 4 NA -3.9 -2.8 NA 0.55 0.36 NA 2
```

1 4 NA -5.3 -6.6 NA 0.28 0.28 NA 2

1 4 NA -1.3 -2.33 NA 0.300144892546482 0.174866373518669 NA 2

1 4 NA -4.1 -5.6 NA 0.49 0.49 NA 2

1 6 NA -2.02 -1.65 NA 0.33 0.33 NA 2

1 7 NA -1.9 -2.2 NA 0.2 0.18 NA 2

1 7 NA -3.6 -3.4 NA 0.396781926800979 0.289427220457975 NA 2

1 7 NA -2.2 -3.77 NA 0.315309909427298 0.203554997166634 NA 2

END

list(

d=c(NA,0,0,0,0,0,0),

sd=.2,

mu=c(-2,2,-1,-1,0,1,-2,1,0,-2,3,-1))

Initial Values

#chain 1

list(d=c(NA, 0,0,0,0), sd=1, mu=c(0, 0, 0, 0, 0, 0, 0))

#chain 2

list(d=c(NA, -1,-3,-1,1), sd=4, mu=c(-3, -3, -3, -3, -3, -3, -3))

#chain 3

list(d=c(NA, 2,2,2,2), sd=2, mu=c(-3, 5, -1, -3, 7, -3, -4))

list(

d=c(NA,0,0,0,0,0,0),

sd=.2,

mu=c(2,3,3,-2,-1,0,-1,2,3,0,1))

Initial Values

#chain 1

list(d=c(NA, 0,0,0,0), sd=1, mu=c(0, 0, 0, 0, 0, 0, 0))

#chain 2

list(d=c(NA, -1,-3,-1,1), sd=4, mu=c(-3, -3, -3, -3, -3, -3, -3))

#chain 3

list(d=c(NA, 2,2,2,2), sd=2, mu=c(-3, 5, -1, -3, 7, -3, -4))

Appendix L: Cost-effectiveness analysis – Prophylactic treatment of migraine

L.1 Introduction

This economic analysis explores the cost effectiveness of different prophylactic treatments for migraine. The topic of prophylactic 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 patients at some point. Original economic analysis was initially planned for migraine, tension type headache and cluster headache; however no quality of life data was identified for tension type or cluster headache.

One economic study[112] comparing topiramate with usual care for prophylaxis of migraine was included in our systematic review of economic literature. Other four studies [7,113,261,865] 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[112] were in agreement with the findings of our original economic model (see L.3.4).

L.1.1 Model overview

A cost-utility analysis was undertaken where costs and QALYs were considered from a UK NHS and personal social services perspective.

L.1.1.1 Comparators

The comparators initially considered for the model were oxycarbazepine, sodium valproate/semisodium valproate (Divalproex), acupuncture, telmisartan, propranolol, topiramate and no treatment. Oxycarbazepine and sodium valproate/semisodium valproate (Divalproex) were associated with an increase in migraine days of 0.38 and 0.11 per month respectively compared to no treatment (see K.3.1). We therefore do not consider these two treatments in the analysis since they are dominated by no treatment; that is they are more costly and less effective.

L.1.1.2 Population

The population entering the model comprises patients with population characteristics as in the clinical review: patients aged 12 or over, diagnosed with migraine.

L.1.1.3 Time horizon and discounting

The time horizon considered in the model was 6 months; we chose this time horizon to reflect the relatively short term nature of the treatment and the duration of the trials.

L.1.2 Approach to modelling

L.1.2.1 Model structure

We built a decision analysis based on the results of the network meta-analysis (NMA) conducted for this review question and on the results of the acute treatment model described in Appendix J:.

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 (Appendix J:), assuming the most cost-effective acute treatment (Triptan + NSAID) would be used in the event of a migraine attack.

Figure 284- Model schematic

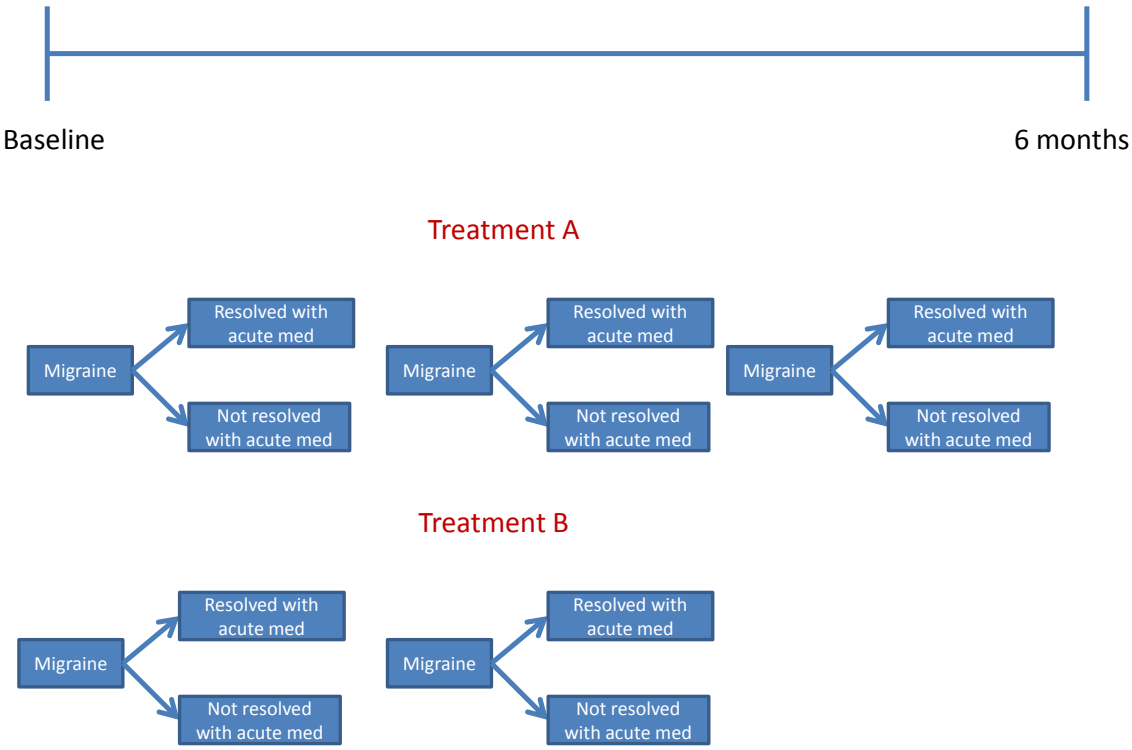


Figure 284 shows an example pathway for patients in the model; patients on each treatment experience a certain number of headaches over 6 months, which are treated with acute medication. The difference in QALYs is therefore driven by the reduction in migraine episodes that arises during a prophylactic treatment. Figure 284 shows the situation where treatment B avoids one more migraine than treatment A over a 6 month time horizon.

L.1.2.2 Uncertainty

We conducted a probabilistic sensitivity analysis in order to explore the uncertainty in model results. In probabilistic sensitivity analysis, each parameter is assigned a distribution reflecting its uncertainty; random draws are then taken from this distribution and propagated through the model, to calculate costs and QALYs. This process was repeated 50,000 times and results representing an average of the simulations were computed.

One way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters.

L.1.3 Model inputs

L.1.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with

clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 27 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 27 - Summary of base-case model inputs

Input	Data	Source
6 month course[(a)] of topiramate	£43.73	BNF 61[403] – see L.1.3.4
6 month course[(a)] of telmisartan	£119.00	BNF 61[403] – see L.1.3.4
6 month course[(a)] of propranolol	£16.08	BNF 61[403] – see L.1.3.4
6 month course[(b)] of acupuncture	£232.5	PSSRU[180] - see L.1.3.4
6 month course[(a)] of Oxcarbazepine	£250.56	BNF 61[403] – see L.1.3.4
6 month course[(a)] of sodium valproate/semisodium valproate (Divalproex)	£26.73	BNF 61[403] see L.1.3.4
Cost per acute migraine episode (Triptan + NSAID)	£2.23	See 0
Cost per GP visit	£41.00	PSSRU[180]
Average reduction in migraine days per month - Telmisartan	0.5134	See K.3.1
Average reduction in migraine days per month - Topiramate	1.039	See K.3.1
Average reduction in migraine days per month - Propranolol	0.5175	See K.3.1
Average reduction in migraine days per month - Acupuncture	0.09266	See K.3.1
Average reduction in migraine days per month - Oxcarbazepine	-0.3753	See K.3.1
Average reduction in migraine days per month - sodium valproate/semisodium valproate (Divalproex)	-0.1043	See K.3.1
Utility weight for a patient experiencing a migraine attack	-0.3	Evans et al (1997)[265]
Utility weight following successful migraine treatment[c]	0.81	Kind et al (1998)[437]

(a) Cost of drug only.
(b) Cost of 15 acupuncture visits (weighted number of sessions based on included RCTs) – see J.2.3.5.
(c) Assumed to be equal to the utility of the general population in the UK.

L.1.3.2 Relative treatment effects

To calculate relative treatment effects, a NMA was conducted in Winbugs (Appendix K:). The aim of the NMA was to calculate the change migraine days per month associated with each treatment (Table 28).

Table 28- Data of clinical effectiveness of treatments in ascending order of effectiveness - results of the NMA from the clinical review

Treatment	Migraine days avoided per month vs. no treatment
No treatment	-
Oxcarbazepine	-0.3753
Sodium valproate/semisodium valproate (Divalproex)	-0.1043
Telmisartan	0.5134
Propranolol	0.5175

Treatment	Migraine days avoided per month vs. no treatment
Acupuncture	0.583
Topiramate	1.039

In Table 28 oxcarbazepine and sodium valproate/semisodium valproate (Divalproex) have a negative number of migraine days avoided since patients in these treatment arms in the included RCTs experienced more days of migraine compared to patients in the placebo arm. For this reason the model was run after the exclusion of these treatments which would never be recommended.

L.1.3.3 Utilities

The effectiveness in the model is based on the number of migraine days avoided with the prophylactic treatment. However, when a migraine attack occurs the patient is assumed to be treated with the most cost-effective treatment, triptan in combination with NSAID, as identified in the acute treatment model (Appendix J:). The effectiveness estimates of triptan + NSAID are attached to the prophylactic model to adjust the actual quality of life gain from the avoided attack. For example, if a treatment is associated with a reduction of one migraine day compared to no treatment, the QALY gain would not be equal to the QALY of one day of migraine (-0.0008219) but to the QALY of a migraine treated with Triptan + NSAID (0.00000045). For details of this estimate, please see section J.2.4.3.

L.1.3.4 Resource use and cost

The GDG decided to consider resource use in terms acquisition costs for prophylactic drugs, consultations and acute medication use. The following tables show the total cost of each treatment considered in the model based on the cost of drugs and consultations.

Table 29 - Cost of six-month treatment with topiramate

Item	Unit cost	Quantity [(c)]	Total cost
Topiramate 25mg	£6.17 [(a)]	One pack needed for first few days of treatment.	£6.17
Topiramate 100mg	£12.52 [(a)]	Three packs needed for remainder of treatment course over 6 months.	£37.56
GP visit	£41.00 [(b)]	Two visits needed in a six month treatment course.	£82.00
		Total	***£125.73***

(a) Source: BNF61[403]
(b) Source: PSSRU[180]
(c) Source: expert opinion.

Table 30 – Cost of six-month treatment with propranolol

Item	Unit cost	Quantity [(c)]	Total cost
Propranolol 25mg	£4.02 [(a)]	Four packs needed in a six-month treatment course. Dose: 160mg a day for the duration of treatment.	£16.08
GP visit	£41.00 [(b)]	Two visits needed in a six month treatment course.	£82.00
		Total	***£98.08***

(a) Source: BNF61[403]

(b) Source: PSSRU[180]
(c) Source: expert opinion.

Table 31- Cost of six-month treatment with telmisartan

Item	Unit cost	Quantity [(c)]	Total cost
Telmisartan 80mg	£17.00 [(a)]	Seven packs needed in a six-month treatment course.	£119
GP visit	£41.00 [(b)]	Two visits needed in a six month treatment course.	£82
		Total	***£201***

(a) Source: BNF61[403]
(b) Source: PSSRU[180]
(c) Source: expert opinion.

Table 32 - Cost of six-month treatment with oxcarbazepine

Item	Unit cost	Quantity [(c)]	Total cost
Oxcarbazepine 150mg	£4.55 [(a)]	Four packs needed in a six-month treatment course. Dose: 150 mg per day initially, then escalated by 150 mg every 5 days up to 1200 mg per day.	£18.20
GP visit	£41.00 [(b)]	Two visits needed in a six month treatment course.	£82.00
		Total	***£100.20***

(a) Source: BNF61[403]
(b) Source: PSSRU[180]
(c) Source: expert opinion.

To calculate the cost of acupuncture (Table 33), we derived the resource utilisation (number of acupuncture sessions and duration) from the RCTs included in the NMA (Appendix K:) which inform the clinical outcome considered in the model (change in migraine days).

Table 33 - Cost of six-month treatment with acupuncture

Item	Unit cost	Quantity [(b)]	Total cost
Specialist visit	£15.5[(a)]	Fifteen visits needed in a six month treatment course.	£232.5
		Total	***£232.5***

(a) Source: PSSRU[180] - cost of one community physiotherapist visit (31 per hour) based on the average visit time (30 minutes) reported in the RCTs included in the clinical review
(b) Source: weighted average from RCTs: Li et al (2012)[494], Diener et al (2006)[221], Linde et al (2005)[501].

To calculate the cost of treatment with sodium valproate/semisodium valproate (Divalproex) we estimated the proportion of patients treated with each possible dosage in the RCTs included in our clinical review (Appendix K:). The calculation of the weighted cost of drugs only is reported in Table 34, while the overall cost of treatment including GP visits is reported in Table 35.

Table 34: Weighted cost of drug treatment with sodium valproate/semisodium valproate (Divalproex)

Daily dose	% patients (A)	Cost for 6 months (B)	Weighed cost for 6 months (A*B)
250 mg	14%	£24.68	£3.48
400	6%	£18.62	£1.14

Daily dose	% patients (A)	Cost for 6 months (B)	Weighed cost for 6 months (A*B)
500	37%	£16.94	£6.18
1000	36%	£33.87	£12.13
1500	7%	£50.81	£3.80
		Total	***£26.73***

(a) In some studies patients could have either 500 mg or 1000 mg. For these studies we assumed half of the patients had 500 mg and the other half had 1000 mg.

Table 35 - Cost of six-month treatment with sodium valproate/semisodium valproate (Divalproex)

Item	Unit cost	Quantity	Total cost
Sodium valproate/semisodium valproate (Divalproex) – drug cost	See Table 34	See Table 34	£26.73
GP visit	£41.00 (a)	Two visits needed in a six month treatment course (b).	£82.00
		Total	***£108.73***

(a) Source: PSSRU[180]
(b) Source: experts opinion

A combination of triptan and NSAID was considered to be the choice of acute medication, since our previous analysis (0) found it to be the most cost effective acute treatment. The total cost of prophylactic treatments were adjusted by the cost of acute treatment (£2.33) according to the number of migraine days avoided.

L.1.4 Computations

The mean cost and effectiveness of the strategies compared were calculated using Winbugs. Due to the instability of the ICER node in Winbugs, ICERs were calculated in Excel using the Winbugs output for the mean incremental costs and effects for each treatment. Incremental net benefits were exported from Winbugs to Excel using the CODA function in order to calculate rank-probability plots.

L.1.4.1 Calculating QALYs

To calculate the incremental QALYs vs no treatment (Q_T) associated with each treatment, we calculated the incremental QALY gain associated with a reduction in migraine days over 6 months, assuming each migraine was treated with triptan + NSAID.

We first calculate the utility weight associated with a day of migraine, when treated with triptan + NSAID ($\boldsymbol{U_{treat}}$**.**). We make the same assumptions for QALY calculations as in the acute treatment model (J.2.4.1). Let $\boldsymbol{p}$, $\boldsymbol{U_{mig}}$ and $\boldsymbol{U_{well}}$ denote the probability of response with triptan + NSAID, the utility weight associated with migraine and the utility weight associated with no migraine, respectively. Note that to be consistent with the acute treatment model, we assume that response occurs at two hours, and thus a scaling factor of 22/24 is used as a multiplier for the QALYs of patients who responded.

$$\boldsymbol{U_{treat}} = \frac{\mathbf{22}}{\mathbf{24}} \times \left(\boldsymbol{p} \times \boldsymbol{U_{well}} + (\mathbf{1} - \boldsymbol{p}) \times \boldsymbol{U_{mig}}\right) + \frac{\mathbf{2}}{\mathbf{24}} \times \boldsymbol{U_{mig}}$$

Let $\boldsymbol{\delta}$ be the efficacy of a given treatment measured in migraine days avoided per month as reported in J.2.3.3. We calculate the QALYs gained over 6 months, $\boldsymbol{Q_T}$ associated with this treatment as follows:

II $$Q_T = \frac{6 \times \delta \times (U_{well} - U_{treat})}{365}$$

L.1.4.2 Calculating costs

To work out the incremental costs of a six-month treatment vs no treatment (C_{trt}) we consider the acquisition costs of a six-month course of prophylactic medication C_{med}, the costs of consultations for patients on prophylactic medication C_{cons} and the costs of administering acute medication C_{acu} over a six-month period. Since a reduction in migraine days will lead to a reduction in acute medication, this is explicitly accounted for in calculating costs, using the treatment efficacy δ:

III $$C_{trt} = C_{med} + C_{cons} - (\delta \times C_{acu}) * 6$$

L.1.4.3 Calculating cost-effectiveness

It is possible, for a particular cost-effectiveness threshold, to express cost-effectiveness results in term of incremental net monetary benefit (INMB) vs no treatment. This is calculated by multiplying the total incremental QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total incremental costs (see equation IV). The decision rule then applied is that the comparator with the highest INMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation INMB is used to identify the optimal strategy in the probabilistic analysis simulations.

For a given treatment strategy x:

IV $$INMB_X = INCQALYS_X \times \lambda - INCCOST_X$$

Where:

$INCQALYS_X$ = total incremental QALYs vs no treatment for strategy x

λ = cost-effectiveness threshold

$INCCOST_X$ = total incremental cost vs no treatment of strategy x.

The probabilistic analysis was run for 50,000 simulations. For each simulation, total discounted costs and total discounted QALYs were calculated for each strategy. The incremental net benefit was also calculated and the most cost-effective option identified (that is, the one with the highest incremental net benefit vs no treatment), at a threshold of £20,000 per QALY gained.

The results of the probabilistic analysis were summarised in terms of mean discounted costs and QALYs with rank-probability plots, where cost effectiveness rankings were calculated for each strategy and the probability of a given treatment attaining a certain rank determined by the number of times the treatment achieved that rank in all the simulations, divided by the number of simulations. For example, suppose treatment 2 achieved rank 1, that is, it had the highest net benefit in 200 simulations, the probability of treatment 2 being ranked 1st is $\frac{200}{10000} = 2\%$

L.1.5 Sensitivity analyses

Uncertainty was explored through probabilistic sensitivity analysis and deterministic sensitivity analysis.

L.1.5.1 Probabilistic analysis

Due to the information available and the fact that the only costs included were drug costs from the BNF, we only assigned distributions to treatment effects in the model for the probabilistic sensitivity analysis. We were unable to assign a distribution to utilities since no estimate of their uncertainty is available. Since the model was constructed in the same Winbugs file as the NMA (K.6), the uncertainty in treatment effects is automatically accounted for in the analysis.

L.1.5.2 Deterministic sensitivity analysis

We conducted a threshold analysis on the utility of a patient experiencing a migraine (-0.3 in the base case) in order to establish the utility weight for migraine at which the most cost-effective treatment was no longer cost effective compared to no treatment at a willingness to pay threshold of £20,000 per QALY.

We also conducted a one-way sensitivity analysis on the number of sessions of acupuncture in the acupuncture strategy. In fact, in an RCT conducted in the UK[826], where patients assigned to the acupuncture arm could receive a maximum of 12 session, the average number of sessions was 9. Based on this estimate, the cost of acupuncture was £144 instead of £232. We also decided to conduct a threshold sensitivity analysis on the number of acupuncture sessions should the results appear to be sensitive to this parameter.

L.1.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC.

L.1.7 Interpreting results

The strategy with the highest net benefit is the one that should be recommended. However, since we were unable to capture the incidence or disutilities of treatment specific adverse events, caution should be exercised in recommending treatments where there is some concern about side effects. It should also be noted that this economic analysis applies to migraine only, since, due to the paucity of quality of life data we were unable to conduct an equivalent analysis in tension type or cluster headache.

L.2 Results

L.2.1 Base case

Firstly we considered the results of the clinical review in the form of intermediate outcome (change in migraine days) as reported in J.2.3.3. Oxcarbazepine and sodium valproate/semisodium valproate (Divalproex) were associated with an increase in migraine days of 0.38 and 0.11 per month respectively when compared to no treatment. We did not include these two treatments in the incremental analysis since they are dominated by no treatment.

Table 36 - Cost and efficacy of treatments not ruled out by simple dominance vs no treatment

Treatment	Incremental cost vs no treatment (£)	Migraine days avoided per month vs no treatment

Treatment	Incremental cost vs no treatment (£)	Migraine days avoided per month vs no treatment
No treatment	0	0
Propranolol	£90	0.594
Topiramate	£112	1.065
Telmisartan	£194	0.510
Acupuncture	£228	0.583

After converting the intermediate outcome (migraine days) into QALYs as described in L.1.4.1 and calculating the costs, we assessed the incremental cost-effectiveness of treatments which were not dominated by no treatment.

In the base case, model inputs were set as shown in Table 27 and the model was run probabilistically. Results including the ranking according to mean INMB can be found in Table 37.

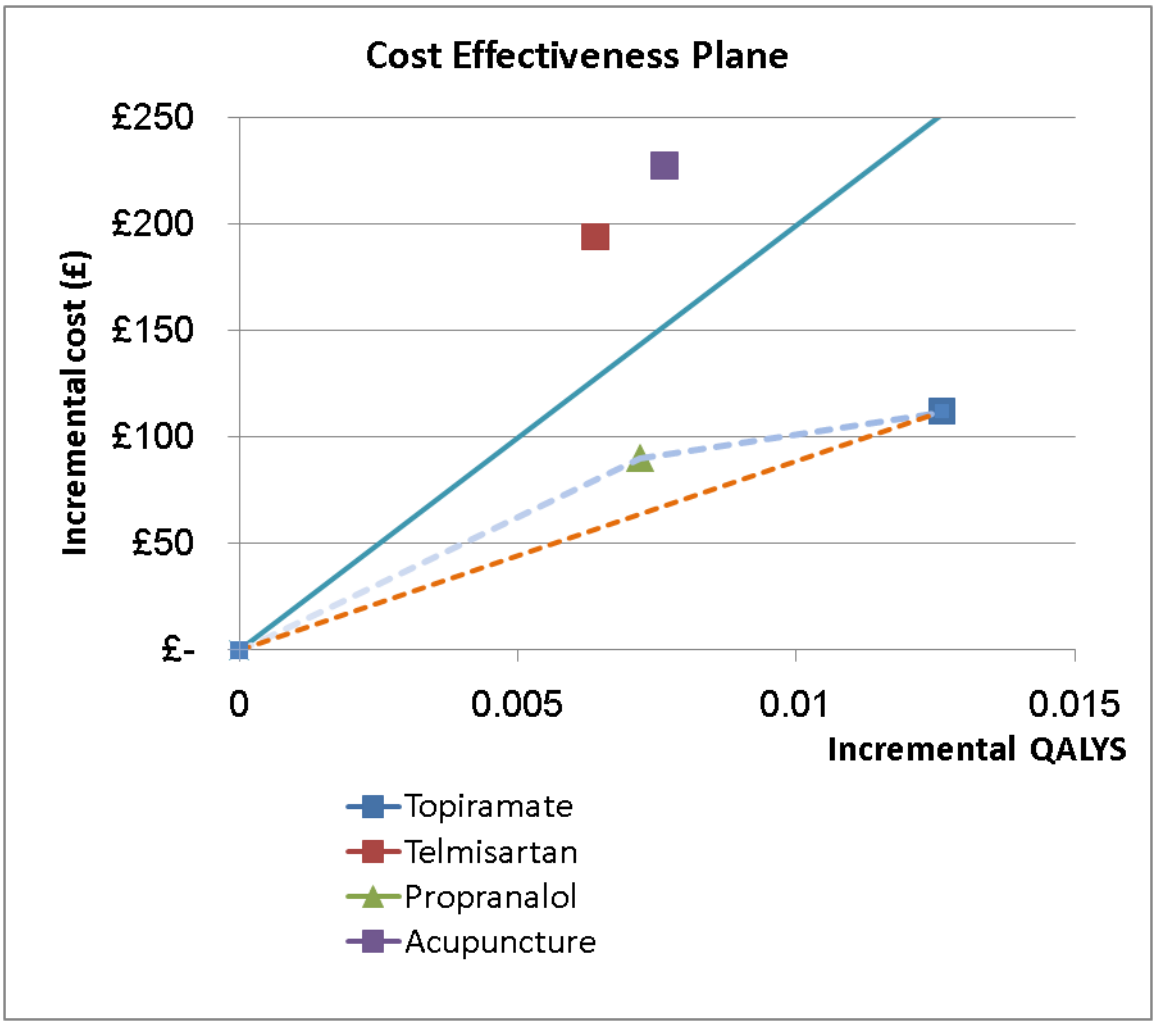
Table 37 Base case cost-effectiveness results (probabilistic)

Treatment	Mean cost per patient(£)	Mean QALYs	INMB vs No trreatment* [£20k per QALY]	Probability that strategy is most cost-effective [£20k per QALY]	Rank (95% CI)*
No treatment	0	0	0	2.2%	3 (2 , 5)
Propranolol	90	0.007199	53.63	25.5%	2 (1, 5)
Topiramate	112	0.01261	139.9	45.2%	1 (1, 4)
Telmisartan	194	0.006381	-66.53	20.7%	4 (1, 5)
Acupuncture	228	0.00763	-75.21	6.4%	5 (1 , 5)

** 1=most cost-effective, 5=least cost-effective [£20k per QALY]*

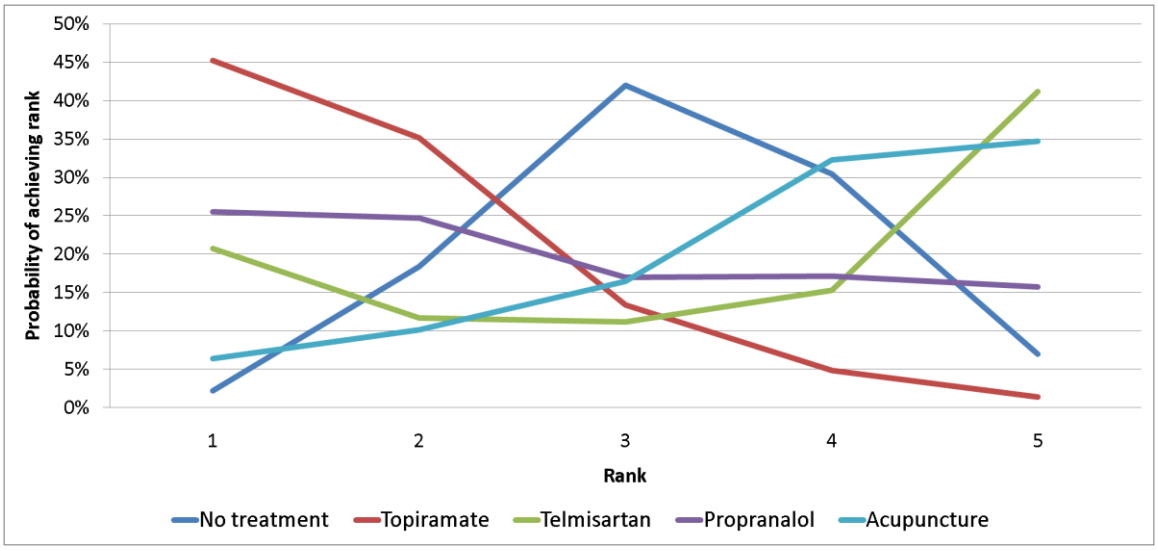
Table 37 shows that topiramate was the most cost effective treatment as it was associated with the highest incremental net monetary benefit. . The cost-effectiveness plane in Figure 285 provides a visual demonstration of the cost-effectiveness of the compared treatments. The treatments to the right of the £20,000 per QALY threshold (the blue solid line) are the ones with positive INMB compared to no treatment and therefore more cost-effective than no treatment (topiramate and propranolol). Those treatments to the left of the £20,000 per QALY threshold are not cost-effective (acupuncture and telmisartan) and have in fact a negative INMB. To establish which of the treatments with positive INMB is the most cost-effective, we can look again at the graph. It can be seen in Figure 285 that the line representing the ICER of propranolol is steeper than the line representing the ICER of topiramate. This shows that propranolol is extendedly dominated by topiramate and therefore topiramate is the most cost-effective treatment in the base case analysis.

Figure 285 - Cost effectiveness plane – strategies below the blue line representing the £20,000/QALY threshold are considered cost-effective.



The model was run probabilistically and in each of the 50,000 simulations a strategy could be the optimal one based on the INMB as determined by the values of the parameters sampled in the distributions. For each strategy we could then calculate in what proportion they ranked 1 to 5 across all the simulations (Figure 286).

Figure 286 – Rank-probability plot



The treatment with the highest probability of being cost effective was topiramate (around 45%) followed by propranolol (around 25%) and telmisartan (around 21%). These figures highlight the uncertainty in the analysis.

L.2.2 Sensitivity analysis

A threshold analysis on migraine utility was conducted, as described in L.1.5.2. 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 (Table 38).

Table 38 One-way sensitivity analysis on number of acupuncture visits - results (probabilistic)

Treatment	Mean cost per patient(£)	Mean QALYs	INMB vs No trreatment* [£20k per QALY]	Probability that strategy is most cost-effective [£20k per QALY]	Rank (95% CI)*
No treatment	0	0	0	1.5%	3 (2 , 5)
Propranolol	90	0.007199	53.63	24.1%	2 (1, 5)
Topiramate	112	0.01261	139.9	40.8%	1 (1, 4)
Acupuncture	136	0.00763	16.29	13.9%	4 (1 , 5)
Telmisartan	194	0.006381	-66.53	19.7%	5 (1, 5)

** 1=most cost-effective, 5=least cost-effective [£20k per QALY]*

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. 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).

L.3 Discussion

L.3.1 Summary of results

Our cost effectiveness analysis shows that, based on a NMA conducted using RCT data, acquisition costs, consultation costs and cost of administering acute medication, topiramate is the most cost effective treatment for prophylactic treatment of migraine. We note that the probabilistic sensitivity analysis showed a high level of uncertainty in these results.

L.3.2 Limitations and interpretation

This model is based on findings from RCTs and therefore any issues concerning interpretation of the clinical review also apply to the interpretation of this 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. Had we adopted a longer time horizon, the high initial costs of topiramate would have been diluted, therefore topiramate might come out more cost-effective. On the other hand, should the effectiveness decline with time, any prophylactic treatment would be less cost-effective compared to no treatment when a longer time-horizon is adopted.

L.3.3 Generalisability to other populations / settings

All of our findings relate mostly to an adult population as this was the population in the trial and the cost of treatment was calculated for adult dosages. Furthermore, the model relates to a one stage “6 month” course of treatment and should not be used to inform decisions regarding sequential and long term treatment.

L.3.4 Comparisons with published studies

We reviewed one study[111] which compared topiramate to no treatment and found it to be cost effective. This study was conducted in the same population as the study from our clinical review and used the results of a meta-analysis containing some, but not all of the clinical effectiveness data from our review. 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.

One study[826] evaluating the cost-effectiveness of acupuncture compared to usual care found that acupuncture is cost-effective. 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.

L.3.5 Conclusion = evidence statement

Our analysis suggests that topiramate is the most cost effective treatment for prophylactic pharmacological treatment of migraine. However there is some uncertainty around this conclusion and some of the other strategies have some probability of being cost-effective.

Acupuncture is not cost-effective if the strategy comprises an average of 15 visits; however it is cost-effective if fewer visits (9 in our sensitivity analysis) are assumed.

Appendix M: Research recommendations

M.1 Imaging for diagnosis in people with suspected cluster headache

Research question:

Is imaging of people with a first occurrence of cluster headache a clinically and cost effective diagnostic tool to exclude serious intra-cranial disorders?

Why this is important:

Many clinicians experienced in the management of cluster headache advise routine imaging to exclude serious intracranial disorders as a cause for the patient's symptoms. The incidence of abnormality in people without a prior history of bouts of cluster headache is unknown.

A prospective cohort of people presenting with a first diagnosis of cluster headaches, or a case control study comparing people with cluster headache and age/sex matched controls drawn from a community sample is needed to assess the clinical and cost effectiveness of ruling out serious intracranial disorders in this population. Outcomes should include incidence of serious intracranial disorder. If the actual incidence of serious intracranial pathology in those presenting for the first time with cluster headaches is low then routine imaging will be unnecessary. This would have significant cost implications for the NHS.

Criteria for selecting high-priority research recommendations:

PICO question	For people diagnosed clinically with cluster headache does routine imaging identify substantially more serious intra-cranial pathology than could be expected by chance?
Importance to patients or the population	Results would inform recommendations for, or against, routine imaging for people newly diagnosed with cluster headaches.
Relevance to NICE guidance	A high prevalence of serious intra-cranial abnormalities would inform a positive recommendation for imaging; a high prevalence of chance findings, in the absence of a high prevalence of serious intra-cranial abnormalities would inform a strong recommendation against imaging.
Relevance to the NHS	There are significant concerns that cluster headaches may be associated with serious intracranial pathology and that it is important that the NHS identifies these early to ensure timely treatment.
National priorities	No.
Current evidence base	There are no suitable studies addressing this.
Equality	The research question has no particular equality issues.
Study design	Prospective cohort of people presenting with a first diagnosis of cluster headaches, or a case control study comparing people with cluster headache and age/sex matched controls drawn from a community sample. Outcomes should include patient centred outcome measures.
Feasibility	Since new diagnoses of cluster headaches are likely to be made by specialist services (secondary care / GPwSI) this research should probably take place in a specialist environment rather than primary care.
Other comments	None.
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

M.2 Amitriptyline to prevent recurrent migraine

Research question:

Is amitriptyline a clinically and cost effective prophylactic treatment for recurrent migraine?

Why this is important:

Effective prevention has the potential to make a major impact on the burden of disability caused by recurrent migraine. There are few pharmacological agents that have been proven to prevent recurrent migraine.

Amitriptyline is widely used, off-label, to treat chronic painful disorders, including migraine. Inadequate evidence was found in the review for this guideline for the effectiveness of amitriptyline in the prophylaxis of migraine. A double-blind randomised controlled trial (RCT) is needed to assess the clinical and cost effectiveness of amitriptyline compared with placebo. The definition of migraine used should be that in the International classification of headache disorders II or this guideline. Outcomes should include change in patient-reported headache days, responder rate and incidence of serious adverse events. If amitriptyline is shown to be effective, it will widen the range of therapeutic options, in particular for people in whom recommended medications are ineffective or not tolerated.

Criteria for selecting high-priority research recommendations:

PICO question	In children and adults, is amitriptyline superior to placebo in preventing recurrent migraine attacks?
Importance to patients or the population	The current draft guidance includes amitriptyline, although it has no marketing. There is limited evidence for use of prophylactic drugs in the prevention of chronic migraine. Topiramate, the only drug with good evidence of effectiveness may be poorly tolerated by many people and is teratogenic. There is a need for alternative prophylactics drugs of proven effectiveness.
Relevance to NICE guidance	Future NICE guidance may recommend amitriptyline as an alternative prophylactic drug for recurrent migraine.
Relevance to the NHS	Amitriptyline 50 mg/day is about a fifteenth of the cost of topiramate 100 mg/day (BNF listing 2007) so if found to be effective may reduce NHS expenditure when compared to use of topiramate. There would be minimal additional implications for service delivery or configuration: there would be a requirement for the new guidance to be disseminated and for GPs and hospital physicians and neurologists and the general public and support groups to become aware of the findings and for prescribers to change their recommendations.
National priorities	Improving the care of people with migraine is in line with the National Service Framework for Long Term Conditions. If amitriptyline is effective more people would reap the benefits and have fewer attacks, need to use fewer acute / rescue medicines, and have fewer days off work. There would be health benefits and cost benefits to the NHS and the wider economy.
Current evidence base	The NICE headache guideline development systematic review found inadequate evidence to support the use of amitriptyline as a first line treatment.
Equality	The research question has no particular equality issues.
Study design	Double blind RCT compared to placebo. The trials should be independently powered for both age groups (children and young people aged under 18 years and adults). Outcomes should include patient centred outcome measures.
Feasibility	Given the high prevalence of migraine, and evidence that one third of people have had preventative treatment at some time and that 10% are on preventative treatment at any time, there is no shortage of potential participants in England.

Other comments	None.
Importance	The use of medication to prevent migraine is a key part of the guideline. The importance is therefore high: the research is essential to inform future updates of key recommendations in the guideline.

M.3 Pizotifen to prevent recurrent migraine

Research question:

Is pizotifen a clinically and cost effective prophylactic treatment for recurrent migraine?

Why this is important:

There are few data to inform guidance on the prevention of migraine in children and young people.

Pizotifen is a popular treatment for migraine prevention in the UK, especially in children and young people. It has been in use since the 1970s and appears to be well tolerated. Inadequate evidence was found in the review for this guideline for the effectiveness of pizotifen in the prophylaxis of migraine. A double-blind RCT either head-to-head with best available treatment, or placebo controlled, is needed to assess the clinical and cost effectiveness of pizotifen in young people aged under 18 and adults. The trial should enrol people aged under 18 and adults. The definition of migraine used should be that in the International classification of headache disorders II or this guideline. Outcomes should include change in patient-reported migraine days, responder rate and incidence of serious adverse events. If pizotifen is shown to be effective, it will widen the range of therapeutic options, in particular for young people in whom recommended medications are ineffective or not tolerated.

Criteria for selecting high-priority research recommendations:

PICO question	In young people aged under 18 and adults, is pizotifen superior to placebo in preventing recurrent migraine attacks?
Importance to patients or the population	Current options for prophylactic treatment for migraine are limited and there are very few data directly applicable to people aged under 18. Knowing if pizotifen is effective would inform current practice and improve the care of children and young people with migraine, as well as ascertaining whether pizotifen is an effective alternative prophylaxis for adults with migraine..
Relevance to NICE guidance	Future NICE guidance may be able to recommend an additional treatment for prevention recurrent migraine attacks.
Relevance to the NHS	There would be minimal additional implications for service delivery or configuration if pizotifen was found to be effective.
National priorities	Improving the care of children and young people with migraine is in line with the National Service Framework for Long Term Conditions and the National Service Framework for Children and Young People and Maternity Services. If effective more children and young people would reap the benefits and have fewer attacks, need to use fewer acute / rescue medicines, have fewer days off school. Also their parents would have fewer days off work to look after them: so there would be health benefits and possibly cost benefits to the NHS and the wider economy.
Current evidence base	The NICE headache guideline development systematic review found no adequate evidence to support or condemn the use of pizotifen. No research has been done to modern standards.
Equality	This research recommendation focuses on a vulnerable group: namely children and young people with migraine for which there are currently few specific research data to inform practice.

Study design	An RCT comparing pizotifen to either best standard care or to placebo. The trials should be independently powered for both age groups (children and young people aged under 18 years and adults). Outcomes should include patient centred outcome measures.
Feasibility	Given the high prevalence of migraine, and the evidence that one third of young people have had preventative treatment at some time and that 10% are on preventative treatment at any time there is no shortage of potential participants in England. Other trials in this population have had problems recruiting so a feasibility study would be needed to show the acceptability of the study to children and their parents.
Other comments	Since migraine in children is often not diagnosed consideration should be given to recruiting from a non-clinical environment e.g. schools.
Importance	The use of medication to prevent migraine is a key part of the guideline. The question is important given the relative lack of evidence on effectiveness for so many medicines in common use in children. The importance is therefore high: the research is essential to inform future updates of key recommendations in the guideline.

M.4 Topiramate to prevent recurrent cluster headache

Is topiramate a clinically and cost effective prophylactic treatment for recurrent cluster headache?

Why this is important

Cluster headache is an excruciatingly painful and highly disabling disorder. The management of cluster headache includes the use of preventive treatments to stop the attacks as quickly and safely as possible. There is a significant unmet clinical need for effective preventive treatments in cluster headache and few data to inform guidance on prophylaxis of cluster headache. Although numerous agents including verapamil, topiramate, lithium, methysergide and gabapentin are used in routine clinical practice, this is largely based on clinical experience as very few RCTs have been performed.

Several open-label studies have reported on the efficacy of topiramate in the preventive treatment of cluster headache. There is therefore a need for a high-quality RCT of topiramate in the prevention of cluster headaches.

Criteria for selecting high-priority research recommendations:

PICO question	In adults aged over 18, is topiramate superior to placebo in preventing recurrent cluster headache attacks?
Importance to patients or the population	Cluster headache is an excruciatingly painful and highly disabling disorder. The current preventative treatment options in cluster headache are very limited. While numerous preventative treatments are used in routine clinical practise, the controlled evidence base is largely limited to verapamil. A significant proportion of people with cluster headache either don't respond to verapamil or are unable to tolerate it. Determining whether topiramate is effective would increase the treatment options based on good quality evidence and improve the care of this patient group.
Relevance to NICE guidance	Future NICE guidance may be able to recommend an additional treatment for the preventative treatment of cluster headache.
Relevance to the NHS	Verapamil is associated with cardiac blocks, atrioventricular block. The dose of verapamil therefore has to be titrated on a fortnightly basis with regular ECG monitoring, which has implications for service delivery. Topiramate can be titrated rapidly with minimal monitoring.
National priorities	Improved quality of life for those living with chronic headache syndromes may

	reduce work loss due to headaches.
Current evidence base	Several open label studies have reported on the efficacy of topiramate in the preventative treatment of cluster headache (1-6). The NICE headache guideline development systematic review did not find any controlled evidence to support the use of topiramate in cluster headache.
Equality	The research question has no particular equality issues.
Study design	Randomised double-blind placebo- controlled trial in episodic and chronic cluster headache. Outcomes should include patient centred outcome measures.
Feasibility	An adequately powered randomised controlled trial can be carried out within 1-2 years.
Other comments	None.
Importance	The use of medication to prevent cluster headache is a key part of the guideline. The question is important given the relative lack of evidence on effectiveness for medicines in common use for cluster headache. The importance is therefore high: the research is essential to inform future updates of key recommendations in the guideline.

M.5 Manual therapies to manage chronic headache disorders

Does treatment with manual therapies improve headache outcomes and quality of life for people with chronic headache disorders (chronic migraine or chronic tension-type headache)?

Why this is important

There are few data to support the use of non-pharmacological approaches to the management of chronic headache disorders. Manual therapies, including techniques aimed at joint mobilisation and manipulation, soft tissue mobilisation and release, trigger point therapies and a variety of soft tissue and joint stretching techniques are used for people living with chronic painful disorders. A study of the clinical and cost effectiveness of manual therapies for people with chronic headache disorders has the potential to substantially improve their quality of life.

A RCT is required to assess the clinical and cost effectiveness of manual therapies in comparison to an active control for the management of people with chronic headaches. Patient centred headache outcomes such as change in patient-reported headache days, responder rate and headache-specific quality of life should be included.

Criteria for selecting high-priority research recommendations:

PICO question	For people with chronic headache disorders (chronic migraine or chronic tension type headache) does treatment with manual therapies improve headache outcomes and quality of life?
Importance to patients or the population	Current treatments for chronic headache disorders are of limited effectiveness. If manual therapies are effective, they will help people to live better with their headache disorder when treatment options, including pharmacological treatment, are ineffective.
Relevance to NICE guidance	Future NICE guidance may be able to offer a wider range of non-drug treatment options for chronic headache disorders.
Relevance to the NHS	An effective programme should reduce need for secondary care services for management of chronic headache disorder, and potentially reducing costs.
National priorities	Improved quality of life for those living with chronic headache disorders may reduce work loss due to headaches.

Current evidence base	The evidence base to support the use of manual therapies in comparison to an active control for the management of chronic headache disorders is currently inconclusive.
Equality	The research question has no particular equality issues.
Study design	Pragmatic RCT comparing manual therapy to an active control.. The trials should be independently powered for both age groups (children aged under 18 years and adults). Outcomes should include patient centred outcome measures.
Feasibility	Chronic headache disorders are very common so there will be an adequate pool of potential participants. Before any trial there will be a need to evaluate the treatment package and to decide on the most appropriate outcome measures to be used.
Other comments	A definition of what is an active control will need to be established prior to start of the trial.
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

M.6 Psychological interventions to manage chronic headache disorders

Does a psychological intervention such as cognitive behavioural therapy (CBT) improve headache outcomes and quality of life for people with chronic headache disorders (chronic migraine, chronic tension-type headache or medication overuse headache)?

Why this is important

Psychological interventions such as CBT are widely recommended for people with chronic painful disorders. An effective psychological intervention based on cognitive behavioural principles for people with chronic headache disorders has the potential to substantially improve their quality of life. There are few data to support the use of these interventions to manage chronic headache disorders.

A pragmatic RCT is needed to assess the impact of a psychological intervention compared with an active control. Mood disorders are commonly comorbid with headache disorders, but the trial needs to address the impact of a psychological intervention on headache alone, using appropriate headache outcomes such as change in patient-reported headache days and headache-specific quality of life.

Criteria for selecting high-priority research recommendations:

PICO question	For people with chronic headache disorders (chronic migraine, chronic tension type headache, medication overuse headache) is a psychological intervention based on cognitive behavioural principles more effective than an active control to improve headache outcomes and quality life?
Importance to patients or the population	Current treatments for chronic headache disorders are of limited effectiveness. A psychological intervention based on cognitive behavioural principles will allow those living with chronic headaches who receive inadequate relief from pharmacological treatments by conventional treatments live better with their headache disorder.
Relevance to NICE guidance	Future NICE guidance may be able to offer a wider range of non-drug treatment options for chronic headache disorders.
Relevance to the NHS	An effective programme should reduce need for secondary care services for management of chronic headache disorders, and potentially reducing costs.
National priorities	Improved quality of life for those living with chronic headache disorders may

	reduce work loss due to headaches.
Current evidence base	There is no current evidence to support the use of psychological treatments in the management of chronic headache disorders compared to an active control.
Equality	The research question has no particular equality issues.
Study design	Pragmatic RCT comparing psychological therapy to an active control. The trials should be independently powered for both age groups (children aged under 18 years and adults). Outcomes should include patient centred outcome measures.
Feasibility	Chronic headache disorders are very common so there will be an adequate pool of potential participants. Before any trial there will need to be a programme of work to develop and evaluate the treatment package and to decide on the most appropriate outcome measures to be used.
Other comments	Depression is a common co-morbidity with headache disorders. Psychological treatments such as CBT are widely used in the treatment of mood disorders. The study should address the effect of psychological intervention on headache alone as well as on co-morbid conditions.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

M.7 Exercise programmes to manage chronic headache disorders

Does an exercise programme added to usual care improve headache outcomes and quality life for people with chronic headache disorders (chronic migraine, chronic tension-type headache or medication overuse headache)?

Why this is important

There are some data supporting the use of exercise programmes in the treatment of chronic headache disorders. These data are not directly applicable to the UK and are based on interventions that are unlikely to be practicable in the NHS. Nevertheless, exercise shows potential as a non-pharmacological approach to the management of chronic pain disorders and has been shown to be effective in reducing chronic low back pain. If exercise programmes are effective for people living with chronic headache disorders, they have the potential to substantially improve quality of life at low cost.

A RCT is needed to assess the clinical and cost effectiveness of exercise as a complex intervention in the treatment of chronic headache disorders. A programme of work will be required before the RCT to identify an appropriate exercise programme. Headache outcomes such as change in patient-reported headache days, responder rate and headache-specific quality of life should be included.

Criteria for selecting high-priority research recommendations:

PICO question	For people with chronic headache disorders (chronic migraine, chronic tension type headache and/or medication overuse headache) does exercise added to usual care improve headache outcomes and quality life?
Importance to patients or the population	Current treatments for chronic headache disorders are of limited effectiveness. If yoga is effective it will help those who receive inadequate relief from pharmacological treatments by conventional treatments to live better with their headache disorder.
Relevance to NICE guidance	Future NICE guidance may be able to offer a wider range of non-drug treatment options for chronic headache disorders.
Relevance to the NHS	An effective programme should reduce need for secondary care services for management of chronic headache disorders, and potentially reducing costs.
National priorities	Improved quality of life for those living with chronic headache disorders may

	reduce work loss due to headaches.
Current evidence base	There are some data supporting the use of exercise programmes[401,819]. They are, however, not all directly applicable to, or implementable in, the UK. There is a need to test a yoga package appropriate to the UK and the NHS or an appropriate exercise programme.
Equality	The research question has no particular equality issues.
Study design	Pragmatic RCT comparing exercise added to usual care to care alone. The trials should be independently powered for both age groups (children aged under 18 years and adults). Outcomes should include patient centred outcome measures.
Feasibility	Chronic headache disorders are very common so there will be an adequate pool of potential participants. Before any trial there will need to be a programme of work to develop and evaluate the treatment package and to decide on the most appropriate outcome measures to be used.
Other comments	None.
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

M.8 Education and self-management to manage chronic headache disorders

Does an education and self-management programme improve headache outcomes and quality of life for people with chronic headache disorders (chronic migraine, chronic tension-type headache or medication overuse headache)?

Why this is important

There are few data to support the use of non-pharmacological approaches to the management of chronic headache disorders. Self-management programmes that include education and self-care advice are widely recommended for people living with chronic painful disorders but are potentially costly. A study of the clinical and cost effectiveness of self-management programmes for people with chronic headache disorders has the potential to substantially improve their quality of life.

A RCT is required to compare an education and self management package with usual care. Before any trial there will need to be a programme of work to develop and evaluate an appropriate treatment package and to decide on the most appropriate outcome measures to be used. Headache outcomes such as change in patient-reported headache days, responder rate and headache-specific quality of life should be included.

Criteria for selecting high-priority research recommendations:

PICO question	For people with chronic headache disorders (chronic migraine, chronic tension type headache, and/or medication overuse headache) does an education and self-management programme added to usual care improve headache outcomes and quality of life?
Importance to patients or the population	Current treatments for chronic headache disorders are of limited effectiveness. A self-management and education programme will allow those living with chronic headaches to make the most appropriate use of treatment options and to help them live better with their headache disorder when treatment options are ineffective.
Relevance to NICE guidance	Future NICE guidance may be able to offer a wider range of non-drug treatment options for chronic headache disorders.
Relevance to the NHS	An effective programme should reduce need for secondary care services for

	management of chronic headache disorder, and potentially reducing costs.
National priorities	Improved quality of life for those living with chronic headache disorders may reduce work loss due to headaches. Potentially this may reduce both chronic worklessness due to headaches and also short term work absence due to acute headache attacks.
Current evidence base	There is no current evidence to support the use of education and self-management programmes in the management of chronic headache disorders.
Equality	An effective self-management programme should allow disadvantaged groups to make better use of available NHS services and treatments.
Study design	Pragmatic RCT of education and self-management programmes compared to usual care. The trials should be independently powered for both age groups (children aged under 18 years and adults).Outcomes should include patient centred outcome measures.
Feasibility	Chronic headache disorders are very common so there will be an adequate pool of potential participants. Before any trial there will need to be a programme of work to develop and evaluate the treatment package and to decide on the most appropriate outcome measures to be used.
Other comments	Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

M.9 Pharmacological treatment with steroids or treatments for headache prophylaxis to aid withdrawal treatment in medication overuse headache

Does a course of steroid treatment or pharmacological treatments used for headache prophylaxis, help people with medication overuse headaches withdraw from medication?

Why this is important

Medication overuse headache is a common disorder. Current best advice is for abrupt withdrawal without any supportive pharmacological treatment. Many people with medication overuse headache find it difficult to withdraw abruptly because in the short term their headaches can become much worse. The use of steroids may aid withdrawal and for those who have an underlying headache disorder such as migraine or tension-type headache, appropriate prophylaxis may assist in treating the headache.

Double-blind RCTs are needed in people with suspected medication overuse headache who have an identifiable primary headache disorder. There should be two separate trials, one to investigate withdrawal of medication with placebo versus withdrawal of medication with steroid treatment, and the other to investigate withdrawal of medication with placebo versus withdrawal of medication with appropriate pharmacological prophylaxis. Outcomes should include change in acute medication use, proportion of patients who no longer have suspected medication overuse headache, change in patient-reported headache days and headache-specific quality of life.

Criteria for selecting high-priority research recommendations:

PICO question	For people with medication overuse headache who are withdrawing from medication, does a course of steroid tablets, or a course of prophylactic medication, when compared to placebo, improve quality of life and increase the proportion who successfully withdraw from medication?

Importance to patients or the population	Medication overuse headache is a common problem. There is no current pharmacological support that can be given to aid withdrawal. If steroids, or a course of prophylactic medication, are effective this could have major health impact.
Relevance to NICE guidance	A positive result from the trial will inform a revision of NICE guidance.
Relevance to the NHS	If steroids, or appropriate prophylactic medication, are effective, they will reduce need for specialist services (secondary care and GPWSI), GP consultations and prescribing costs.
National priorities	No.
Current evidence base	There is limited good quality objective evidence on the use of steroids, or prophylactic pharmacological treatment, for aiding withdrawal of overused medications in people with medication overuse headaches[93,605].
Equality	Medication overuse headache preferentially affect the more socio-economically deprived members of the community[405].
Study design	Placebo controlled randomised controlled trials with cost effectiveness analysis. Outcomes should include patient centred outcome measures.
Feasibility	The most appropriate location for this trial is likely to be specialist services (secondary care or GPWSI) rather than primary care to ensure diagnosis is robust and that only the more severely affected are included.
Other comments	A definition of withdrawal will need to be established before the trial starts.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

Appendix N: Excluded studies

N.1 Excluded clinical studies

N.1.1 Indications for consideration of additional investigation

Ref Id	Reason for exclusion
Ahmed et al. 2010[11]	Mean age under 12 years
Antunes et al. 2001[39]	Headache not in isolation of other symptoms
Argyriou et al. 2006[44]	Headache not in isolation of other symptoms
Berger et al. 1996[75]	Assesses prevalence of headache in HIV + and HIV – populations
Brew et al. 1993[107]	Assesses prevalence of headache in HIV + and HIV – populations
Burton et al. 1997[118]	Population not relevant to protocol (mean age under 12 years)
Clarke et al. 2010[152]	Headache not in isolation of other symptoms
Christiaans et al. 2002[148]	Headache not in isolation of other symptoms
Clouston et al. 1992[153]	Headache not in isolation of other symptoms
Conicella et al. 2008[163]	Mean age under 12 years
Evers et al. 2000[268]	Evaluates course of headache in people with HIV
Fodden et al. 1989[274]	Headache not in isolation of other symptoms
Katwere et al. 2009[425]	Headache not in isolation of other symptoms
Kernick et al. 2008[432]	Population not relevant to protocol

Ref Id	Reason for exclusion
Kernick et al. 2008[433]	Population not relevant to protocol
Kernick et al. 2009[431]	Population not relevant to protocol
Korkmaz et al. 2002[448]	Mean age under 12 years
Li et al. 2002[492]	Assesses characteristics of primary headache
Locker et al. 2006[511]	Headache not in isolation of other symptoms
Mack et al. 2004[521]	Assesses frequency of primary headache
Pengiran Tengah et al. 2003[618]	Headache not in isolation of other symptoms
Ramirez er al. 1997[649]	Headache not in isolation of other symptoms
Rana et al. 2011[651]	Does not assess primary headache
Ray et al. 2009[657]	Mean age under 12 years
Rothman et al. 1999[673]	Headache not in isolation of other symptoms
Schievink et al. 2011[703]	Headache not in isolation of other symptoms
Sham et al. 1992[714]	Headache not in isolation of other symptoms
Stevenson et al. 1998[763]	Headache not in isolation of other symptoms
Taylor et al. 2012[774]	No relevant risk factors assessed
Tso et al. 1993[804]	No control group
Vazquez et al. 1994[821]	Retrospective from people with tumours
Vikovi et al. 2009[832]	Abstract
You et al. 2011[864]	No control group

N.1.2 Identifying people with primary headache

Ref Id	Reason for exclusion
Ayzenberg et al. 2011[50]	Population based door-to-door survey
Brighina et al. 2005[109]	Preliminary analysis of Brighina et al. 2007 (included)
Cady et al. 2004[124]	Not all participants diagnosed by ICHD criteria
Cousins et al. 2011[169]	Systematic review
Di Piero et al. 2007[194]	Participants not consecutively recruited
Hagen et al. 2000[351]	General population sample, not just headache
Hagen et al. 2010[350]	General population sample, not just headache
Hershey et al. 2005[373]	Assesses sensitivity of the ICHD rather than the questionnaire
Kallela et al. 2001[410]	All patients already diagnosed with migraine by ICHD criteria
Kirchmann et al. 2006[439]	Participants not consecutively recruited; genetics study
Kukava et al. 2007[460]	Population based door-to-door survey
Lainez et al. 2005[463]	Participants not consecutively recruited or randomly enrolled
Lainez et al. 2010[462]	Primary care population sample, not just headaches
Lipton et al. 1992[508]	Survey not focussing on questionnaires
Maizels & Burchette 2003[524]	Three populations, grouped as one for analysis (not all consecutively recruited, not all blinded for reference standard and index test results)
Marcus et al. 2004[530]	Population recruited from the community, sample size too low (<25 per arm)
Pryse-Phillips et al. 2002[642]	Inappropriate reference standard for this review
Rasmussen et al. 1991[655]	Population from cross-sectional survey of general population, not suspected primary headache

Ref Id	Reason for exclusion
Rueda-Sanchez & Diaz-Martinez 2004[676]	Population solely psychology students
Siva et al. 2008[738]	Population not people presenting with suspected primary headaches only
Tepper et al. 2008[777]	Survey not focussing on questionnaires for case finding
Valentinis et al. 2009[814]	Population not people with suspected primary headache
van Oosterhout et al. 2011 [817]	Not clinical study (research purposes)
Yoon et al. 2008[863]	General population sample, not just headache patients
Zarifoglu et al. 2008[867]	Population not people with suspected primary headache

N.1.3 Headache diaries for the diagnosis and management of primary headaches and medication overuse headache

Ref Id	Reason for exclusion
Anciano 1987[23]	Survey
Blanchard et al. 1981[83]	Not assessing diary use
Blanchard 1983[82]	Not assessing diary use
Diamond et al. 2006[198]	Review
Jensen & Bendtsen 2005[399]	Not assessing diary use
Laurell et al. 2003[479]	No relevant outcomes
Lipton et al. 2003[503]	Abstract
Marcus et al.2010[529]	Review
Metsahonkala et al. 1997[556]	Meanage under 12 years
Moloney et al. 2009[565]	Not assessing diary use
Nappi et al 2006[580]	Systematic review
Nielsen et al. 2000[590]	Not assessing diary use
Niere & Jerak 2004[591]	Not assessing diary use
Richardson et al 1983[664]	Not assessing diary use
Russell et al. 1994[678]	Review
Sances et al. 2003[684]	Not assessing diary use
Shin et al 2008[719]	Not assessing diary use
Stensland &Malterud 2001[762]	Not assessing diary use
Stewart et al 1999[765]	Not assessing diary use
Stewart et al 2000[764]	Not assessing diary use
Tepper et al. 2004[776]	No relevant outcomes
Torelli & Jensen 2010[796]	Systematic review
van den Brink et al. 2001[816]	Not assessing diary use

N.1.4 Imaging for diagnosis in people with suspected primary headaches

Ref Id	Reason for exclusion
Ahmed et al. 2010[11]	Children only, mean age not provided
Akpek et al. 1995[15]	Unclear if all participants had suspected primary headache
Alehan et al. 2002[17]	Mean age under 12 years
Ang et al. 2009[34]	Audit, not clinical study
Aysun et al. 1998[49]	Not all patients imaged. Not clear how patients were selected for imaging

Ref Id	Reason for exclusion
Baker et al. 1983[55]	Unclear if all patients had suspected primary headache. Not clear how patients selected for imaging
Chan et al. 2006[142]	Mean age under 12 years
Clarke et al. 2010[152]	Not all participants had suspected primary headache. Results not separated
Cull et al. 1995[175]	
De Benedittis et al. 1995[188]	Case control study. Reporting of outcomes unclear
Demaerel et al. 1996[190]	Not suspected primary headache
Duarte et al. 1996[241]	Not clear if participants had suspected primary headache
Dutto et al. 2009[243]	Not all participants had suspected primary headache, results not separated
Ellawela et al. 2010[256]	Abstract
Elliot et al. 2011[257]	Not all participants had suspected primary headache
Frishberg et al. 1994[300]	Review
Graf et al. 2008[334]	Mean age under 12 years. Not all participants were imaged
Graf et al. 2010[333]	Mean age under 12 years. Not all participants were imaged
Grosskreutz et al. 1991[343]	Not just suspected primary headache
Howard et al. 2005[385]	RCT of imaging for reassurance. No relevant outcomes
Igarashi et al. 1991[392]	No relevant outcomes
Jordan et al. 2009[407]	Economic analysis
Kahn et al. 1993[409]	Not clear if participants had suspected primary headache
Knaus et al. 1978[444]	Not all participants had suspected primary headache
Lewis et al. 2000[489]	Mean age under 12 years. Not all participants were imaged
Locker et al. 2004[510]	Not all participants were imaged
Locker et al. 2006[511]	Not all participants were imaged
Mayta et al. 1995[543]	Not all participants were imaged, majority had other indications
Medical Advisory Secretariat 2010[546]	Review
Medina et al. 1997[548]	Not suspected primary headache in isolation of other symptoms
Mitchell et al. 1993[563]	Not all participants had suspected primary headache
Osborn et al. 1991[599]	No relevant outcomes
Ramchandren et al. 2007[648]	Retrospective case series, not all participants had suspected primary headache
Rana et al. 2011[651]	Not all participants had suspected primary headache
Reyes et al. 2011[661]	Not all participants had suspected primary headache, not all participants were imaged
Rho et al. 2011[662]	Mean age under 12 years. Not all participants imaged
Sargent et al. 1979[695]	No relevant outcomes
Sobri et al. 2003[744]	Not all participants had suspected primary headache
Soges et al. 1988[747]	No relevant outcomes
Sotaniemi et al. 1991[752]	Not clear if all participants had suspected primary headache
Taylor et al. 2012[774]	Not clear if all participants had suspected primary headache
Thomas et al. 2010[788]	Not clear if all participants had suspected primary headache
Valenca et al. 2002[813]	Study on imaging for reassurance, not diagnosis of serious

Ref Id	Reason for exclusion
	intracranial abnormalities.
Weingarten et al. 1992[843]	Not all participants had suspected primary headache
Wober-Bingol[860]	Mean age under 12 years
You et al. 2011[864]	Not all participants had suspected primary headache

N.1.5 Imaging for management

None

N.1.6 Information and support for people with primary headaches

Ref Id	Reason for exclusion
Bekkelund & Salvesen 2001[65,65]	Not about patient information and support
Bekkelund & Salvesen 2002[64,65]	Not about patient information and support
Blau et al. 1995[91,91]	Not about patient information and support
Chibnall et al. 1995[147,147]	Not primary headache
Coeytaux et al. 2007[155,156]	Not about patient information and support
Dowson & Jagger 1999[234,236]	Not about patient information and support
Holmes et al. 2001[378,378]	Not about patient information and support
Kelman 2006[429,430]	Not about patient information and support
Munksgaard et al. 2011[575,575]	Not about patient information and support
Peters et al. 2005[619,622]	Not about patient information and support
Ruiz de Velasco et al. 2003[677,677]	Not about patient information and support
Skomo et al. 2008[740,740]	Not about patient information and support
Wenzel et al. 2003[845,845]	Not about patient information and support

N.1.7 Acute pharmacological treatment of tension type headache

Ref Id	Reason for exclusion
Anneken et al. 2010[35]	Systematic review
Bendtsen et al. 2007[72]	Prophylactic treatment
Bendtsen et al. 2010[73]	Review
Bettucci et al. 2006[76]	Prophylactic treatment
Bigal et al. 2006[80]	Commentary
Borges et al. 1976[99]	Drug not in protocol
Boz et al. 2003[103]	Prophylactic treatment
Cerbo et al. 2005[139]	Drug withdrawn due to safety concerns
Cicek et al. 2004[149]	No relevant outcomes
Diamond et al. 1983[200]	No relevant outcomes
Diener et al. 2005[226]	Non-English language
Diener et al. 2011[223]	Post-hoc subgroup analysis of previously reported data
Evers et al. 2005[266]	Review
Friedman et al. 1986[293]	Drug not in protocol
Friedman et al. 1988[294]	No relevant outcomes
Gallagher et al. 1987[304]	Abstract
Gilbert et al. 1976[322]	No relevant outcomes

Ref Id	Reason for exclusion
Gladstone et al. 2003[323]	Review
Glassman et al. 1980[324]	Drug not in protocol
Glassman et al. 1982[325]	Drug not in protocol
Gupta et al. 2001[345]	Review
Harden et al. 1998[358]	No relevant outcomes
Hwang et al. 1987[391]	Drug not in protocol
Kagan et al. 1978[408]	Drug not in protocol
Kaniecki et al. 2006[417]	Not assessing acute TTH treatment
Kochi et al. 1994[445]	Review
Krusz et al. 2004[454]	Book chapter
Langemark et al. 2987[472]	No relevant outcomes
Langemark et al. 1985[470]	No relevant outcomes
Latsko et al. 2011[478]	Not assessing acute TTH treatment
La Veneziana et al. 1996[480]	No relevant outcomes
Lujan et al. 1992[518]	Not RCT
Manzano et al. 2010[528]	Systematic review
Migliardi et al. 1994[559]	No relevant outcomes
Miller et al. 1987[560]	Data only available in graph format
Monteith et al. 2010[571]	Review
Nebe et al. 1995[584]	Sample size too low (<25 per arm)
Peters et al. 1983	No relevant outcomes
Ryan et al. 1977	No relevant outcomes
SCHACHTEL 1991	Outcomes only reported in graphs
Schachtel et al. 1996[699]	Outcomes only reported in graphs
Shaughnessy et al. 2001[717]	Series of abstracts
Solomon et al. 2002[748]	Narrative paper reviewing treatments for TTH
Tfelt-Hansen et al. 2007[779]	Review
Thomas et al. 1994[789]	Intervention and outcome not relevant to protocol
Torelli et al. 2010[795]	Literature review
Verhagen et al. 2005[822]	Review
Verhagen et al. 2006[823]	Systematic review
Von Graffenried et al. 1980[830]	Systematic review
Wojcicki et al. 1977[861]	No relevant outcomes
Worzi et al. 1990[862]	Prophylactic treatment
Zhao et al. 2003[874]	Review
Zhou et al. 2006[875]	Non-English language
Zissis et al. 2007[876]	Prophylactic treatment

N.1.8 Acute pharmacological treatment of migraine

Ref Id	Reason for exclusion
Adam et al. 1987[6]	Placebo comparison
Anon 1971[1]	No relevant outcomes
Anon 1973[2]	Open label

Ref Id	Reason for exclusion
Anon 1991[786]	Placebo comparison
Anon 1991[787]	Placebo comparison
Anthony et al. 1968[37]	Placebo comparison
Aurora et al. 2011[48]	Placebo comparison
Azzopardi et al. 2008[52]	Systematic review
Belgrade et al. 1989[67]	Sample size too low (<25 per arm)
Bell et al. 2006[68]	Open label
Block et al. 1998[92]	Single blind vs usual care
Boureau et al. 1995[101]	Single blind vs usual care
Bussone et al. 2000[122]	Placebo comparison
Cady et al. 2000[125]	Placebo comparison
Cady et al. 2011[126]	Placebo comparison
Callaham et al. 1986[129]	Placebo comparison
Carleton et al. 1998[130]	No relevant outcomes
Cete et al. 2005[141]	Drug not in protocol
Cicek et al. 2004[149]	No relevant outcomes
Codispoti et al. 2001[154]	Placebo comparison
Colman et al. 2005[161]	Systematic review
Colman et al. 2004[160]	Systematic review
Colman et al. 2008[162]	Systematic review
Crooks et al. 1964[174]	Compares routes of administration
Cull et al. 1997[176]	Placebo comparison
Cutler et al. 1995[181]	Placebo comparison
Davis et al. 1995[187]	Sample size too low (<25 per arm)
Diamond et al. 1999[201]	Review
Diamond et al. 1976[199]	No relevant outcomes
Diav-Citrin et al. 2011[206]	Drug not in protocol
Dib et al. 2002[208]	Placebo comparison
Dib et al. 2003[207]	Abstract
Diener et al. 2003[209]	Abstract
Diener et al. 2011[212]	Placebo comparison
Diener et al. 2011[223]	Post hoc subgroup analysis of previously reported data
Dimonda et al. 2003[193]	Open label
Donaldson et al. 2008[229]	Placebo comparison
Dowson et al. 2006[235]	Within class comparison
Edwards et al. 2001[245]	Prophylactic treatment
Ellis et al. 1993[258]	No relevant outcomes
Ferrari et al.2001[271]	Systematic review
Ferrari et al. 2002[270]	Not RCT
Fiesseler et al. 2011[273]	Placebo comparison
Foldes et al. 1972[276]	Drug not in protocol
Frampton et al. 2011[285]	Review
Frederick et al. 1997[286]	Systematic review

Ref Id	Reason for exclusion
Freitag et al. 1993[288]	Placebo comparison
Freitag et al. 2001[289]	Drug not in protocol
Friedman et al. 2006[298]	Sample size too low (<25 per arm)
Friedman et al. 2007[297]	Placebo comparison
Friedman et al. 2008[299]	Systematic review
Gamzu Elkan et al. 1995[306]	Abstract
Gawel et al. 2001[309]	Not RCT
Geraud et al. 2000[314]	Placebo comparison
Geraud et al. 2003[313]	Abstract
Gerber et al. 1991[316]	Abstract
Gerber et a. 1994[317]	Open label
Goadsby et al. 2000[327]	Placebo comparison
Goldstein et al. 1998[329]	Placebo comparison
Griffith et al. 2008[341]	Not RCT
Haberer et al. 2010[347]	Open label
Hakkarainen et al. 1978[354]	Drug not in protocol
Hakkarainen et al. 1980[355]	No relevant outcomes
Hamalainen et al. 1997[356]	Mean age under 12 years
Haugh et al. 1992[360]	Abstract
Havanka et al. 2000[361]	Placebo comparison
Innes et al. 1999[394]	Placebo comparison
Jones et al. 1994[404]	Placebo comparison
Kallos et al. 1971[413]	Not RCT
Kangasniemi et al. 1992[416]	No relevant outcomes
Kellstein et al. 2000[427]	Placebo comparison
Kelly et al. 1997[428]	Open label
Kinnunen et al. 1988[438]	No relevant outcomes
Klapper et al. 1991[441]	Abstract
Klapper et al. 1993[443]	Sample size too low (<25 per arm)
Kostic et al. 2010[450]	No relevant outcomes
Lane et al. 1989[469]	Sample size too low (<25 per arm)
Larkin et al. 1992[473]	Sample size too low (<25 per arm)
Latsko et al. 2011[478]	Not assessing acute treatment of migraine
Limmroth et al. 1999[497]	No relevant outcomes
Lipton et al. 2000[504]	Placebo comparison
Lipton et al. 2000[507]	Placebo comparison
Massiou et al.1996[535]	Abstract
Misra et al. 2004[561]	Drug withdrawn due to safety concerns
Myers et al. 1995[576]	Drug not in protocol
Nappi et al. 1994[581]	Placebo comparison
Padma et al. 1998[603]	Placebo comparison
Patten et al. 1991[612]	Placebo comparison
Pearce et al. 1983[614]	No relevant outcomes

Ref Id	Reason for exclusion
Peatfield et al. 1983[615]	No relevant outcomes
Pfaffenrath et al. 1998[623]	Placebo comparison
Pilgrim et al. 1991[629]	Not RCT
Pini et al. 1995[633]	Placebo comparison
Pini et al. 1999[632]	Placebo comparison
Pradalier et al. 1985[636]	Open label
Prior et al. 2010[640]	Placebo comparison
Reches et al. 1999[658]	Abstract
Rederich et al. 1995[659]	Placebo comparison
Richman et al. 2002[665]	No relevant outcomes
Salazar et al. 2011[681]	Not double blind
Sandrini et al. 1998[686]	Placebo comparison
Saper et al. 2006[687]	Drug withdrawn due to safety concerns
Sargent et al. 1995[691]	Placebo comparison
Sargent et al. 1988[694]	No relevant outcomes
Savani et al. 1999[698]	Placebo comparison
Scherl et al. 1995[702]	Sample size too low (<25 per arm)
Schulman et al. 2003[708]	Sample size too low (<25 per arm)
Seeburger et al. 2011[711]	Placebo comparison
Sharma et al. 2002[716]	Sample size too low (<25 per arm)
Shrestha et al. 1996[720]	Sample size too low (<25 per arm)
Singh et al. 2008[736]	Systematic review
Slawson et al. 2000[741]	Abstract
Stiell et al. 1991[766]	No relevant outcomes
Stronks et al. 2003[768]	Sample size too low (<25 per arm)
Tek et al. 1987[775]	Sample size too low (<25 per arm)
Tepper et al. 2011[778]	Placebo comparison
Tietjen et al. 2005[792]	Sample size too low (<25 per arm)
Tfelthansen et al. 1984[782]	No relevant outcomes
Tfelthansen et al. 1998[784]	Placebo comparison
Titus et al. 2001[793]	No relevant outcomes
Treves et al. 1992[801]	No relevant outcomes
Ueberall et al. 2001[809]	Review
Visser et al. 1996[828]	Placebo comparison
Waters et al. 1970[839]	Abstract
Wells et al. 2001[844]	Duplicate data from previously reported
Wilkinson et al. 1999[851]	Abstract
Wilson et al. 1998[853]	Drug not in protocol
Winner et al. 1994[855]	Open label

N.1.9 Acute pharmacological treatment of cluster headache

Ref Id	Reason for exclusion
Abiusi et al. 2000[4]	Non-English language

Ref Id	Reason for exclusion
Andersson et al. 1986[27]	No relevant outcomes
Anthony et al. 1978[38]	Drug not in protocol
Bahra et al. 2000[54]	Data reported in graphs, unclear population
Cittadini et al. 2008[150]	Duplicate of previously reported data
Di Sabato et al. 1993[195]	No relevant outcomes
Drummond et al. 1985[238]	No relevant outcomes
Frampton et al. 2011 [285]	Review
Matharu et al. 2004[537]	Drug not in protocol
Nilsson Remahl et al.2002[593]	No relevant outcomes
Rozen et al. 2004[674]	Not RCT

N.1.10 Prophylactic pharmacological treatment of tension type headache

Ref Id	Reason for exclusion
Bettucci et al. 2006[76]	Drug not in protocol
Diamond et al. 1971[203]	No relevant outcomes
Gabrielidou et al. 1998[302]	Crossover trial
Goadsby et al. 2002[326]	Review
Holroyd et al. 2001[383]	No relevant outcomes
Lance et al. 1972[466]	Crossover trial
Lance et al. 1963[468]	Sample size too low
Langemark et al. 1990[471]	No relevant outcomes
Mitsikostas et al. 2011[564]	Review
Oguzhanoglu et al. 1999[596]	Open label
Pfaffenrath et al. 1991[624]	Not full report of RCT
Rampello et al. 2004[650]	Open label
Singh et al. 2002[737]	No relevant outcomes
Vernon et al. 2009[824]	Trial prematurely stopped; results not reported
Walker et al. 1998[834]	Sample size too low (<25 per arm)
Yurekli et al. 2008[866]	Sample size too low (<25 per arm)
Zissis et al. 2007[876]	Sample size too low (<25 per arm)

N.1.11 Prophylactic pharmacological treatment of migraine

Ref Id	Reason for exclusion
Ahuja et al. 1985[14]	Sample size too low (<25 per arm)
Andersson et al. 1973[25]	Within class comparison
Andersson et al. 1983[26]	Outcomes measured at 8 weeks
Ansell et al. 1988[36]	No relevant outcomes
Arthur et al. 1971[45]	Crossover trial
Ashrafi et al. 2005[46]	Mean age under 12 years
Ashtari et al. 2008[47]	Outcomes measured at 8 weeks
Bademosi et al. 1978[53]	Sample size too low (<25 per arm)
Bank et al. 1994[57]	Within class comparison
Battistella et al. 1990[61]	Crossover trial

Ref Id	Reason for exclusion
Battistella et al. 1993[60]	Crossover trial
Behan et al. 1980[63]	Crossover trial
Behan et al. 1982[62]	Open label
Bellavance et al. 1990[71]	No relevant outcomes
Bidabadi et al. 2010[77]	Mean age under 12 years
Bille et al. 1977[81]	Crossover trial
Borgesen et al. 1974[100]	Crossover trial
Carroll et al. 1975[135]	Crossover trial
Chen et al. 2001[145]	Crossover trial
Couch et al. 1979[168]	Outcomes reported at 4 weeks
Couch et al. 2011[167]	No relevant outcomes
Dalsgaard-Nielsen et al. 1968[184]	Drug not in protocol
DePinto et al. 1967[189]	Population includes cluster headaches
Diamond et al. 1975[205]	Abstract
Diamond et all. 1976[199]	Crossover trial
Diamond et al. 1982[204]	Crossover trial
Diamond et al. 2005[197]	Duplicate of previously reported data
Diener et al. 1996[217]	Drug not in protocol
Diener et a. 2001[222]	Drug not in protocol
Diener et al. 2007[211]	Open label
Diener et al. 2007[215]	Sample size too low (<25 per arm)
Diener et al. 2007[214]	Erratum
Domingues et al. 2009[228]	Outcomes reported at 8 weeks
Dooley et al. 1999[231]	Review
Drummond et al. 1985[237]	Open label
Edwards et al. 2003[246]	Sample size too low (<25 per arm)
Eftedal et al. 2004[247]	Drug not in protocol
Eiland et al. 2007[248]	Review
Ekbom et al. 1972[251]	Sample size too low (<25 per arm)
Ekbom et al. 1975[250]	Crossover trial
Forssman et al. 1972[278]	Crossover trial
Forssman et al. 1983[279]	Crossover trial
Forsythe et al. 1984[280]	Crossover trial
Freitag et al. 1984[291]	Sample size too low (<25 per arm)
Gallagher et al. 1987[305]	Not RCT
Gelmers et al. 1983[310]	No relevant outcomes
Gerber et al. 1991[315]	Sample size too low (<25 per arm)
Gerber et al. 1995[319]	Drug not in protocol
Goadsby et al. 2002[328]	Review
Gomersall et al. 1973[332]	Crossover trial
Grahame et al. 1960[335]	Drug not in protocol
Havanka et al. 1985[362]	Crossover trial
Havanka et al. 1982[363]	Sample size too low (<25 per arm)

Ref Id	Reason for exclusion
Heathfield et al. 1977[366]	Crossover trial
Herrmann et al. 1977[372]	Within class comparison
Hubbe et al. 1973[387]	Crossover trial
Hudgson et al. 1967[388]	Crossover trial
Jacobs et al. 1972[395]	Sample size too low (<25 per arm)
Kangasniemi et al. 1979[415]	Crossover trial
Klapper et al. 1996[442]	Open label
Krymchantowski et al. 2012[457]	Outcomes reported at 6 weeks
Lance et al. 1970[467]	Not RCT
Lawrence et al. 1977[483]	Sample size too low (<25 per arm)
Limmroth et al. 2007[498]	Pooled data from 3 different trials
Ludvigsson et al. 1974[517]	Sample size too low (<25 per arm)
Malvea et al. 1973[525]	Crossover trial
Mansoureh et al. 2008[527]	Drug comparison not in protocol
Martinez et al. 2003[534]	Open label
Mathew et al. 1981[538]	Open label
Mathew et al. 2001[540]	Incomplete data reporting
Mathew et al. 2003[539]	Review
Mehvari et al. 2005[550]	Outcomes reported at 45 days
Mei et al. 2006[552]	Inappropriate population
Nair et al. 1975[578]	Sample size too low (<25 per arm)
Nanda et al. 1978[579]	Crossover trial
Nattero et al. 1991[583]	Abstract
Nelles et al. 2010[585]	Not RCT
Nicolodi et al. 1997[589]	Not RCT
Noone et al. 1980[594]	Crossover trial
Orholm et al. 1986[598]	Drug not in protocol
Ozyalcin et al. 2005[600]	Sample size too low (<25 per arm)
Palferman et al. 1983[608]	Crossover trial
Paterna et al. 1992[611]	Non- English language
Pedersen et al. 1966[616]	Crossover trial
Pita et al. 1977[634]	Sample size too low (<25 per arm)
Pradalier et al. 1989[637]	Duplicate of previously reported data
Presthus et al. 1971[639]	Crossover trial
Rao et al. 2000[653]	No relevant outcomes
Rosen et al. 1983[669]	Not RCT
Ryan et al. 1982[680]	Sample size too low (<25 per arm)
Saper et al. 1994[690]	No relevant outcomes
Sargent et al. 1985[693]	Inappropriate population
Schrader et al. 2001[707]	Crossover trial
Silcocks et al. 2010[731]	Not RCT
Silvestrini et al. 2004[733]	Inappropriate population
Sjaastad et al. 1972[739]	Sample size too low (<25 per arm)

Ref Id	Reason for exclusion
Steardo et al. 1982[753]	Open label
Steiner et al. 1985[756]	Abstract
Steiner et al. 1988[755]	Drug not available in UK
Steiner et al. 1988[759]	Outcomes reported at 2 months
Swanson et al. 2005[770]	Review
Tarlaci et al. 2009[771]	Within class comparison
Tfelthansen et al. 1984[783]	Crossover trial
Viswanathan et al. 1991[829]	Sample size too low (<25 per arm)
Weber et al. 1972[841]	Crossover trial
Wessely et al. 1987[846]	Sample size too low (<25 per arm)
Whewell et al. 1966[847]	Crossover trial
White et al. 2006[849]	Incomplete data reported
Wideroe et al. 1974[850]	Not RCT
Winner et al. 2005[856]	Mean age under 12 years
Winner et al. 2006[858]	Pooled data from 3 different trials
Zeeberg et al. 1981[869]	Drug not in protocol

N.1.12 Prophylactic pharmacological treatment of cluster headache

Ref Id	Reason for exclusion
Ambrosini et al. 2005[22]	No relevant outcomes
Bussone et al. 1979[119]	Not RCT
Bussone et al. 1990[121]	No relevant outcomes
Caccia et al. 1975[123]	Participants acted as their own controls. Population not relevant to review question.
Ekbom et al. 1969[249]	Not RCT
Jammes et al. 1975[396]	No relevant outcomes
Medina et al. 1980[547]	No relevant outcomes
Meyer et al. 1983[558]	Compares high and low dose of the same drug
Moore et al. 2001[572]	Abstract
Saper et al. 2002[689]	Drug not in protocol
Saper et al. 2003[688]	Abstract
Steiner et al. 1997A[758]	No relevant outcomes

N.1.13 Prophylactic non-pharmacological management of primary headaches with acupuncture

N.1.13.1 Migraine & TTH

Ref Id	Reason for exclusion
Agro et al. 2005[10]	No relevant outcomes
Ahonen et al. 1983[12]	Sample size too low (<25 per arm)
Ahonen et al. 1984[13]	Sample size too low (<25 per arm)
Alecrim-Andrade et al. 2008[16]	Sample size too low (<25 per arm)
Allais et al. 2002[18]	Comparison = pharmacological treatment not in protocol
Allais et al. 2011[19]	Acute treatment
Ceccherelli et al. 1987[138]	Abstract

Ref Id	Reason for exclusion
Cerrato et al. 2003[140]	Commentary
Coeytaux et al. 2005[156]	Headache type not in protocol (chronic daily headache)
Dowson et al. 1985[236]	No placebo control
Hayhoe et al. 2004[364]	Not RCT
Henry et al. 1985[369]	Sample size too low (<25 per arm)
Jena et al. 2008[398]	No placebo control
Lavies 1998 [481]	Sample size too low (<25 per arm)
Li et al. 2009[493]	Acute treatment
Linde et al. 2006[499]	No relevant outcomes
Linde et al. 2007[500]	Previously reported data
Loh et al. 1984[516]	Sample size too low (<25 per arm)
Martin et al. 2006[532]	Commentary
Melchart et al. 2003[555]	Acute treatment
Melchart et al. 2005[554]	Previously reported data
Qin et al. 2006[644]	Acute treatment
Soderberg et al. 2011[746]	No relevant outcomes
Streng et al. 2006[767]	No placebo control
Tavola et al. 1992[773]	Sample size too low (<25 per arm)
Vickers et al. 2004[826]	No placebo control
Vincent et al. 1989[827]	Sample size too low (<25 per arm)
Wang et al. 2011[837]	Comparison = pharmacological treatment not in protocol
White et al. 2000[848]	Sample size too low (<25 per arm)
Zhang et al. 2009[873]	Not RCT

N.1.14 Prophylactic non-pharmacological management of primary headaches with manual therapies

N.1.14.1 Migraine & TTH

Ref Id	Reason for exclusion
Boline 1992[96]	Incomplete report of Boline 1995
Boline et al. 1995[97]	Outcomes reported at < 3 months
Bryans et al. 2011[115]	Guideline
Carlsson et al. 1990[131]	Duplicate data
Donkin et al. 2002[230]	Sample size too low (<25 per arm)
Ernst 1999[262]	Commentary
Foster et al. 2004[281]	Sample size too low (<25 per arm)
Hanten et al. 1999[357]	Sample size too low (<25 per arm)
Hobson et al. 1996[376]	Letter to editor
Hoyt et al. 1979[386]	Sample size too low (<25 per arm)
Lawler & Cameron 2006[482]	Sample size too low (<25 per arm)
Moran 2005[573]	Commentary
Parker et al. 1978[609]	Within therapy comparison
Torelli et al. 2004[797]	Sample size too low at final analysis

N.1.15 Prophylactic non-pharmacological management of primary headaches with psychological therapies

N.1.15.1 Migraine & TTH

Ref Id	Reason for exclusion
Andrasik et al. 1980[31]	No active control
Andrasik & Holroyd 1983[32]	No relevant outcomes
Andrasik et al. 1984[29]	No relevant outcomes
Andrasik 2004[33]	Not RCT
Appelbaum et al. 1990[42]	Within therapy comparison
Arena et al. 1995[43]	Within therapy comparison
Basler et al. 1996[59]	No active control
Bell et al. 1983[69]	No active control
Blanchard et al. 1978[90]	No active control
Blanchard et al. 1990[84]	No relevant outcomes
Blanchard et al. 1990[85]	No relevant outcomes
Blanchard et al. 1990[86]	No relevant outcomes
Blanchard et al. 1991[87]	Within therapy comparison
Blanchard et al. 1997[89]	Sample size too low (< 25 total)
Bruhn et al. 1979[114]	No active control
Budzynski et al. 1973[116]	Sample size too low (< 25 total)
Bussone et al. 1998[120]	No relevant outcomes
Calhoun & Ford 2007[128]	Study duration too short and blinding broken at 6 weeks
Chesney 1976[146]	Sample size too low (< 25 total)
Cohen et al. 1980[158]	Within therapy comparison
Cox et al. 1975[170]	Sample size too low (< 25 total)
Cram 1980[171]	Sample size too low (< 25 total)
Daly et al. 1983[185]	Within therapy comparison
Daly et al. 1985[186]	Within therapy comparison
Drury et al. 1979[239]	No active control
Engel & Rapoff 1990[260]	Sample size too low (< 25 total)
Fichtel et al. 2004[272]	Sample size too low (< 25 total)
French et al. 1997[292]	No active control
Gada 1984[303]	Within therapy comparison
Gauthier et al. 1981[308]	Within therapy comparison
Gerber et al. 1985[318]	Non-English language
Gray et al. 1980[338]	Sample size too low (< 25 total)
Hedborg et al. 2011 [367]	No active control
Health and Public Policy Committee ACoP 1985 [365]	Not RCT
Holroyd et al. 1977[380]	Within therapy comparison
Holroyd et al. 1980[379]	Not RCT
Holroyd et al. 1991[382]	No active control
Holroyd et al. 1995[381]	No active control
Holroyd et al. 2010[384]	No active control

Ref Id	Reason for exclusion
Hudzinski 1984[389]	Within therapy comparison
Ilacqua 1994[393]	No relevant outcomes
Janssen & Neutgens 1986[397]	Within therapy comparison
Kang et al. 2009[414]	No active control
Kaushik et al. 2005[426]	No active control
Kewman & Roberts 1980[434]	Sample size too low (< 25 total)
Kroner-Herwig et al. 1993[452]	Not RCT
Kroner-Herwig et al. 1998[453]	Mean age under 12 years
Kroener-Herwig et al. 2002[451]	No active control
Labbe & Williamson 1984[461]	No active control
Larsson & Carlsson 1996[475]	No active control
Loew et al. 2000[514]	No relevant outcomes
Mannix et al. 1999[526]	Not RCT
Martin et al. 1989[531]	Comparison not in protocol
Matchar et al. 2008[536]	No active control
McGrady et al. 1994[544]	Sample size too low(< 25 total)
Passchier et al. 1990[610]	Not RCT
Rains & Penzien 2005[647]	Duplicate of previously reported data
Rains 2008[646]	Not RCT
Rangaswamy et al. 1988[652]	Not RCT
Richardson et al. 1989[663]	No active control
Rokicki et al. 1997[668]	No active control
Sargent et al. 1986[692]	Within therapy comparison
Sartory et al. 1998[697]	Mean age under 12 years
Scharff et al. 2002[701]	No relevant outcomes
Seng & Holroyd 2010[713]	Duplicate of previously reported data
Silver et al. 1979[732]	Duplicate of previously reported data
Soderberg et al. 2006[745]	No active control
Soderberg et al. 2011[746]	No relevant outcomes
Sorbi 1986[749]	Within therapy comparison
Sorbi et al. 1989[750]	Within therapy comparison
Steger & Harper 1980[754]	Sample size too low (< 25 total)
Trautmann& Kroner-Herwig 2008[799]	Sample size too low (< 25 total)
Wauquier et al. 1995[840]	No relevant outcomes

N.1.16 Prophylactic non-pharmacological management of primary headaches with dietary supplements and herbal remedies

N.1.16.1 Migraine & TTH

Ref Id	Reason for exclusion
Bigal et al. 2002[78]	Acute treatment
Burke et al. 2002[117]	Sample size too low (<25 per arm)
Crawford et al. 2006[172]	Not a RCT
Harel et al. 2002[359]	Crossover trial, sample size too low (<25 per arm)

Ref Id	Reason for exclusion
Lea et al. 2009[485]	Sample size too low (<25 per arm)
Maclennan et al. 2008[522]	Mean age under 12 years
Mauskop et al. 1998[542]	Review
Pfaffenrath et al. 1996[627]	No relevant outcomes
Sandor et al. 2005[685]	Not RCT
Wang et al. 2003[835]	Mean age under 12 years
Zencirci et al. 2010 [871]	Not assessing treatment efficacy

N.1.17 Prophylactic non-pharmacological management of primary headaches with exercise

N.1.17.1 Migraine & TTH

Ref Id	Reason for exclusion
Abbott et al. 2007[3]	Sample size too low (<25 per arm)
Mongini et al. 2008[567]	Not RCT
Mongini et al. 2009[568]	Duplicate of previously reported data
Mongini et al. 2010[569]	Duplicate of previously reported data
Soderberg et al. 2011[746]	No relevant outcomes

N.1.18 Prophylactic non-pharmacological management of primary headaches with education and self-management

N.1.18.1 Migraine & TTH

Ref Id	Reason for exclusion
Allen et al 1998[20]	Sample size too low (<25 total)
Andersson et al. 2003[24]	Within therapy comparison
Blanchard et al. 1991[88]	No relevant outcomes
Bond et al. 2004[98]	N too low at follow up
Cady et al. 2009[127]	Acute treatment
DeVineni et al. 2005[192]	Crossover trial
Hoffmann et al. 2008[377]	Not RCT
Lemstra et al. 2002[486]	Multidisciplinary care package, not relevant to review protocol
McGrath et al. 1988[545]	No relevant outcomes
Trautmann et al. 2010[800]	Sample size too low (<25 total)
Winkler et al. 1989[854]	No relevant outcomes

N.1.19 Management of medication overuse headache

Ref Id	Reason for exclusion
Altierie et al. 2009[21]	Sample size too low (< 25 per arm)
Andrasik et al. 2007[28]	No control group; prophylactic medications include unlicensed drugs
Andrasik et al. 2010[30]	No control group; prophylactic medications include unlicensed drugs
Bigal et al. 2004[79]	Intervention not in protocol
Boe et al. 2007[93]	Intervention not in protocol

Ref Id	Reason for exclusion
Boe et al. 2009[94]	Compares effect of withdrawal therapy for MOH patients by physician follow up (Neurologist v Primary care)
Boe et al. 2009[95]	Follow up study of previously reported data
Descombes et al. 2001[191]	Sample size too low (<25 per arm)
Diener et al. 2001[220]	Review
Evers et al. 2011[267]	Guideline
Fontanillas et al. 2010[277]	No control group
Fritsche et al. 2001[301]	No control group
Gaul et al. 2011[307]	Data specific to medication overuse patients could not be extracted
Grande et al. 2011[336]	No control group, intervention not in protocol
Granella et al. 1987[337]	Does not look at treatment of medication overuse headache
Grazzi et al. 2002[339]	Intervention not in protocol/not licensed, no control group
Grazzi et al. 2004[340]	Intervention not in protocol/not licensed, no control group
Hagen et al. 2010[353]	Systematic review
Hagen et al. 2011[352]	Follow up of previously reported data; not reported by group
Hagen et al. 2011[349]	Follow up of previously reported data; not reported by group
Hering et al. 1991[370]	No control group
Hering-Hanit et al. 2001[371]	No control group
Katsarava et al. 2003[423]	No control group
Katsarava et al. 2005[424]	Follow up of previously reported data
Kossoff et al. 2006[449]	Population inappropriate; study in children aged 6-17 years (mean age 12.6) with comorbidities including epilepsy, Chiari malformation, surgically resected astrocytoma
Krymchantowski et al. 2000[455]	No control group
Krymchantowski et al. 2003[456]	No control group
Lake III 2006[465]	Review
Limmroth et al. 2007[498]	Pooled data from 3 RCTs, data specific to medication overuse headache not extractable.
Linton-Dahlof et al. 2000[502]	Retrospective study, no control group
Martin et al. 2009[533]	Commentary
Mei et al. 2006[552]	Intervention not in protocol
Obermann et al. 2007[595]	Review
Paemeleire et al. 2006[604]	Case series
Pageler et al. 2005[607]	Commentary
Pageler et al.2 008[605]	Sample size too low (<25 per arm)
Pini et all. 2001[630]	Does not look at treatment of medication overuse headache
Ravishankar et al. 2008[656]	Does not look at management of medication overuse headache
Rizzato et al. 2011[667]	Intervention not in protocol
Rossi et al. 2009[672]	Review
Sances et al. 2010[683]	No control group
Schnider et al. 1996[704]	No control group
Silberstein et al. 1992[729]	Retrospective study, no control group
Silvestrini et al. 2004[733]	Sample size too low (<25 per arm)

Ref Id	Reason for exclusion
Tfelthansen et al. 1981[781]	No control group
Trible et al. 2001[802]	No control group; looks at predictive factors for long term outcome after withdrawal in MOH
Trucco et al. 2005[803]	No control group, preliminary results
Usai et al. 2004[810]	Abstract
Usai et al. 2008[811]	No control group
Usai et al. 2009[812]	No control group
Vasconcellos et al. 1998[820]	Retrospective study, no control group
Walker et al. 1993[833]	Intervention not in protocol, no control group
Warner et al. 2001[838]	Case series
Zed et al. 1999[868]	Systematic review
Zeeberg et al. 2006[870]	Case series, no control group

N.1.20 Management of primary headaches during pregnancy

Ref Id	Reason for exclusion
Banhidy et al. 2008[56]	Abstract
Cassina et al. 2010[136]	Review
Charlton et al. 2008[144]	Inappropriate comparison for this review
Conner et al. 2005[164]	Review
Contag et al. 2010[165]	Review
Cunnington et al. 2009[178]	Case control study, higher quality evidence available
Cunnington et al. 2009[177]	Abstract
Duong et al. 2010[242]	Review
Elkharrat et al. 1991[255]	Wrong exposure (carbon monoxide poisoning or hyperbaric oxygen treatment)
Fox 2000[282]	Letter
Fox et al. 2002[284]	Review
Fox 2004[283]	Letter
Hilaire et al. 2004[375]	Review
Kallen et al. 2001[411]	Case control study, higher quality evidence available
Kallen et al. 2011[412]	Case control study, higher quality evidence available
Koren et al. 1991[447]	Wrong exposure (carbon monoxide poisoning or hyperbaric oxygen treatment)
Loder et al. 2003[513]	Review
Magee et al. 1996[523]	Does not provide results specific to drug of interest (verapamil)
Reiff-Eldridge et al. 2000[660]	Case control study, higher quality evidence available
Shanklin et al. 1967[715]	Inappropriate population for this review (oxygen use in newborn infants, not pregnant women)
Shields et al. 2004[718]	Inappropriate intervention/ comparison for this review (Varicella and montelukast)
Silberstein et al. 1993[724]	Review
Sorensen et al. 2001[751]	Does not provide results specific to drug of interest (verapamil)

N.1.21 Combined hormonal contraceptive use in girls and women with migraine

Ref Id	Reason for exclusion
Azarpazhooh et al. 2008[51]	Sample size too low (migraine n=49)
Benson & Rebar 1986[74]	Review
Collaborative Group for the Study of Stroke in Young Women[159]	Hormonal contraceptives used are not used in current practice; raw data not presented to calculate odds ratios
Cook et al. 2002[166]	No data on women with migraine who were taking hormonal contraceptives
Curtis et al. 2006[179]	Review
Etminan et al. 2005[264]	Review
Haapaniemi et al. 1997[346]	Compares stroke risk in women taking hormonal contraceptives to men
Hunton 1976[390]	No control group; sample size too small (migraine n=18)
Karsay 1990[421]	No control group, constituents of contraceptives not detailed
Kelman 2004[430]	No control group
Li et al. 2009[491]	Does not review use of hormonal contraceptives
Lidegaard 1995[495]	Sample size too low; no data presented
MacClellan et al. 2007[519]	Data only available in graph format
Machado et al. 2010[520]	Cross-sectional study design; Evaluates worsening of migraine headaches in association with hormonal contraceptive use
Nightingale & Farmer 2004[592]	Sample size too low (migraine n=16)
Schurks et al. 2009[709]	Review
Schwartz et al. 1998[710]	Pooled analysis of 2 case-control studies; data specific to women with migraine could not be extracted
Tietjen2000[791]	Commentary
Tzourio et al. 1995[808]	Raw data not provided for calculation of the odds ratios
Vessey & Painter 1995[825]	Sample size too low (migraine n=172); no relevant outcomes
Vree & Schmidt 2001[831]	Inappropriate population for this review (not migraine)

N.2 Excluded economic studies

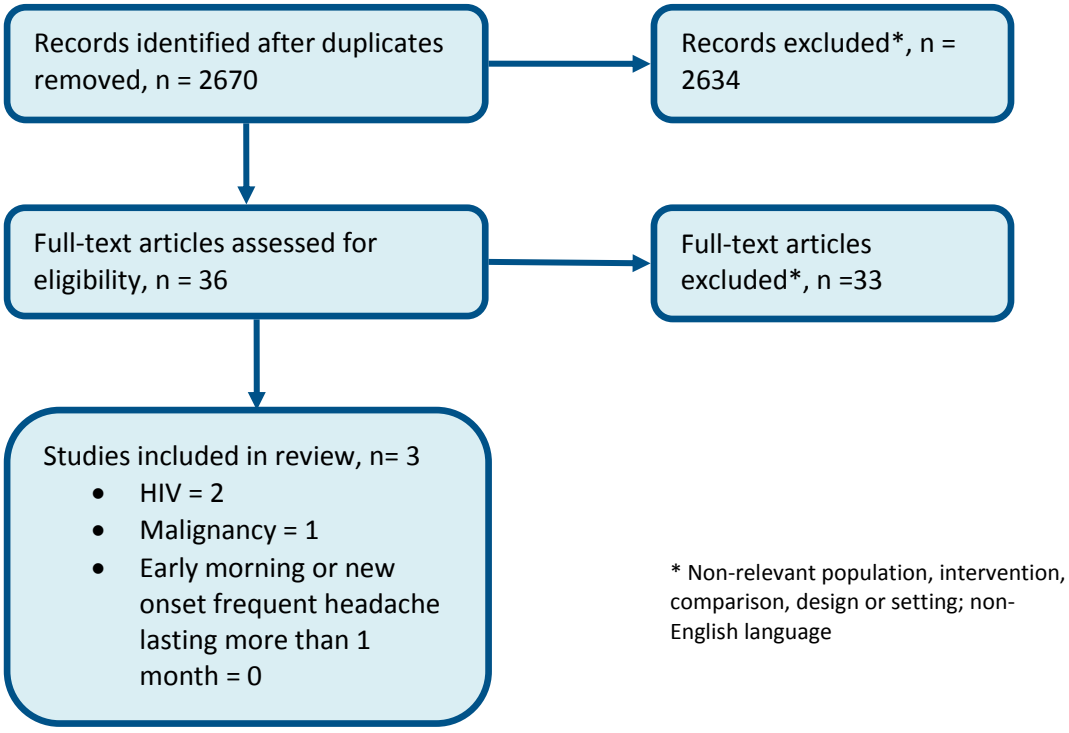
Ref Id	Reason for exclusion
Adelman et al 2002[7]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Akpek et al 1995[15]	Unclear if all participants had suspected primary headache.
Baker 1983[55]	Unclear if all participants had suspected primary headache. Not clear how patients were selected for imaging.
Brown et al 2006[113]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Caro et al 2001[133]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Caro et al 2001[134]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Ergun et al 2007[261]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC

Ref Id	Reason for exclusion
	on the same review question).
Evans et al 1997[265]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Jordan et al 2000[406]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Kahn et al 1993[409]	Not clear if participants had suspected primary headache.
Larson 1980[474]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Lofland et al 2001[515]	The comparator was not a specific intervention (usual care).
Payne et al 1996[613]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Thompson et al 2005[790]	The comparator was not a specific intervention (usual care).
Witt et al 2008[859]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Yu et al 2010[865]	Not applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).
Zhang and Hay 2005[872]	Partially applicable (an original economic analysis which was directly applicable to the UK NHS was developed by the NCGC on the same review question).

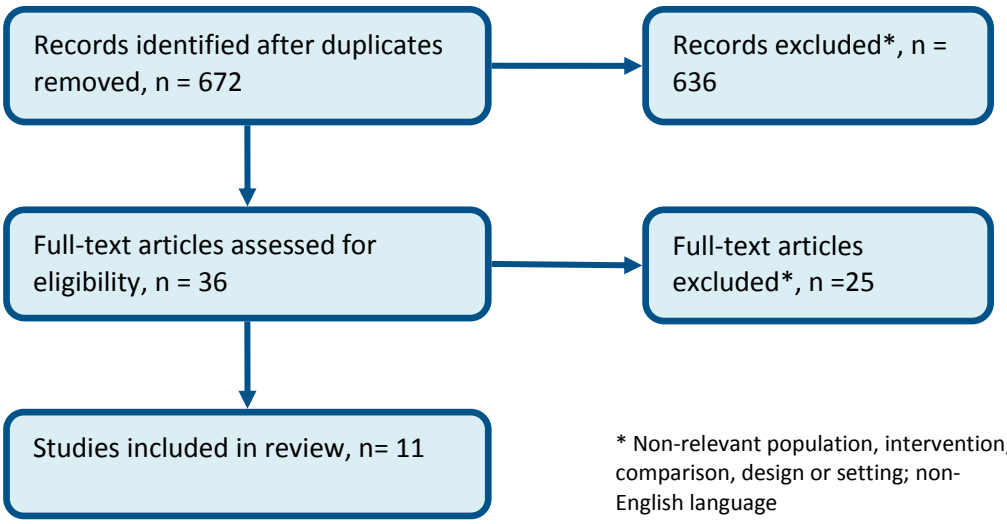
Appendix O: Adapted PRISMA flow diagrams

O.1 Assessment and diagnosis

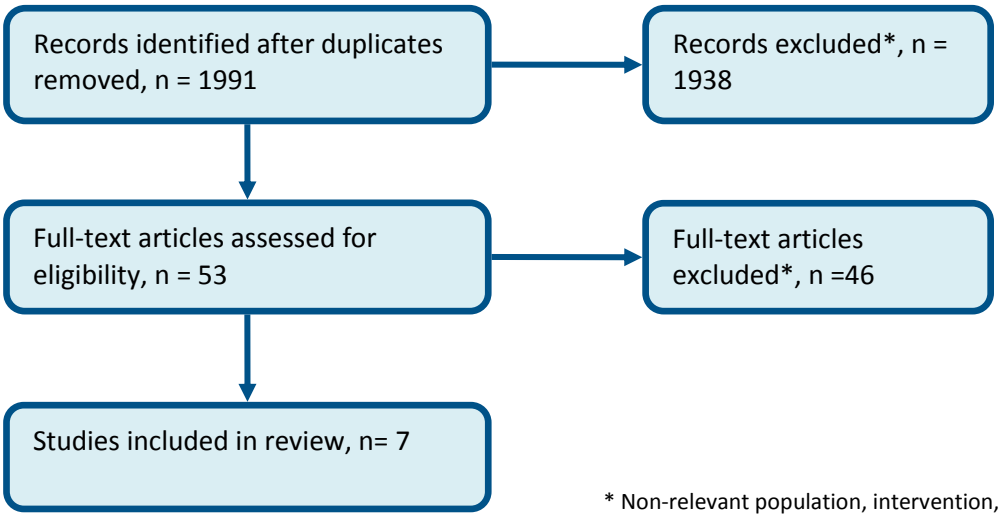
O.1.1 Indications for consideration of additional investigations



O.1.2 Screening questionnaires for primary headache

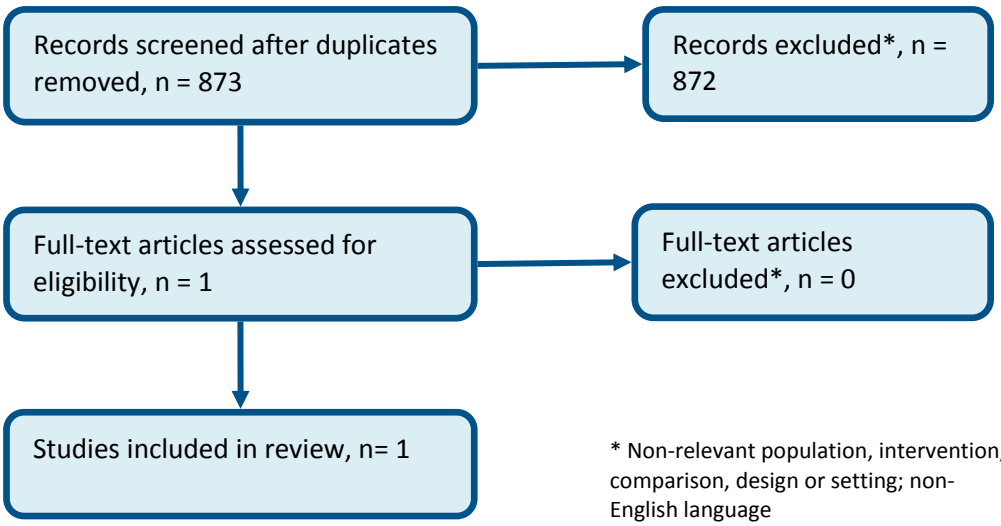


O.1.3 Imaging for the diagnosis of primary headaches



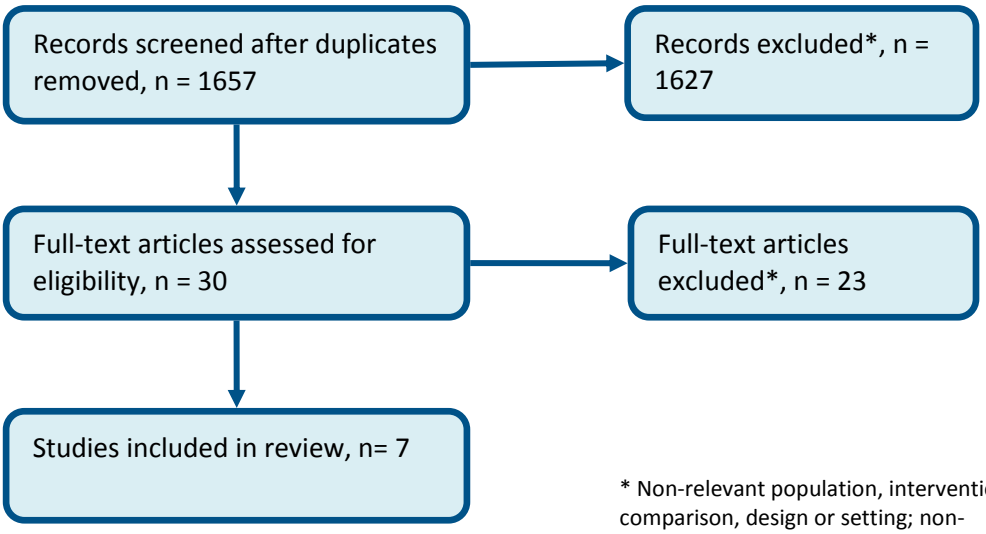
* Non-relevant population, intervention, comparison, design or setting; non-English language

O.1.4 Imaging as a management strategy for primary headaches



* Non-relevant population, intervention, comparison, design or setting; non-English language

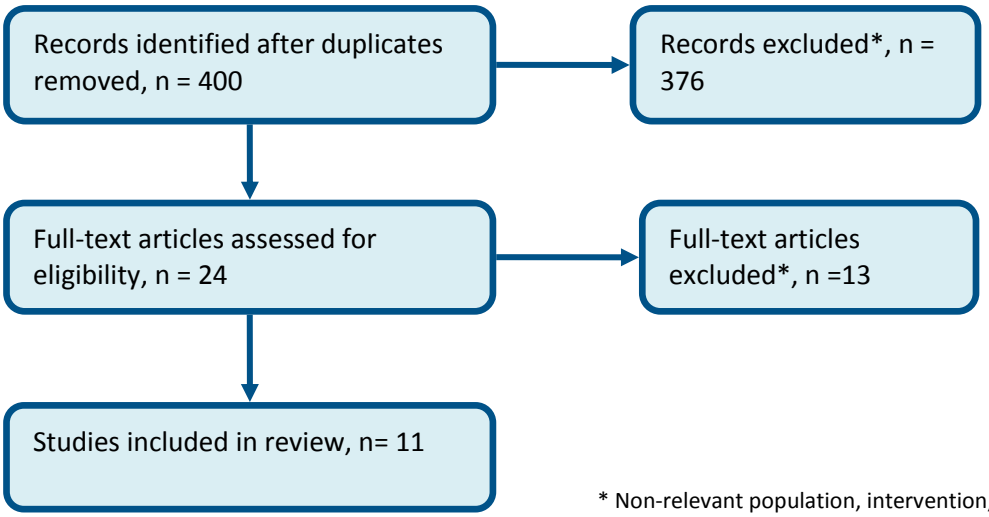
O.1.5 Patient diaries for diagnosis and management of primary headaches



* Non-relevant population, intervention, comparison, design or setting; non-English language

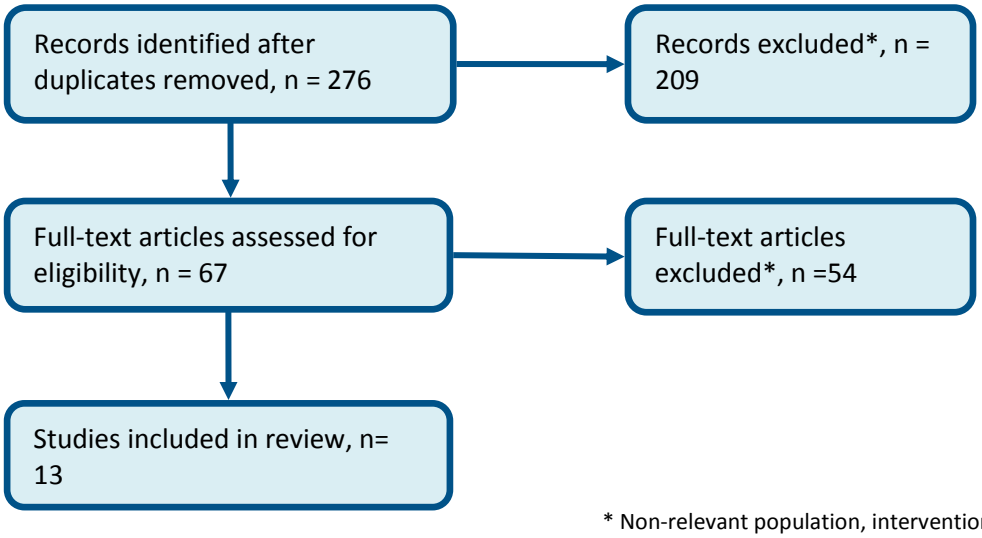
O.2 Management

O.2.1 Patient information and support in headache management



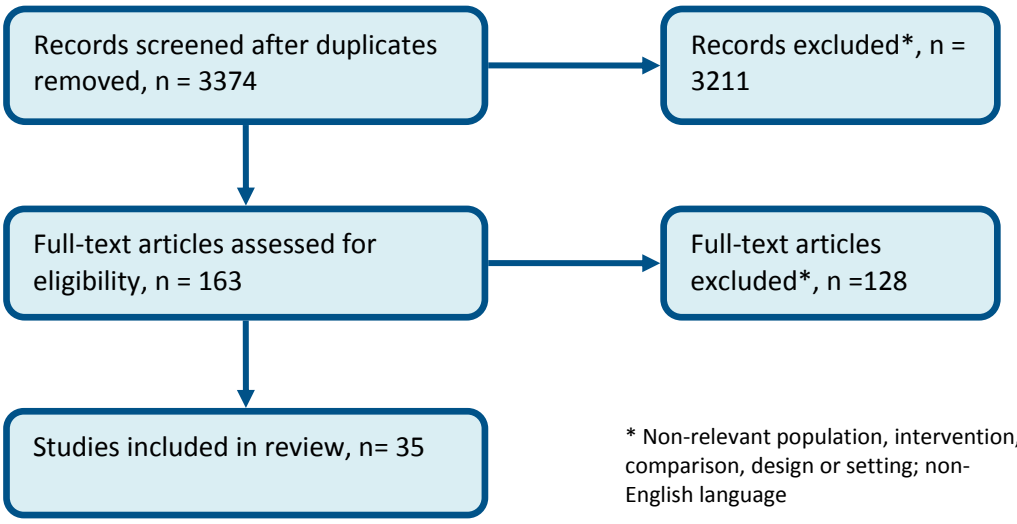
* Non-relevant population, intervention, comparison, design or setting; non-English language

O.2.2 Acute pharmacological treatment of tension type headache

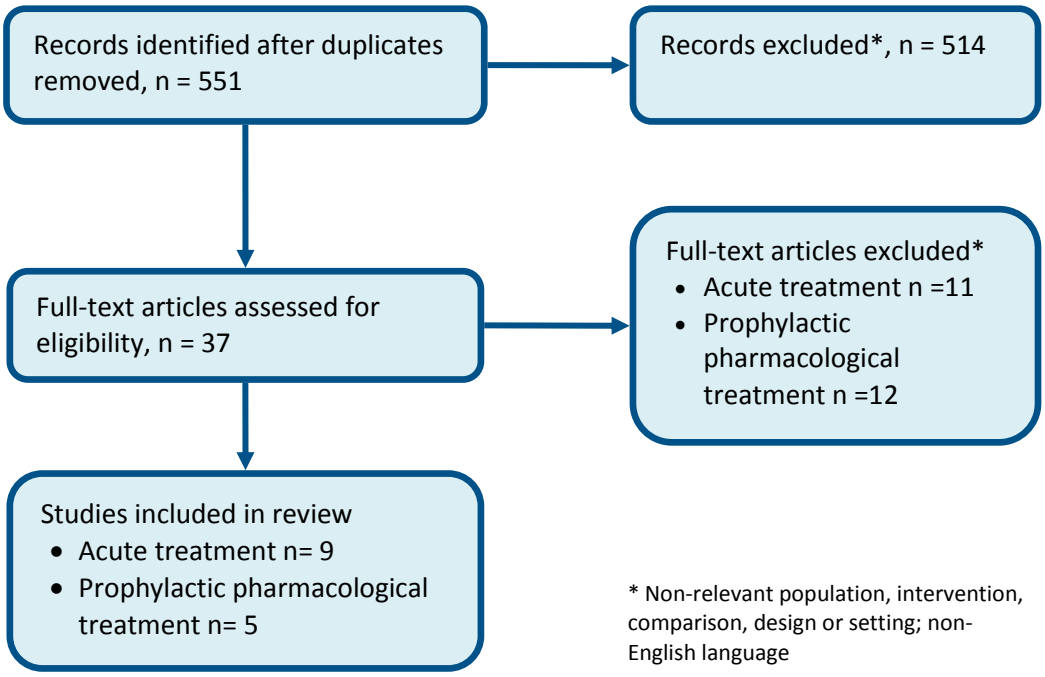


* Non-relevant population, intervention, comparison, design or setting; non-English language

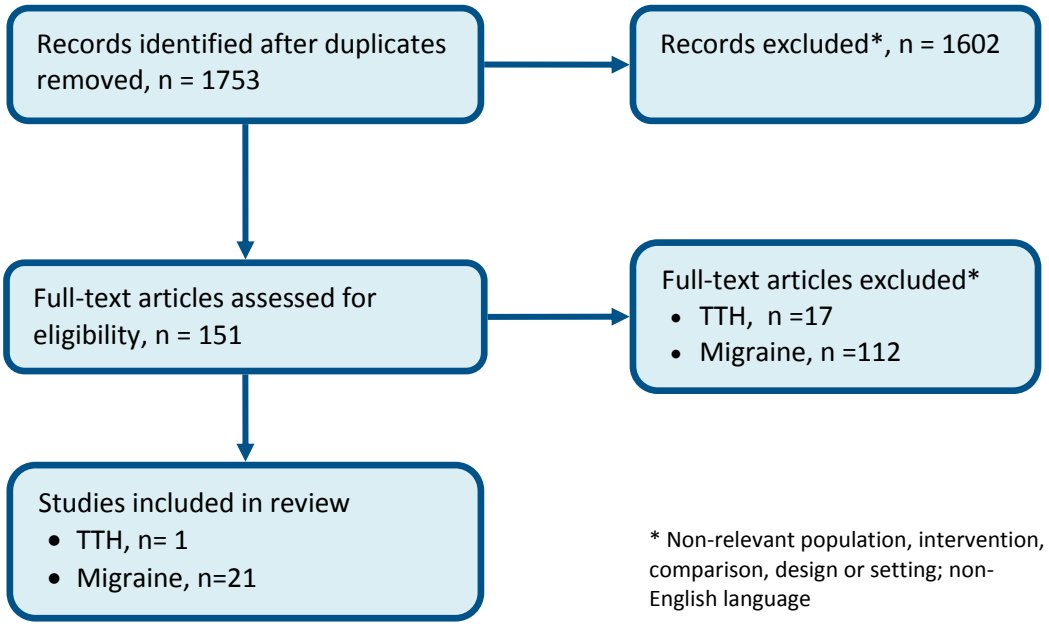
O.2.3 Acute pharmacological treatment of migraine



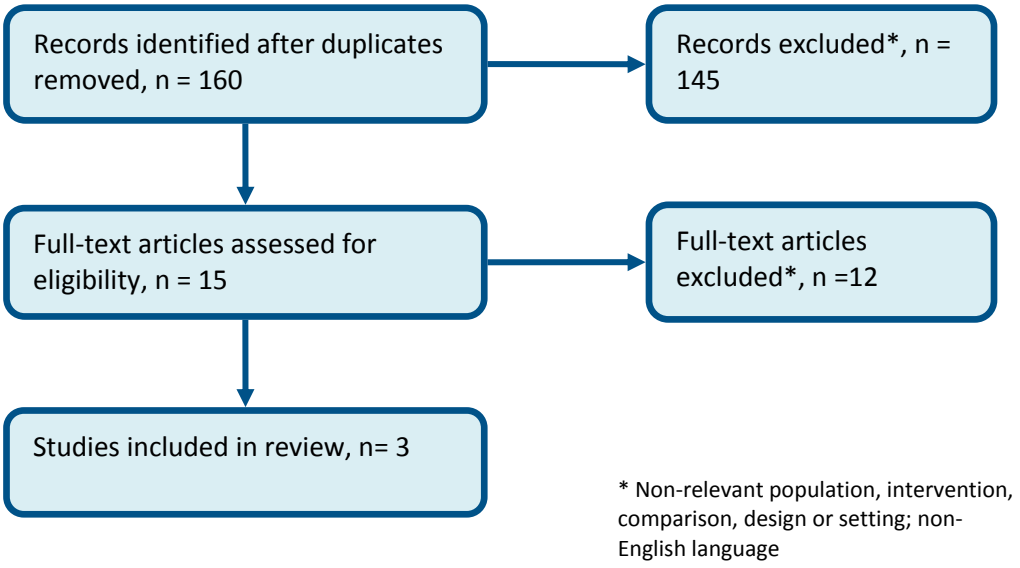
O.2.4 Treatment of cluster headache



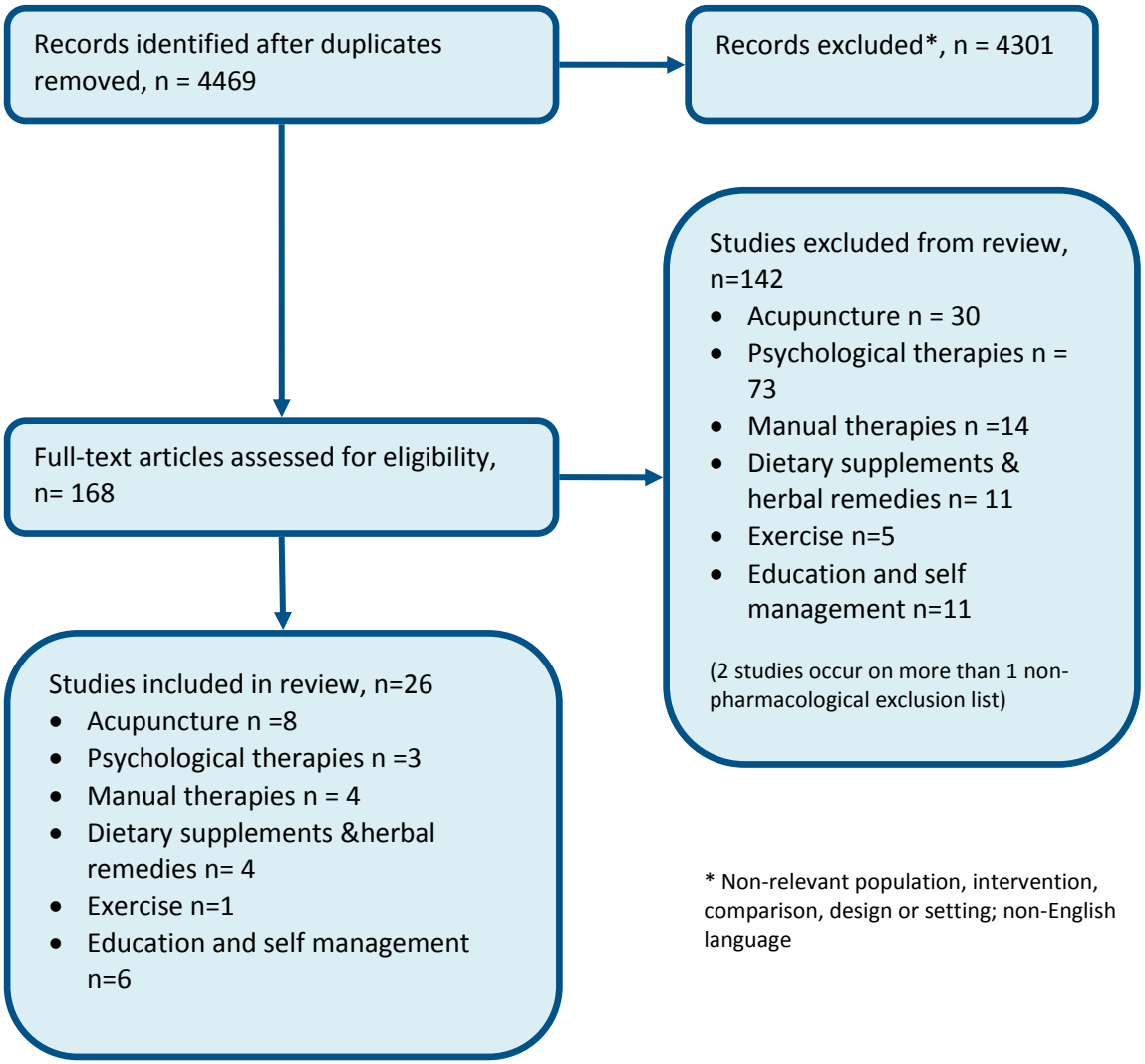
O.2.5 Prophylactic pharmacological treatment of tension type headache & migraine



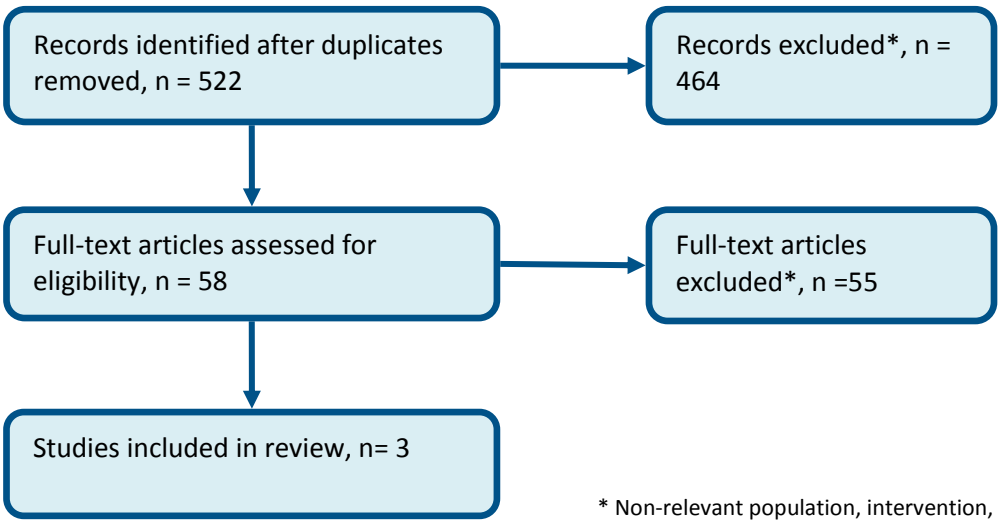
O.2.6 Prophylactic pharmacological treatment of menstrual migraine



O.2.7 Non-pharmacological treatment of primary headaches



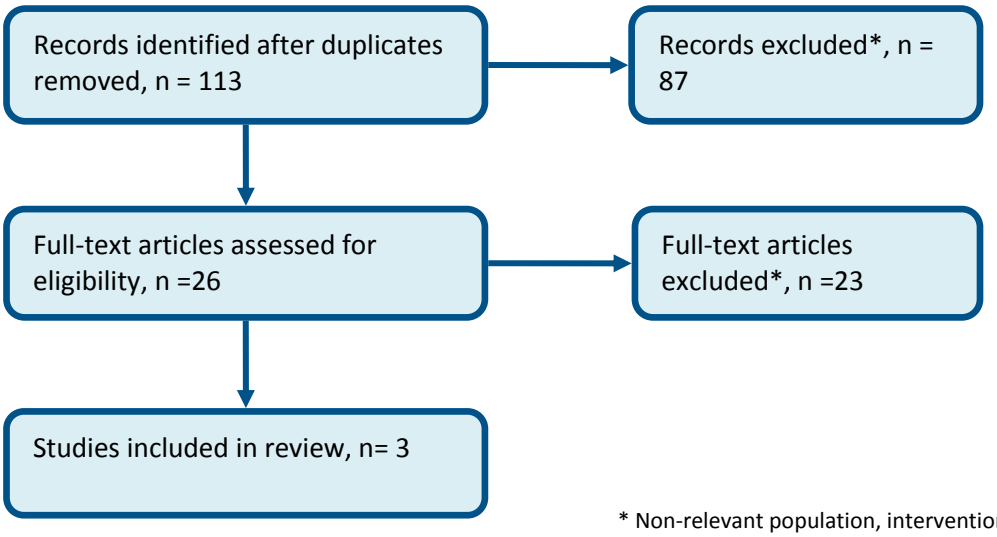
O.2.8 Management of medication overuse headache



* Non-relevant population, intervention, comparison, design or setting; non-English language

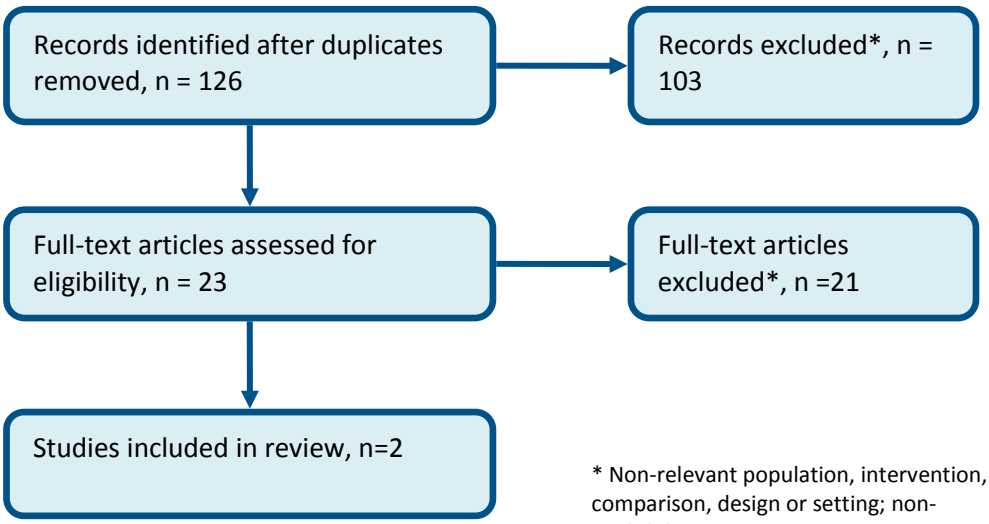
O.3 Management during pregnancy and contraceptive use

O.3.1 Management of primary headache during pregnancy



* Non-relevant population, intervention, comparison, design or setting; non-English language

O.3.2 Contraception use in girls and women with migraine



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