



**Diagnosis and management of
headache in adults**

A national clinical guideline



November 2008

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

- 1⁺⁺ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- 1⁺ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- 1⁻ Meta-analyses, systematic reviews, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A** At least one meta-analysis, systematic review, or RCT rated as 1⁺⁺, and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
- C** A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2⁺⁺
- D** Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2⁺

GOOD PRACTICE POINTS

- Recommended best practice based on the clinical experience of the guideline development group.

NHS Quality Improvement Scotland (NHS QIS) is committed to equality and diversity. This guideline has been assessed for its likely impact on the six equality groups defined by age, disability, gender, race, religion/belief, and sexual orientation.

For the full equality and diversity impact assessment report please see the “published guidelines” section of the SIGN website at www.sign.ac.uk/guidelines/published/numlist.html. The full report in paper form and/or alternative format is available on request from the NHS QIS Equality and Diversity Officer.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on our web site www.sign.ac.uk

Scottish Intercollegiate Guidelines Network

**Diagnosis and management of
headache in adults**

A national clinical guideline



November 2008

ISBN 978 1 905813 39 1

Published November 2008

SIGN consents to the photocopying of this guideline for the
purpose of implementation in NHSScotland

**Scottish Intercollegiate Guidelines Network
Elliott House, 8 -10 Hillside Crescent
Edinburgh EH7 5EA**

www.sign.ac.uk

Contents

1	Introduction	1
1.1	The need for a guideline	1
1.2	Remit of the guideline.....	1
1.3	Definitions	2
1.4	Statement of intent	2
2	Key recommendations	3
2.1	Symptoms and signs.....	3
2.2	Assessment tools	3
2.3	Investigations	4
2.4	Migraine	4
2.5	Trigeminal autonomic cephalalgias	4
2.6	Medication overuse headache.....	5
3	Symptoms and signs.....	6
3.1	Introduction	6
3.2	Primary headache	6
3.3	Secondary headache	9
4	Assessment tools.....	13
5	Investigations.....	15
5.1	Neuroimaging.....	15
5.2	Lumbar puncture in subarachnoid haemorrhage.....	17
5.3	Erythrocyte sedimentation rate, C-reactive protein and plasma viscosity in giant cell arteritis	18
5.4	Other investigations	18
6	Migraine	19
6.1	This section is superseded by SIGN 155: Pharmacological management of migraine	
6.2	This section is superseded by SIGN 155: Pharmacological management of migraine	
7	Tension-type headache	30
7.1	Acute treatment.....	30
7.2	Pharmacological prophylaxis.....	30
8	Trigeminal autonomic cephalalgias	32
8.1	Acute treatment of cluster headache.....	32
8.2	Pharmacological prophylaxis.....	33
8.3	Treatment of paroxysmal hemicrania, hemicrania continua and SUNCT	34
9	Medication overuse headache	35
9.1	Definitions and assessment	35
9.2	This section is superseded by SIGN 155: Pharmacological management of migraine	

10	Pregnancy, contraception, menstruation and the menopause	38
10.1	Pregnancy	38
10.2	Oral contraception	38
10.3	This section is superseded by SIGN 155: Pharmacological management of migraine	
10.4	This section is superseded by SIGN 155: Pharmacological management of migraine.	
11	Lifestyle factors	41
11.1	Diet.....	41
11.2	Trigger avoidance.....	41
11.3	Exercise.....	41
11.4	Sleep.....	41
11.5	Stress management.....	42
12	Psychological therapies	43
13	Physical therapies.....	44
13.1	Manual therapy	44
13.2	Massage	45
13.3	Transcutaneous electrical nerve stimulation	45
13.4	Acupuncture	45
13.5	Oral rehabilitation.....	46
14	Complementary therapies.....	47
14.1	Homeopathy	47
14.2	Reflexology	47
14.3	Minerals, vitamins and herbs.....	47
15	Information provision.....	48
15.1	Frequently asked questions	48
15.2	Sources of further information	49
16	Implementing the guideline	51
16.1	Resource implications	51
16.2	Auditing current practice.....	51
16.3	Advice to NHSScotland from the Scottish Medicines Consortium	51
17	The evidence base	52
17.1	Systematic literature review	52
17.2	Recommendations for research	52
17.3	Review and updating	52
18	Development of the guideline	53
18.1	Introduction	53
18.2	The guideline development group.....	53
18.3	Consultation and peer review.....	53
	Abbreviations.....	56
	Annexes	58
	References	76

1 Introduction

1.1 THE NEED FOR A GUIDELINE

Headache is common, with a lifetime prevalence of over 90% of the general population in the United Kingdom (UK).¹ It accounts for 4.4% of consultations in primary care² and 30% of neurology outpatient consultations.^{3,4}

Headache disorders are generally classified as either primary or secondary, and these classifications are further divided into specific headache types. Primary headache disorders are not associated with an underlying pathology and include migraine, tension-type, and cluster headache. Secondary headache disorders are attributed to an underlying pathological condition and include any head pain of infectious, neoplastic, vascular, or drug-induced origin.⁵

Migraine is the most common severe form of primary headache affecting about six million people in the UK in the age range 16-65, and can cause significant disability.⁶ The World Health Organisation (WHO) ranks migraine in its top 20 disabling conditions for women aged 15 to 44.⁷ It is estimated that migraine costs the UK almost £2 billion a year in direct and indirect costs,⁸ with over 100,000 people absent from work or school because of migraine every working day.⁹ Tension-type headache affects over 40% of the population at any one time. Although less of a burden to the individual sufferer than migraine, its higher prevalence results in a greater societal burden, with as many lost days from work as with migraine.¹⁰ Chronic headache, defined as headache on 15 or more days per month, affects three per cent of people worldwide.¹⁰

Healthcare professionals often find the diagnosis of headache difficult and both healthcare professionals and patients worry about serious rare causes of headaches such as brain tumours.^{2,11} General practitioners (GPs) are often uncertain about when to refer patients to secondary care.² GPs refer 2-3% of patients consulting for headaches to neurological clinics.² This may allow the exclusion of secondary headache but often does not provide a headache management service. Most primary headache can be managed in primary care and investigations are rarely needed.¹²

There are effective therapies for many of the primary headaches^{11,13} but treatments can cause headache themselves.¹¹ Despite this many patients are inappropriately prescribed analgesics and many patients with headache never consult their doctor because of poor expectations of what doctors can offer.^{14,15}

1.2 REMIT OF THE GUIDELINE

This guideline provides recommendations based on evidence for best practice in the diagnosis and management of headache in adults. The International Classification of Headache Disorders lists over 200 headache types and a comprehensive review of all headaches is beyond the scope of these guidelines.¹⁶ This guideline focuses on the more common primary headaches such as migraine and tension-type headache, and addresses some of the rarer primary headaches which have recognisable features with specific treatments. Secondary headache due to medication overuse is addressed, as the overuse of headache medication can compromise the management of primary headache. "Red flags" for secondary headache are highlighted. A guide to the main investigations used in headache is provided.

Disorders that primarily cause facial pain, such as trigeminal neuralgia, are outwith the remit of this guideline, as is treatment of meningitis.

This guideline will be of interest to healthcare professionals in primary and secondary care, including general practitioners, community pharmacists, opticians and dental practitioners, and patients with headache.

1.3 DEFINITIONS

The guideline uses the definitions given in the International Headache Society International Classification of Headache Disorders, 2nd edition (see *Annex 2*).¹⁶

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.4.1 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in section 16.3.

1.4.2 DRUG LICENSING STATUS

The majority of headache treatments commonly used do not have a specific licence for this indication in the UK. In this guideline, recommendations which include the use of licensed drugs outwith the terms of their licence reflect the evidence base reviewed. More details on licensing status are given in Annex 6.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as being clinically very important. They are the key clinical recommendations that should be prioritised for implementation. The clinical importance of these recommendations is not dependent on the strength of the supporting evidence.

2.1 SYMPTOMS AND SIGNS

C Patients who present with a pattern of recurrent episodes of severe disabling headache associated with nausea and sensitivity to light, and who have a normal neurological examination, should be considered to have migraine.

Migraine has specific treatment options. It is often underdiagnosed with up to 50% of patients misdiagnosed with another headache type.¹⁷⁻²⁰ Better recognition allows more effective treatment.

D Patients who present with headache and red flag features for potential secondary headache should be referred to a specialist appropriate to their symptoms for further assessment.

Most patients have primary headache and do not require further investigation.^{12,20} Red flag warning features highlight which patients require further investigation for potential secondary headache.

D Patients with a first presentation of thunderclap headache should be referred immediately to hospital for same day specialist assessment.

Thunderclap headache is a medical emergency as it may be caused by subarachnoid haemorrhage.

D Giant cell arteritis should be considered in any patient over the age of 50 presenting with a new headache or change in headache.

Giant cell arteritis is a medical emergency because of the possibility of neurological and visual complications and availability of effective treatment.

2.2 ASSESSMENT TOOLS

D Practitioners should consider using headache diaries and appropriate assessment questionnaires to support the diagnosis and management of headache.

The use of diaries and questionnaires can aid diagnosis and prompt discussion of symptoms and the impact of the headaches on quality of life. This can help guide treatment and ensure appropriate follow up.

2.3 INVESTIGATIONS

D Neuroimaging is not indicated in patients with a clear history of migraine, without red flag features for potential secondary headache, and a normal neurological examination.

Magnetic resonance imaging (MRI) and computerised tomography (CT) can identify neurological abnormalities incidental to the patient's presenting complaint, which may result in heightened patient anxiety and clinician uncertainty.^{21,22} Further investigation and treatment of incidental abnormalities can cause both morbidity and mortality and investigation should generally be reserved for patients with "red flag features".

D In patients with thunderclap headache, unenhanced CT of the brain should be performed as soon as possible and preferably within 12 hours of onset.

C Patients with thunderclap headache and a normal CT should have a lumbar puncture.

Subarachnoid blood degrades rapidly. Performing CT brain imaging as soon as possible maximises the chance of accurate diagnosis. Even timely CT brain imaging may not pick up subarachnoid blood, so lumbar puncture is also required. Lumbar puncture should be delayed till 12 hours after headache onset.

2.4 MIGRAINE

Recommendations in this section have been superseded by [SIGN 155: Pharmacological management of migraine](#).

B Women with migraine with aura should not use a combined oral contraceptive pill.

Migraine with aura and the combined oral contraceptive pill are both independent risk factors for ischaemic stroke. Although the absolute increased risk of stroke is small, this increased risk is unacceptable when equally effective alternative methods of contraception are available.

2.5 TRIGEMINAL AUTONOMIC CEPHALALGIAS

A Subcutaneous injection of 6 mg sumatriptan is recommended as the first choice treatment for the relief of acute attacks of cluster headache.

Individual attacks of cluster headache are very severe and build up rapidly. The onset of action of oral triptans is too long and subcutaneous or nasal triptans are required.

2.6 MEDICATION OVERUSE HEADACHE

D Medication overuse headache must be excluded in all patients with chronic daily headache (*headache ≥ 15 days / month for > 3 months*).

D Clinicians should be aware that patients using any acute or symptomatic headache treatment are at risk of medication overuse headache. Patients with migraine, frequent headache and those using opioid-containing medications or overusing triptans are at most risk.

Medication overuse results in the development of chronic daily headache. Stopping the overused medication usually results in improvement in headache frequency and severity. The risks of medication overuse headache should be discussed with all patients when initiating acute treatment for migraine.

3 Symptoms and signs

3.1 INTRODUCTION

Most patients with headache who present in primary care have primary headache.²⁰ Patients may have more than one type of primary headache (eg migraine without aura and tension-type headache) and each headache type should be dealt with separately.¹⁶ Presentation with secondary headache is rare. In primary headache, findings on neurological examination are usually normal and investigations are not helpful for diagnosis.^{12,23}

2+

4

The individual patient's history is of prime importance in the evaluation of headache.^{11,23} The aim of the history is to classify the headache type(s) and screen for secondary headache using "red flag" features (see section 3.3). An inadequate history is the probable cause of most misdiagnosis of the headache type.¹¹ The British Association for the Study of Headache has produced a list of questions to help with taking a patient's headache history (see Annex 4). Diaries and tools to aid diagnosis are discussed in section 4.

4

The evidence base regarding signs and symptoms is limited to observational studies and the recommendations are based mainly on case series and expert opinion.

3.2 PRIMARY HEADACHE

3.2.1 MIGRAINE

Migraine is the most common severe primary headache disorder.^{6,10} The global lifetime prevalence is 10% in men and 22% in women.¹⁰

A migraine headache is characteristically:

- unilateral
- pulsating
- builds up over minutes to hours
- moderate to severe in intensity
- associated with nausea and/or vomiting and/or sensitivity to light and/or sensitivity to sound
- disabling
- aggravated by routine physical activity.¹⁶

4

Migraine is classified by the presence or absence of aura.¹⁶ A typical aura comprises fully reversible visual and/or sensory and/or dysphasic speech symptoms. Symptoms may be positive (eg flickering lights, spots, zig zag lines, tingling) and negative (eg visual loss, numbness). Symptoms characteristically evolve over ≥ 5 minutes and resolve within 60 minutes.¹⁶ Different aura symptoms may occur in succession. A transient ischaemic attack should be considered if the aura has a very rapid onset, there is simultaneous rather than sequential occurrence of different aura symptoms, the aura is purely negative or is very short.^{24,25} Prolonged aura should raise the possibility of a secondary cause (see section 3.3).^{24,25} Aura may occur without headache.

4

3

Recurrent attacks lasting four to 72 hours, occur as infrequently as one per year or as often as daily. The median frequency is one to two per month.²⁶ Chronic migraine is classified as migraine occurring on 15 or more days per month for more than three months.^{16,27} In chronic migraine the headache may have features more typical of tension-type headache (see Annex 2).

4

Fifty per cent of patients with migraine are misdiagnosed with another headache type.¹⁷⁻²⁰ Often the wrong diagnosis of episodic tension-type headache is given. When prospective diaries were reviewed for headaches diagnosed as episodic tension-type headache, in the Landmark study, 82% of the physician diagnoses were changed to migraine or probable migraine.²⁰

2+

As many as 75% of patients with migraine describe neck pain associated with migraine attacks. Patients may present with more than one headache type. Any single International Classification of Headache Disorders (ICHD-II) criterion will be missing in up to 40% of patients; 40% of patients report bilateral pain, 50% describe the pain as non-pulsating, and vomiting occurs in less than 33%.²⁴

4

Given the difficulty in differentiating between migraine without aura and infrequent episodic tension-type headache the ICHD-II criteria require five attacks before a diagnosis of migraine without aura can be made. Two attacks are required for the diagnosis of migraine with aura.¹⁶ In patients with more than one type of headache the International Headache Society (IHS) suggests a hierarchical diagnostic strategy with the diagnosis based on the most severe headache.

4

Cohort studies and case studies have highlighted the features of a history that help to differentiate migraine from other headache. Not all have to be present to make the diagnosis:

- episodic severe headache that causes disability^{13,28,29}
- nausea^{23,28}
- sensitivity to light during headache^{23,28}
- sensitivity to light between attacks³⁰
- sensitivity to noise²³
- typical aura (in 15–33% of patients with migraine)^{23,24}
- exacerbation by physical activity²³
- positive family history of migraine.^{23,31}

2+

4

3

When combined with assessment of functional impairment, the features which give the greatest sensitivity and specificity for the diagnosis of migraine are nausea and sensitivity to light.²⁸

3

C Patients who present with a pattern of recurrent episodes of severe disabling headache associated with nausea and sensitivity to light, and who have a normal neurological examination, should be considered to have migraine.

3.2.2 TENSION-TYPE HEADACHE

Tension-type headache (TTH) is the most common primary headache disorder.¹⁰ It has a global lifetime prevalence of 42% in men and 49% in women. The pain is generally not as severe as in migraine.¹⁰

The pain is typically bilateral, characteristically pressing or tightening in quality and mild to moderate in intensity. Nausea is not present and the headache is not aggravated by physical activity. There may be associated pericranial tenderness, sensitivity to light or sensitivity to noise. Episodic tension-type headache (ETTH) occurs in episodes of variable duration and frequency. Chronic tension-type headache (CTTH) occurs on more than 15 days per month for more than three months.¹⁶

4

Disabling ETTH is rare. Most patients with ETTH do not consult a primary care clinician.^{19,20} Migraine is often mistaken for ETTH in the initial diagnosis (see section 3.2.1).²⁰

2+

C A diagnosis of tension-type headache should be considered in a patient presenting with bilateral headache that is non-disabling where there is a normal neurological examination.

3.2.3 TRIGEMINAL AUTONOMIC CEPHALALGIAS

Trigeminal autonomic cephalalgias (TACs) are rare and are characterised by attacks of severe unilateral pain in a trigeminal distribution.^{16,32} They are associated with prominent ipsilateral cranial autonomic features. Cluster headache (CH) is the most common TAC (estimated prevalence 1 in 1,000). Paroxysmal hemicrania (PH) is probably under-recognised (estimated prevalence 1 in 50,000).³² Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) are very rare.

4

3

Cluster headache attacks cause severe, strictly unilateral pain. The pain is located in one or a combination of orbital, supraorbital, or temporal regions. The ICHD-II classification requires ipsilateral autonomic features to occur with an attack (see Annex 2). Each attack starts and ceases abruptly, lasting 15 minutes to three hours and the patient is restless during an attack. The frequency of attacks varies from one every other day to eight per day. There may be a continuous background headache between attacks and migrainous features may be present (see section 3.2.1). There is often a striking circadian rhythm; attacks often occur at the same time each day and clusters occur at the same time each year.³² Eighty to 90% of patients have episodic cluster headache where attacks “cluster” into periods lasting weeks to months, separated by periods of headache freedom. The remaining 10-20% have chronic cluster headache (no remission within one year or remissions last less than one month).¹⁶

4

Paroxysmal hemicrania has similar characteristics to cluster headache, but attacks are shorter (2-45 minutes), more frequent (up to 40 per day) and it is more common in women. The majority of patients have the chronic rather than episodic form. Most attacks are spontaneous but 10% can be precipitated mechanically by bending or rotating the head. Diagnosis using ICHD-II criteria consists of the presence of a complete response to indometacin and ipsilateral autonomic features during an attack (see Annex 2).^{16,32}

4

SUNCT has similar characteristics to cluster headache and paroxysmal hemicrania. Attacks are shorter (2-250 seconds) and more frequent (up to 30 per hour). They occur as single stabs, groups of stabs or in an overlapping fashion (“sawtooth”). Bouts may last one to three hours at a time. Conjunctival injection and/or tearing are a requirement for the diagnosis. Attacks may be spontaneous or triggered by trigeminal (eg touching face) or extra-trigeminal (eg exercise) manoeuvres. Relapses and remissions are erratic.^{16,32,33} SUNA is a proposed classification for patients with the headache characteristics of SUNCT, but with other cranial autonomic features.

3
4

Secondary mimics are common and need to be excluded before a diagnosis of cluster headache, PH, SUNCT or SUNA can be made. For example, symptomatic cluster headache has been described after infections and with vascular and neoplastic lesions. In the case of PH a good response to indometacin does not exclude a secondary cause.³²

3
4

Features differentiating TACs from migraine are listed in Table 1. Features which differentiate trigeminal autonomic cephalalgias from each other and from trigeminal neuralgia, are listed in Annex 3.

Table 1: Features distinguishing TACs from migraine. ^{23,32,33}

	Headache type			
	SUNCT	PH	CH	Migraine
Duration	2-250 secs	2-45 mins	15 mins–3 hrs	4-72 hrs
Onset	rapid	rapid	rapid	gradual
Frequency	1/day-30/hr	1-40/day	1 every other day-8 /day	< 1/year-1/day (median 1-2/ month)
Restlessness during an attack	50%	50%	100%	0%
Ipsilateral autonomic features	prominent	prominent	prominent	occasional

3
4

D When a patient presents with frequent, brief, unilateral headaches with autonomic features a trigeminal autonomic cephalgia should be considered.

D Patients with a new suspected trigeminal autonomic cephalgia should be referred for specialist assessment.

3.2.4 HEMICRANIA CONTINUA

Hemicrania continua is a continuous strictly unilateral headache that waxes and wanes in intensity without disappearing completely.^{16,32} Brief stabbing pain may be superimposed on the continuous headache and may be accompanied by ipsilateral autonomic features. While it is rare, it is an important diagnosis to consider as there is an absolute response to indometacin.³²

4

Secondary mimics are common and need to be excluded before a diagnosis of primary hemicrania continua can be made. A good response to indometacin does not exclude a secondary cause.³²

4

D When a patient presents with chronic daily headache which is strictly unilateral, hemicrania continua should be considered.

D Patients with a new suspected hemicrania continua should be referred for specialist assessment.

3.2.5 NEW DAILY PERSISTENT HEADACHE

Headache that is daily and unremitting from onset is classified as new daily persistent headache.¹⁶ It is essential to consider secondary headache and allow three months to elapse before a diagnosis of primary new daily persistent headache can be made. New daily persistent headache can have any phenotype. Secondary headaches to consider are subarachnoid haemorrhage (SAH), meningitis, raised intracranial pressure, low cerebrospinal fluid (CSF) pressure, giant cell arteritis and post-traumatic headache.³⁴

4

In patients with new daily persistent headache, referral for specialist assessment should be considered.

3.3 SECONDARY HEADACHE

Secondary headache (ie headache caused by another condition) should be considered in patients presenting with new onset headache or headache that differs from their usual headache. Observational studies have highlighted the following warning signs or red flags for potential secondary headache which requires further investigation:

Red flag features:

- new onset or change in headache in patients who are aged over 50^{12,35-37}
- thunderclap: rapid time to peak headache intensity (seconds to 5 mins)^{35,36,38-41}
- focal neurological symptoms (eg limb weakness, aura < 5 min or > 1 hr)^{24,25,37,39,42,43}
- non-focal neurological symptoms (eg cognitive disturbance)^{38,42}
- change in headache frequency, characteristics or associated symptoms^{12,24,37,38}
- abnormal neurological examination^{12,36,38,43}
- headache that changes with posture^{44,45}
- headache wakening the patient up (NB migraine is the most frequent cause of morning headache)^{12,45}
- headache precipitated by physical exertion or valsalva manoeuvre (eg coughing, laughing, straining)^{12,45}
- patients with risk factors for cerebral venous sinus thrombosis^{42,46,47}
- jaw claudication or visual disturbance^{23,48}
- neck stiffness^{35,49}
- fever⁴⁹
- new onset headache in a patient with a history of human immunodeficiency virus (HIV) infection³⁸
- new onset headache in a patient with a history of cancer.¹¹

4
3

D Patients who present with headache and red flag features of potential secondary headache should be referred to an appropriate specialist for further assessment.

In patients with a stable pattern of headache, neurological examination is normal other than occasional ptosis during and persisting after an attack of cluster headache.^{12,23} The presence of focal or non-focal symptoms and/or abnormal neurological signs significantly increases the chance of there being an abnormality.^{12,23,36,38} An appropriate clinical examination, a neurological examination including fundoscopy, and blood pressure measurement are essential when patients first present.¹¹

3

D Patients presenting with headache for the first time or with headache that differs from their usual headache should have a clinical examination, a neurological examination including fundoscopy, and blood pressure measurement.

- Neurological examination in patients first presenting with headache should include:
 - fundoscopy
 - cranial nerve assessment, especially pupils, visual fields, eye movements, facial power and sensation and bulbar function (soft palate, tongue movement)
 - assessment of tone, power, reflexes and coordination in all four limbs
 - plantar responses
 - assessment of gait, including heel-toe walking.

There should be more detailed assessment if prompted by the history. The examination should be tailored to include any focal neurological symptoms.

3.3.1 THUNDERCLAP HEADACHE

Thunderclap headache may be primary or secondary. It is defined by the ICHD-II as a high-intensity headache of rapid onset mimicking an SAH from a ruptured aneurysm with maximum intensity being reached in less than a minute.¹⁶ In most patients thunderclap headache peaks instantaneously. In a small case series 19% of patients with SAH had headache that reached maximum severity more gradually (up to 5 minutes).⁴¹ Sudden severe headache may also occur during sexual activity or exercise.¹⁶

4

Other causes of sudden severe headache include: intracerebral haemorrhage, cerebral venous sinus thrombosis, arterial dissection and pituitary apoplexy.¹⁶

4

There are no reliable features to differentiate between primary and secondary thunderclap headache and SAH can present with milder sudden onset headache.³⁵ A significant minority of thunderclap headache is secondary. In one case series 11% of patients with thunderclap headache had SAH.³⁵ When a patient presents for the first time with a sudden severe headache they should be referred immediately for consideration of a secondary cause, particularly SAH (this includes delayed presentation).^{35,36,38}

3

If negative results are obtained from both brain computerised tomography and lumbar puncture with cerebrospinal fluid analysis (see section 5.2) within two weeks of onset of thunderclap headache, subarachnoid haemorrhage can be excluded from diagnosis.^{35,38,50}

4

D Patients with a first presentation of thunderclap headache should be referred immediately to hospital for same day specialist assessment.

3.3.2 MEDICATION OVERUSE HEADACHE

Overuse of all acute headache treatments including simple and combination analgesics can cause medication overuse headache (see section 9).¹⁶

4

3.3.3 CERVICOGENIC HEADACHE

The contribution of cervical spine disorders to migraine and tension-type headache is poorly understood. Fourteen to 18% of chronic headaches are cervicogenic in origin, ie result from a musculoskeletal dysfunction in the cervical spine.⁵¹

Cervicogenic headache consists of a unilateral or bilateral pain localised to the neck and occipital region which may project to regions on the head and/or face (see Annex 2).¹⁶ Pain may be precipitated or aggravated by particular neck movements or sustained neck postures and is associated with altered neck posture, movement, muscle tone contour and/or muscle tenderness.^{11,52} Manual examination identifying articular mobility, muscle extensibility and range of motion, in the form of flexion and extension may assist diagnosis.⁵¹ A headache may also be cervicogenic in origin if there is clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine (ICHD-II).¹⁶

D Neck examination should be carried out in all patients presenting with headache including assessment of:

- neck posture
- range of movement
- muscle tone
- muscle tenderness.

3.3.4 RAISED INTRACRANIAL PRESSURE

Headache associated with raised intracranial pressure is usually worse when the patient is lying down and may awaken them from sleep. It may also be precipitated by valsalva manoeuvres (eg coughing, laughing, straining), sexual intercourse, or physical exertion.^{12,38} Visual obscurations, transient changes in vision with change in posture or valsalva, suggest raised CSF pressure.⁴⁵ Any of these symptoms should prompt referral for urgent specialist assessment.

Intracranial tumours rarely produce headache until quite large, particularly in neurologically 'silent' areas such as the frontal lobes.¹¹ Pituitary and posterior fossa tumours are the exception to this. Haemorrhage into a tumour may cause sudden severe headache, but it is more common for these patients to present with seizures or neurological symptoms (eg cognitive change) or signs (eg homonymous hemianopia, hemiparesis). Heightened suspicion is appropriate if there is a history of cancer elsewhere in the body.¹¹

In an audit of 324 patients with an imaging diagnosis of an intracranial tumour, headache was the first symptom in 23% but at the time of presentation was the sole symptom in only 0.2%. All other patients had focal symptoms or signs. Seizure was the most common focal symptom (21%).⁵³ In a large primary care case controlled study of 3,505 patients with primary brain tumour and 17,173 matched controls the positive predictive value (PPV) of isolated headache as the only symptom was 0.09% (95% CI 0.08 to 0.10). The PPV of new onset seizure was 1.2% (95% CI 1.0 to 1.4).⁵⁴

Idiopathic intracranial hypertension (incidence 1-3/100,000 all; 21/100,000 in women aged 15-45) presents with symptoms and signs consistent with raised intracranial pressure, typically normal neuroimaging (including computerised tomography or magnetic resonance venography to exclude cerebral venous sinus thrombosis) and a raised CSF pressure. The headache is initially episodic then usually progresses over weeks to daily headache with features typical of raised intracranial pressure.⁴⁵ Other symptoms and signs commonly present include: transient visual obscurations, pulsatile tinnitus, sixth nerve palsy, enlarged blind spots and papilloedema. It is most frequently seen in obese women of childbearing age. The aetiology is unclear in the majority of cases, but secondary causes to consider include cerebral venous sinus thrombosis, various medications (eg tetracyclines and retinoids) and CSF inflammation, infection or malignancy.

If a patient presents with headache and a combination of all or some of fever, neck stiffness, focal signs or seizures, then infection of the central nervous system (CNS) should be considered.^{35,49} This may be diffuse (meningitis or encephalitis) or localised (brain abscess). Heightened suspicion is appropriate if there is a history of HIV or immunosuppression.³⁸

4

4

4

3

4

3

D Patients with headache and features suggestive of raised intracranial pressure should be referred urgently for specialist assessment.

D Patients with headache and features suggestive of CNS infection should be referred immediately for same day specialist assessment.

3.3.5 INTRACRANIAL HYPOTENSION (SPONTANEOUS OR IATROGENIC)

In patients with reduced CSF pressure there is a clear postural component to the headache. The headache develops or worsens soon after assuming an upright posture and lessens or resolves shortly after lying down.⁴⁴

4

Once the headache becomes chronic it often loses its postural component. Low pressure headache is caused by CSF leakage. The commonest cause is a diagnostic lumbar puncture but spontaneous dural leakage can occur and is often not recognised.

D Intracranial hypotension should be considered in all patients with headache developing or worsening after assuming an upright posture.

3.3.6 GIANT CELL (TEMPORAL) ARTERITIS

Giant cell arteritis (GCA) should be considered in any patient over the age of 50 presenting with headache. Headache is usually diffuse rather than localised to the temple. It is generally persistent and may be severe. The patient may be systemically unwell. Scalp tenderness is common but has a low predictive value of a positive temporal artery biopsy. Jaw claudication is the most reliable predictor, but is not always present. Any patient with jaw claudication and headache should be considered to have GCA until proven otherwise. Visual disturbance is the next most reliable predictor. Prominent, beaded, or enlarged temporal arteries are the most predictive physical sign. A normal erythrocyte sedimentation rate (ESR) makes the diagnosis unlikely, but does not exclude it.⁴⁸

4

D Giant cell arteritis should be considered in any patient over the age of 50 presenting with a new headache or change in headache.

Patients with symptoms suggestive of giant cell arteritis should be referred urgently for specialist assessment.

3.3.7 ANGLE CLOSURE GLAUCOMA

Angle closure glaucoma is rare before middle age. Family history, female sex and hypermetropia are recognised risk factors. Presentation is variable. The patient may have a mid-dilated pupil and red eye with impaired vision, indicating acutely raised intraocular pressure. Alternatively angle closure glaucoma may present as non-specific headache, eye pain, halos around lights or headache mimicking migraine with aura.^{37,55} Intermittent angle closure glaucoma may precede acute angle closure and the eye may not be red.³⁷ The diagnosis should be considered in a patient with headache associated with a red eye, halos or unilateral visual symptoms.

4

D Angle closure glaucoma should be considered in a patient with headache associated with a red eye, halos or unilateral visual symptoms.

Acute angle closure glaucoma is an ophthalmological emergency.

3.3.8 CARBON MONOXIDE POISONING

Symptoms of sub-acute carbon monoxide poisoning include headaches, nausea, vomiting, dizziness, muscular weakness and blurred vision.¹¹

4

4 Assessment tools

A number of tools have been developed to aid headache diagnosis, assess headache impact and related disability and measure response to treatment. Table 2 summarises a number of tools which are readily available via the internet. In clinical practice physicians usually ask questions about headache symptoms. Whilst considering symptoms is important, asking questions about impact can change a clinician's perception of how severe a patient's headache or migraine is.⁵⁶ This information influences treatment choice and the need for follow up.

Patients, primary care clinicians and headache specialists commonly get the diagnosis wrong.^{19,20} This may be because of limited consultation time or poor patient recall. Clinician review and analysis of a prospective diary that records headache symptoms over a few weeks can improve diagnosis.^{11,19,20}

2+
4

D Practitioners should consider using headache diaries and appropriate assessment questionnaires to support the diagnosis and management of headache.

A sample weekly headache diary is displayed in Annex 5.

Table 2 Tools for headache diagnosis and assessment of impact.

Tool	Applications/Benefits	Format	Basis	Limitations
<p>Headache Impact Test (HIT /HIT 6)</p> <p>www.headachetest.com/</p>	<ul style="list-style-type: none"> ▪ assess headache impact ▪ determine diagnostic label ▪ monitor treatment response ^{57,58} <p>Patients with a high HIT-6 score are more likely to be correctly diagnosed and treated for migraine by their GP.</p> <p>Typical scores are chronic headache 57-63 migraine 54-59 TTH 34-45. ^{19,59-61}</p>	<p>Internet or paper based questionnaire</p> <p>5/6 questions</p> <p>Computerised adaptive testing. ^{62,63}</p>	<p>Retrospective tool based on patient's experience of headache over the previous 4 weeks. It assesses:</p> <ul style="list-style-type: none"> ▪ pain ▪ social role limitations ▪ cognitive functioning ▪ psychological distress ▪ vitality 	<p>Limited sensitivity for measuring severity of pain⁶¹</p>
<p>Migraine Disability Assessment (MIDAS)</p> <p>www.midas-migraine.net/edu/question/Default.asp</p>	<ul style="list-style-type: none"> ▪ assess headache impact ▪ monitor treatment response <p>Scores correlate with diagnosis based on physicians' estimates of pain and disability based on patients' medical histories.⁶⁴</p> <p>High internal consistency, test-retest reliability, accuracy and ease of use.^{26, 65-67}</p>	<p>5 item paper based questionnaire</p>	<p>Retrospective tool based on time lost in 3 activity domains over previous 3 months.⁶⁶</p> <ul style="list-style-type: none"> ▪ work or school ▪ household, work and family ▪ social or leisure activities 	<p>Gives all patients with frequent headache a high score. One headache may count multiple times because of the scoring domains.^{65, 68-70}</p> <p>Domains exclude emotional impact.</p>
<p>ID Migraine</p> <p>www.migraineclinic.org.uk/</p>	<ul style="list-style-type: none"> ▪ determine diagnostic label²⁸ <p>Sensitivity for migraine of 0.81 (95% CI, 0.77 to 0.85), specificity of 0.75 (95% CI 0.64 to 0.84) and a positive predictive value of 0.93 (95% CI 0.90 to 0.96).</p>	<p>3 item paper based screening questionnaire</p>	<p>Retrospective based on experience of:</p> <ul style="list-style-type: none"> ▪ gastric symptoms ▪ light sensitivity ▪ functional impairment 	<p>False positive rate of 19%.</p>

5 Investigations

5.1 NEUROIMAGING

When is neuroimaging required?

Investigation should be avoided in principle if it does not lead to a change in management or it is unlikely to reveal a relevant abnormality. Occasionally, neuroimaging may be required on an individual basis if a patient is disabled by fear of serious pathology.⁷¹

4

The vast majority of primary headaches do not require neuroimaging. In a prospective study where patients with headache for more than four weeks underwent neuroimaging (CT, MRI or both), significant intracranial abnormalities were found in 0.4% of patients with migraine, 0.8% of patients with tension-type headache, and in 5% (one out of 20 patients) of those with cluster headache. In a subgroup of 188 patients without clearly defined headache type, significant intracranial abnormality was found in 3.7%.⁷²

2+

A meta-analysis of neuroimaging studies estimated a 0.2% prevalence of significant intracranial abnormalities in patients with migraine and a normal neurological examination.¹² In a retrospective review of 402 patients with chronic headache without neurological symptoms or signs, relevant abnormalities on MRI were found in 0.6% of patients with migraine, 1.4% of patients with tension-type headache and 14.1% of patients with “atypical headache”.⁷³ In another retrospective review MRI revealed relevant intracranial abnormalities in 0.7% of patients with chronic or recurrent headache and a normal neurological examination.⁷⁴

4
3

Neuroimaging in patients with headache and an abnormal neurological examination is significantly more likely to reveal an underlying cause.^{12,39,40} Further investigation is required to exclude secondary aetiology when headache is accompanied by red flags (see section 3.3).

4

Incidental abnormalities

Both MRI and CT can identify neurological abnormalities incidental to the patient’s presenting complaint and which may result in heightened patient anxiety and clinician uncertainty.^{21,22} Cranial MRI in 2,536 healthy young males revealed incidental abnormalities in 6.55%.²² A prospective cohort study of 2,000 volunteers (mean age, 63.3 years; age range 45-96 years) who received brain MRI revealed incidental abnormalities in 13.5%.²¹

3
2+

Patient reassurance

A randomised controlled trial of 150 patients with chronic daily headache in a specialist clinic found that patients who received MRI had a decrease in anxiety levels at three months, but that the reduction in anxiety was not maintained at one year. Patients with high scores on the hospital anxiety and depression scale who did not receive a scan had significantly higher health service costs overall due to a greater use of healthcare resources such as psychiatric and psychology services than comparable patients who received a scan.⁷⁵

1+

CT versus MRI

In ruling out secondary causes of headache MRI is more sensitive than CT in identifying white matter lesions and developmental venous anomalies.¹² The European Federation of Neurological Societies guidelines suggest that MRI is the imaging modality of choice because of this greater sensitivity.⁷⁶ The US headache consortium concluded that MRI may be more sensitive than CT in identifying clinically insignificant abnormalities, but not more sensitive in identifying clinically significant pathology relevant to the cause of the headache.⁷¹

3

- D** Neuroimaging is not indicated in patients with a clear history of migraine, without red flag features for potential secondary headache, and a normal neurological examination.
- D** Clinicians requesting neuroimaging should be aware that both MRI and CT can identify incidental neurological abnormalities which may result in patient anxiety as well as practical and ethical dilemmas with regard to management.
- D** Brain CT should be performed in patients with headache who have unexplained abnormal neurological signs, unless the clinical history suggests MRI is indicated.

5.1.1 COMPUTERISED TOMOGRAPHY AND THUNDERCLAP HEADACHE

ICHD-II classification states that normal brain imaging and CSF are required before a diagnosis of primary thunderclap headache can be made.¹⁶ 4

When SAH is suspected, CT brain scan should be carried out as soon as possible to maximise sensitivity. Sensitivity of CT for subarachnoid haemorrhage is 98% at 12 hours dropping to 93% by 24 hours.⁵⁰ 4

A normal CT brain scan is insufficient to rule out SAH and a lumbar puncture is required in patients with normal CT scans (see section 5.3).

If negative results are obtained from both brain CT and lumbar puncture with cerebrospinal fluid analysis within two weeks of onset of thunderclap headache, then SAH can be excluded from diagnosis.^{35,38,50} 4

Sudden severe headaches precipitated by sexual activity can be diagnosed as primary if they cannot be attributed to another disorder.¹⁶ On first onset of this headache it is essential to exclude SAH and arterial dissection.⁷⁷ 4

- D** In patients with thunderclap headache, unenhanced CT of the brain should be performed as soon as possible and preferably within 12 hours of onset.

5.1.2 MAGNETIC RESONANCE IMAGING

Expert opinion suggests that MRI should be considered in patients with cluster headache, paroxysmal hemicrania or SUNCT, in order to exclude the wide variety of secondary causes.³² 4

In a review of 31 cases in which a TAC or TAC like syndrome was associated with a structural lesion and the treatment of the lesion resulted in significant clinical improvement, 11 out of 31 had a pituitary adenoma. Only 10 out of the 31 cases had atypical presenting features.⁷⁸ In a prospective study of 43 patients with SUNCT and nine patients with SUNA, cranial imaging was carried out in 36 with SUNCT and eight with SUNA. Twelve patients (11 with SUNCT, 1 with SUNA) of the 44 who received cranial imaging had significant intracranial abnormalities.³³ 3
2+

- D** Brain MRI should be considered in patients with cluster headache, paroxysmal hemicrania or SUNCT.

In a retrospective study in patients with cough-induced headaches (n = 30), exertional headaches (n = 28) and sexual headaches (n = 14); 17 out of 30 patients with cough-induced headache had chiari type 1 malformation; 10 out of 28 patients with headache induced by exertion had SAH, 1 had sinusitis and 1 had brain metastases; and 1 out of 13 patients with explosive orgasmic headache had SAH.⁷⁹ 3

Primary cough headache (Valsalva manoeuvre headache) which is precipitated rather than aggravated by coughing, laughing or straining may be diagnosed only after structural lesions are excluded by neuroimaging.¹⁶ Patients with cough headache should have an MRI brain scan to rule out posterior fossa lesion.⁷⁷ 4

- D** Brain MRI should be carried out in patients presenting with headache which is precipitated, rather than aggravated, by cough.

Benign exertional headache which is precipitated rather than aggravated by exertion can be diagnosed as primary if it is not associated with any other disorder (see Annex 2).¹⁶ ICHD-II classification states that on first occurrence subarachnoid haemorrhage or arterial dissection need to be excluded.¹⁶ Similar percentages of patients with benign thunderclap headache and confirmed SAH were provoked by exertion in two prospective case series so exertion alone does not predict SAH.^{35,41} Expert opinion suggests that neuroimaging should be carried out to exclude a structural cause or vascular abnormality in patients with exertional headache. If headaches are prolonged beyond a few hours, are accompanied by focal neurological symptoms or vomiting, or appear de novo after the age of 40 the chance of finding a relevant abnormality is increased.⁷⁷

4

- Further investigation should be considered in patients with headaches which are precipitated, rather than aggravated, by exercise.

A small case control study of spinal MRI in patients with post lumbar puncture headache and spontaneous intracranial hypotension concluded that venous plexus volume at C2 was significantly higher in patients than in the controls. Spinal hygromas were present in 67% of patients with spontaneous intracranial hypotension and 73% of patients with post lumbar puncture headache, but were not present in controls.⁸⁰

3

Several small case series show an association between spontaneous intracranial hypotension and diffuse pachymeningeal gadolinium enhancement on brain MRI.⁸¹⁻⁸³

3

- All patients with suspected low pressure headache should be referred to a specialist for consideration of the most appropriate investigation.

5.2 LUMBAR PUNCTURE IN SUBARACHNOID HAEMORRHAGE

Lumbar puncture (LP) with CSF analysis is appropriate for patients with thunderclap headache and normal neuroimaging to exclude a diagnosis of subarachnoid haemorrhage.^{35,50,84,85} One prospective study found that lumbar puncture was positive for subarachnoid haemorrhage in 21% of patients with thunderclap headache (5 out of 23 patients) who had a normal CT brain scan.³⁵

4

3

2⁺

In a case series, lumbar puncture was performed in 40 out of 81 patients presenting with thunderclap headache and a normal CT brain scan. 15% of these had a lumbar puncture positive for SAH.⁸⁵

3

Since xanthochromia (bilirubin and oxyhaemoglobin) can only be detected in CSF after 12 hours, lumbar puncture and CSF analysis should be delayed 12 hours from the onset of thunderclap headache.^{50,86,87} In patients presenting late, LP can be informative up to two weeks from the onset of the thunderclap headache.^{50,86}

3

Spectrophotometry is the recommended method of CSF analysis and should be performed on the final sample of CSF collected. Following lumbar puncture, the presence of CSF bilirubin is the key result suggestive of SAH, and is usually accompanied by oxyhaemoglobin.⁸⁷

4

Opening pressure should be measured routinely in all lumbar punctures.⁸⁷

4

- C** Patients with thunderclap headache and a normal CT should have a lumbar puncture.
 - D** In patients who require a lumbar puncture for thunderclap headache, oxyhaemoglobin and bilirubin should be included in cerebrospinal fluid analysis.
 - Opening pressure should be measured when lumbar puncture is indicated in patients with headache.
 - In patients with suspected subarachnoid haemorrhage, neuroimaging should be performed prior to lumbar puncture.
 - Lumbar puncture in CT negative patients with suspected subarachnoid haemorrhage should be carried out as soon as possible after 12 hours has elapsed from the onset of symptoms.
- In delayed presentations, lumbar puncture can be performed up to two weeks from onset of symptoms.

5.3 ERYTHROCYTE SEDIMENTATION RATE, C-REACTIVE PROTEIN AND PLASMA VISCOSITY IN GIANT CELL ARTERITIS

Increased erythrocyte sedimentation rate (ESR) may be useful in predicting the presence or absence of GCA in patients with suggestive symptoms. Mean ESR in patients with GCA was 88 mm/hr compared with a mean ESR of 10 mm/hr in patients without GCA. The difference was not statistically significant.⁴⁸ Four per cent of patients with positive temporal artery biopsy results had a normal value ESR.⁴⁸

2+

A retrospective case series of 363 patients who underwent temporal artery biopsy for suspected GCA found that both ESR and C-reactive protein (CRP) had a high sensitivity for detection of GCA. C-reactive protein had a higher sensitivity than ESR (100% vs 92%). Combining ESR and CRP gave the highest specificity (97%) than CRP alone (83% in men and 79% in women).⁸⁸ In patients with suspected GCA, the odds of a positive biopsy were 3.2 times greater with CRP above 24.5 mg/l (p=0.0208); two times greater with an ESR between 47 and 107 mm/hr compared to an ESR less than 47 mm/hr (p=0.0454); the odds of a positive biopsy was 2.7 times greater than 107 mm/hr relative to an ESR less than 47 mm/hr (p=0.0106).⁸⁸

3

- D** ESR and/or CRP (but preferably a combination of these diagnostic tests to maximise sensitivity and specificity) should be measured in patients with suspected giant cell arteritis.

Plasma viscosity is used in the diagnosis of GCA, but no studies on its effectiveness were identified.

5.4 OTHER INVESTIGATIONS

No evidence was identified on the benefits of routine full blood count assessment or the use of X-ray of the cervical spine in the diagnosis of patients with headache.

6 Migraine

This section has been superseded by [SIGN 155: Pharmacological management of migraine](#).

7 Tension-type headache

7.1 ACUTE TREATMENT

A large RCT (n = 638) showed that aspirin had a high response rate for relief of pain at two hours in patients with episodic tension-type headache (75% for 1,000 mg; p = 0.0009 and 70% for 500 mg p = 0.011). Paracetamol 1,000 mg had a similar rate (71% p = 0.007) and both performed well compared with response to placebo (54.5%).¹⁴³

1++

No studies were identified on any other therapies for the acute treatment of patients with tension-type headache.

A Aspirin and paracetamol are recommended for acute treatment in patients with tension-type headache.

7.2 PHARMACOLOGICAL PROPHYLAXIS

7.2.1 ANTIHYPERTENSIVES

High blood pressure does not usually cause headache, although blood pressure lowering treatments can reduce the prevalence of headache.¹⁴⁴

2++

A meta-analysis indicated that angiotensin II receptor antagonists reduce the frequency of headache.¹⁴⁵ An RCT showed that lisinopril has a significant effect on the reduction of hours and days with headache and migraine.¹⁴⁶ Neither of these studies specified headache type or identified patients with hypertension within the trial.

1-

1+

7.2.2 ANTIEPILEPTICS

One RCT was identified which showed a 9.1% difference in headache free rates benefiting patients with chronic daily headache who were treated with gabapentin versus those on placebo (p = 0.0005).¹⁴⁷

1+

7.2.3 ANTIDEPRESSANTS

A Cochrane review has shown no significant difference between treatment with placebo and fluoxetine for reduction in headache frequency and severity.¹³⁰

2++

Tricyclic antidepressants are more effective in reducing chronic headache than SSRIs.^{129,130} A significantly higher intake of analgesic medication was seen in patients treated with SSRIs than in patients treated with tricyclic antidepressants, equivalent to five or more doses per month (95% CI 1 to 9). Tricyclic antidepressants also reduced headache duration by 1.26 hours per day and headache index scores based on frequency and severity. Amitriptyline in doses of 25-75 mg was the most commonly studied tricyclic antidepressant.¹²⁹

1+

A Tricyclic antidepressants, particularly amitriptyline, 25-150 mg per day, are recommended as the agents of choice where prophylactic treatment is being considered in a patient with chronic tension-type headache.

A small RCT (n = 24) of mirtazapine in patients with chronic tension-type headache showed a significant reduction in headache frequency (p = 0.005), duration (p = 0.03) and intensity (p = 0.03) compared to placebo.¹⁴⁸

1-

Sertraline did not show a significant improvement on severity and frequency of chronic tension-type headache when compared to placebo.¹⁴⁹

1+

A small RCT (n = 60) on the efficacy of venlafaxine extended release tablets (150 mg per day) in the prophylactic treatment of patients with tension-type headache showed that the median number of days with headache decreased from baseline in the venlafaxine group in two out of the three periods studied, but not in the placebo group (p = 0.05 and 0.033). The number needed to treat for responders (> 50% reduction in days with headache) was 3.48.¹⁵⁰

1+

7.2.4 OTHER THERAPIES

A multicentre RCT assessing the efficacy of botulinum toxin A in the prophylactic treatment of chronic tension-type headaches showed no statistically significant difference between placebo and the four botulinum toxin A groups in the number of TTH free days per month.¹⁵¹ A statistically significant difference favouring placebo versus botulinum toxin A 150U was observed (4.5 versus 2.8 tension headache free days per month, $p = 0.007$).

1+

Botulinum toxin A has been shown to be effective for the treatment of patients with headache associated with neck dystonias.¹⁵²

1+

B Botulinum toxin A is not recommended for the preventive treatment of chronic tension-type headache.

Tizanidine has been shown to be superior to placebo in reducing headache (as measured by combination of frequency, duration and intensity) in patients with a chronic daily headache (migraine and tension-type, $p = 0.0025$).¹⁵³

1+

8 Trigeminal autonomic cephalalgias

8.1 ACUTE TREATMENT OF CLUSTER HEADACHE

Few well conducted trials have been carried out on patients with cluster headache, possibly due to the spontaneous course of the condition.¹⁵⁴

8.1.1 TRIPTANS

Subcutaneous injection of 6 mg sumatriptan relieves pain in 73-96% of patients with acute cluster headache within 15 minutes.¹⁵⁵⁻¹⁵⁸ Nasal administration of 20 mg sumatriptan acts more slowly, relieving pain in 57% of patients at 30 minutes.¹⁵⁹

2-
1++

Nasal zolmitriptan 5 mg and 10 mg provide acute attack relief at 30 minutes in 50% and 63% of cluster headache patients respectively.¹⁶⁰ Oral zolmitriptan 10 mg relieves acute attack pain in 47% patients with episodic cluster headache at 30 minutes.¹⁶¹

1++

A Subcutaneous injection of 6 mg sumatriptan is recommended as the first choice treatment for the relief of acute attacks of cluster headache.

A Nasal sumatriptan or zolmitriptan is recommended for treatment of acute attacks of cluster headache in patients who cannot tolerate subcutaneous sumatriptan.

8.1.2 OXYGEN

In a small double blind crossover study conducted over 20 years ago, 19 men with cluster headache were treated with 100% oxygen versus air inhalation at 6 l/minute via a non-rebreathable mask over 15 minutes. The average relief score for all oxygen treated patients was 1.93 ± 0.22 (out of a possible score of 3.0). For air the treatment relief score was 0.77 ± 0.23 .¹⁶² In a previous study it was reported that 75% of 52 randomly selected patients with cluster headaches, reported significant pain relief when treated with 100% oxygen at a rate of 7 l/min for 15 minutes.¹⁶³

1+

A tight fitting, non-rebreathing mask should be used. Information on availability of suitable masks and loan of appropriate regulator equipment is available from www.ouchuk.org/html/

100% oxygen (7-12 litres per minute) should be considered for the treatment of acute attacks in all patients with cluster headache.

Trials have been conducted on the use of hyperbaric oxygen but no consistent prophylactic effect has been demonstrated.^{140,164,165}

1++
1+
1-

8.1.3 LIDOCAINE

An RCT demonstrated that 10% nasal drops of lidocaine brought pain relief within 37 minutes in patients with acute cluster headache, compared to 59 minutes for those on a saline placebo ($p < 0.001$).¹⁶⁶

1+

For patients whose attacks of cluster headache are not well relieved by subcutaneous or nasal triptan and inhaled 100% oxygen, 10% intranasal lidocaine drops can be considered to help speed relief for acute attacks.

8.2 PHARMACOLOGICAL PROPHYLAXIS

8.2.1 CALCIUM CHANNEL BLOCKERS

Open label studies show that verapamil reduces the frequency and severity of cluster headaches.³² | 4

In a small double blind study 86% of patients receiving verapamil (360 mg per day) showed an improvement of > 50% reduction in headache frequency while the placebo group showed no response.¹⁶⁷ | 1+

Higher doses of verapamil (up to 960 mg per day) have been used and are recommended for the preventive treatment of cluster headaches. Regular electrocardiogram monitoring is required.¹⁶⁸ | 4

B Verapamil 240-960 mg is recommended for the prophylaxis of cluster headache.

8.2.2 LITHIUM

A small double blind placebo-controlled trial using lithium (800 mg per day) in patients with cluster headache was stopped early because superiority over placebo could not be established.¹⁶⁹ Both lithium and verapamil have been shown to be superior to placebo in one small trial.³² | 1-
4

8.2.3 ERGOTS

Ergotamine has previously been used for the preventive treatment of cluster headaches but no trial evidence for this is available.³² | 4

8.2.4 5-HT ANTAGONISTS

There are no contemporary placebo-controlled trials on the use of methysergide in cluster headaches. A small trial found pizotifen to be effective for cluster headaches but a further review has concluded that the effect is minimal.¹⁶⁸ | 4

8.2.5 MELATONIN

In a small double blind study (20 patients with cluster headache) melatonin significantly reduced headache frequency compared with placebo ($p < 0.03$).¹⁷⁰ | 1-

8.2.6 ANTIEPILEPTICS

A double blind placebo-controlled trial of valproate for treatment of cluster headaches found no beneficial effect. The study had an unusually high placebo response rate.¹⁷¹ | 1-

In open label studies topiramate and gabapentin have been found to be effective for patients with cluster headaches.³² | 4

8.2.7 STEROIDS

A double blind placebo-controlled trial compared suboccipital injection of a mixture of long and rapid acting betamethasone with the injection of physiological saline in patients with episodic and chronic cluster headache. Eighty five per cent of patients injected with steroid became headache free in the first week after injection compared to none in the placebo group ($p = 0.0001$). At four weeks eight of 11 responders remained attack free ($p = 0.0026$).¹⁷² | 1+

Expert opinion suggests that oral steroids can be used for the short term preventive treatment of cluster headaches although no contemporary trial evidence is available.¹⁶⁸ | 4

8.3 TREATMENT OF PAROXYSMAL HEMICRANIA, HEMICRANIA CONTINUA AND SUNCT

Responsiveness to indometacin is integral to the diagnosis of paroxysmal hemicrania and hemicrania continua. Indometacin is effective in doses of up to 225 mg per day.³² | 4

Lamotrigine may be effective for the treatment of the SUNCT syndrome.^{32,168} | 4

D Indomethacin up to 225mg is recommended for the prophylaxis of paroxysmal hemicrania and hemicrania continua.

9 Medication overuse headache

9.1 DEFINITIONS AND ASSESSMENT

Medication overuse headache (MOH) is defined as headache which is present for 15 days or more per month and which has developed or worsened while taking regular symptomatic medication (see Annex 2).^{16,27,173} 4

Medication overuse headache is reported in migraine, tension-type headache, hemicrania continua, new daily persistent headache, cluster headache and SUNCT.^{33,174-177} Patients with cluster headache and SUNCT who develop MOH usually have a personal or family history of migraine.^{33,176} 3
4

ICHD-II criteria suggest medication overuse headache should be considered with use on ten days per month for triptans, ergots, opioids or combination analgesics and on 15 days per month for simple analgesics.¹⁷³ 4

Patients with a history of migraine headache who frequently use pain medications for non-headache pain are at increased risk of developing chronic daily headache.¹⁷⁴ 3

Patients who overuse medications are more likely to develop chronic daily headache.^{113,178} The risk depends on which medication is being overused (opioid OR 4.4; triptan OR 3.7; ergot OR 2.9; analgesics OR 2.7).¹¹³ 3

In an audit of nine GP practices fewer than 16.2% of patients who were using triptans for headache met ICHD-II criteria for triptan overuse.¹⁷⁹ 3

Patients with frequent headache are at increased risk of developing chronic daily headache.¹¹³ The more frequent the headache the greater the risk (5-9 headaches per month = OR 7.6; 10-15 headaches per month = OR 25.4). 3

Patients with chronic daily headache meeting the criteria for medication overuse headache evolving from episodic tension-type headache were found to be more likely to have a mood disorder than those with chronic tension-type headache without medication overuse. Patients with chronic daily headache meeting the criteria for medication overuse headache evolving from migraine were found to be more likely to have a mood disorder, depression, anxiety disorder or obsessive compulsive disorder than chronic tension-type headache without medication overuse.¹⁸⁰ 2+

In patients with chronic daily headache the DSM-IV criteria for dependence behaviour were significantly more common in those who met ICHD-II criteria for medication overuse headache.¹⁸⁰ 2+

D Medication overuse headache must be excluded in all patients with chronic daily headache (*headache \geq 15 days / month for $>$ 3 months*).

D Clinicians should be aware that patients using any acute or symptomatic headache treatment are at risk of medication overuse headache. Patients with migraine, frequent headache and those using opioid-containing medications or overusing triptans are at most risk.

C When diagnosing medication overuse headache, psychiatric comorbidity and dependence behaviour should be considered.

C Patients with medication overuse headache who have psychiatric comorbidity or dependence behaviour should have these conditions treated independently. Referral to a psychiatrist or a clinical psychologist should be considered.

9.2 TREATMENT

This section has been superseded by [SIGN 155: Pharmacological management of migraine](#).

10 Pregnancy, contraception, menstruation and the menopause

10.1 PREGNANCY

Where possible, the use of medication in pregnancy should be avoided, particularly in the first trimester. Paracetamol, however, has been used routinely during all stages of pregnancy for relief of headache and overall there seems to be no clear evidence of harmful effects on the fetus.¹⁹⁴⁻¹⁹⁷ If drug treatment is considered essential then paracetamol, at the recommended therapeutic doses, is the analgesic of choice for the short term relief of mild to moderate pain during pregnancy.^{195,197} As with any medication used during pregnancy, paracetamol should be taken at the lowest effective dose for the shortest time necessary.

4

If short term analgesia with an NSAID is required in the first or second trimester, ibuprofen or aspirin can be used.¹⁹⁵ Aspirin is contraindicated during the third trimester of pregnancy.⁹⁰ Whilst limited, the available evidence does not indicate that exposure to ibuprofen before 20 weeks of pregnancy is associated with an increased risk of birth defects or spontaneous abortions. Long term exposure or exposure to high doses in late pregnancy is associated with an increased risk of fetal complications.¹⁹⁵

4

Three systematic reviews found no robust evidence of an increased risk of fetal abnormalities in babies born to mothers who took sumatriptan during pregnancy.¹⁹⁸⁻²⁰⁰ There is a non-significant trend to an increased risk of pre-term births (before 37 weeks) and miscarriages following the use of sumatriptan during pregnancy.^{198,199} There is insufficient evidence to advocate the use of triptans during pregnancy.

2+
2-

Some anti-emetics can be used with caution in pregnancy. There is no evidence for teratogenicity for buclizine and cyclizine.⁹⁰ Prochlorperazine is safe in the first two trimesters.⁹⁰

4

- Paracetamol 1,000 mg is the treatment of choice in pregnancy for all patients with migraine and tension-type headache when the pain is sufficient to require analgesia.
- If paracetamol provides insufficient analgesia aspirin 300 mg or ibuprofen 400 mg can be used in the first and second trimester of pregnancy.

10.2 ORAL CONTRACEPTION

Migraine and the use of the combined oral contraceptive pill (COCP) are both independent risk factors for stroke. It is important to discuss stroke risk with women with migraine who require oral contraception.

The risk of stroke in women aged 25 to 44 is very low. The annual incidence of all types of cerebral infarction has been estimated as four per 100,000 in women aged 25-34 and 11 per 100,000 in women aged 35-44.²⁰¹ The annual incidence of ischaemic stroke in women aged 25-44 has been estimated as 4.4 per 100,000.²⁰²

4
2++

A WHO collaborative showed that for women with migraine the overall odds ratio for all stroke was 1.78 (95% CI 1.14 to 2.77), 3.54 (95% CI 1.30 to 9.61) for ischaemic stroke and 1.10 (95% CI 0.63 to 1.94) for haemorrhagic stroke. The odds ratio for stroke in women with migraine with aura was 3.81 (95% CI 1.26 to 11.5) and for migraine without aura 2.97 (95% CI 0.66 to 13.5).²⁰³ Evidence from other meta-analyses and systematic reviews also suggests a significant increased risk of ischaemic stroke among women with migraine, with a relative risk of between 1.85 (95% CI 1.44 to 2.36) to 2.16 (95% CI 1.89-2.48).^{204,205}

2++

The increased risk of ischaemic stroke with a COCP is related to dose. Studies show an odds ratio varying between 2.08 (95% CI 1.55-2.80) to 2.74 (95% CI 2.24-3.35).²⁰⁶ | 2++

Women with migraine with aura using a COCP have a relative risk of 8.72 (95% CI 5.05 -15.05) for developing stroke.²⁰⁴ | 2++

B Women with migraine with aura should not use a combined oral contraceptive pill.

The WHO advises that women over the age of 35 suffering from migraine without aura also have an increased risk of ischaemic stroke if they take COCP.^{206,207} | 4

D Patients with migraine without aura who are over the age of 35 should not use a combined oral contraceptive pill.

No evidence was identified on the safety or the efficacy of reducing the frequency and severity of menstrual migraine in patients using progesterone or long-acting implantable contraceptives.

10.3 MENSTRUATION

This section has been superseded by [SIGN 155: Pharmacological management of migraine](#).

10.3.1 SIMPLE ANALGESICS

This section has been superseded by [SIGN 155: Pharmacological management of migraine](#).

10.3.2 TRIPTANS

This section has been superseded by [SIGN 155: Pharmacological management of migraine](#).

10.3.3 PROPHYLAXIS FOR MENSTRUAL MIGRAINE

This section has been superseded by [SIGN 155: Pharmacological management of migraine](#).

10.4 MENOPAUSE

This section has been superseded by [SIGN 155: Pharmacological management of migraine](#).

11 Lifestyle factors

The studies reviewed for this section involve combinations of interventions, making assessment of their individual contribution to headaches difficult.

11.1 DIET

Although many patients report that various foods trigger their migraine, an editorial review found no good quality published evidence to support this.²³⁴ No evidence was identified to support the prophylactic effect of general avoidance of cheese or chocolate, or for any other dietary manipulation in patients with migraine.^{11,235,236} | 1-
4
3

Dietary supplementation with omega-3 fatty acids does not reduce the incidence of migraine.²³⁷ | 1+

Expert opinion suggests that omission or altered timing of meals may be associated with migraine in some patients, eg missing breakfast may trigger a late morning attack, and so patients should be encouraged to eat regularly.¹¹ | 4

Patients with migraine should be encouraged not to miss meals.

11.2 TRIGGER AVOIDANCE

Limited and low quality evidence was identified in relation to possible trigger factors for headache.

A survey of patients with headache suggested that a reduction in caffeine intake and addressing sleep problems may reduce disability associated with headache.²³⁸ | 3

No good quality evidence was identified on whether mobile phone signals relate to headache symptoms.

11.3 EXERCISE

The evidence on exercise was mainly limited to exercise included in combined therapies programmes.

For patients with cervicogenic headache, low load cervical exercise and manipulation were effective in reducing frequency and intensity of headache, but there was no additional statistically significant benefit when therapies were combined.²³⁹ This effect may relate to patients' belief in the therapy or therapist.²⁴⁰ | 1+

For patients with migraine, multidisciplinary intervention including group supervised exercise therapy sessions (along with stress management and relaxation therapy lectures, dietary advice and massage therapy) provided improvements in frequency, intensity and duration of headache and quality of life.²⁴¹ | 1+

11.4 SLEEP

No good quality evidence was found relating to sleep and headache. There may be an association between obstructive sleep apnoea and chronic headache, although studies did not include headache as a primary symptom.^{242,243} Changes in sleep pattern, eg sleeping longer at weekends or sleep disturbance due to stress, may be associated with migraine, although there may be confounding factors related to the altered sleep.^{11,235,236} | 2-
4

11.5 STRESS MANAGEMENT

In a prospective analysis of the factors related to headache in migraineurs, tension and stress were associated with increased risk of migraine, whereas holidays, relaxation after stress and after divorce decreased the hazard.²³⁶ 3

Multidisciplinary intervention, including stress management was effective in patients with migraine.²⁴¹ Results from a survey of patients with migraine suggest that reduction in stress can relieve headache symptoms.²⁴⁴ 1+
3

B Stress management should be considered as part of a combined therapies programme to help patients reduce the frequency and severity of migraine headaches.

For patients with chronic TTH, stress management was more effective when combined with antidepressant medication, although stress management alone was still more effective than placebo. This study had a high drop-out rate.²⁴⁵ 1-

12 Psychological therapies

Various methodological problems have been encountered with the research identified in this area. These include:^{246,247}

- difficulties in blinding trials in this area of research
- lack of standardisation and description of patient groups, interventions and their delivery and outcome measures
- use of inappropriate self selected patient groups
- ethical issues around pharmacological versus psychological interventions.

For patients with migraine, a single RCT suggests multidisciplinary intervention, including exercise, stress management, relaxation, diet and massage are effective in reducing pain frequency duration and intensity and improving quality of life, but it is unclear which specific intervention has the greatest benefit.²⁴¹ Stress management is discussed in section 11.5.

1+

No good quality contemporary evidence was identified for cognitive behavioural therapy or any specific relaxation therapy or biofeedback technique. The US Headache Consortium guidelines for migraine headache included evidence from 1966-1996 and recommended that relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback and cognitive behavioural therapy may be considered as treatment options for prevention of migraine.²⁴⁸

4

No good quality evidence was identified for hypnotherapy.

13 Physical therapies

It is not possible to conduct blinded trials of physical therapies. Studies are subject to attention and placebo effects which may introduce bias. A number of studies examine the effects of combinations of treatments making the effectiveness of the individual therapies difficult to ascertain. The role of exercise is discussed in section 11.3.

13.1 MANUAL THERAPY

Manual therapy covers a number of interventions including spinal manipulation therapy (SMT) and spinal mobilisation.

Cervicogenic headache

In a Cochrane systematic review five studies of spinal manipulation therapy for cervicogenic headache were described. SMT was compared with placebo, mobilisation, NSAIDs, exercise and massage plus placebo laser.²⁴⁹ Although the studies were too dissimilar for results to be pooled, there was moderate evidence that SMT is superior to no treatment in reducing headache pain and frequency one week and 12 months following six weeks of treatment and superior to placebo SMT for pain, disability and number of headache sites three weeks after treatment. A comparison with massage plus placebo laser found SMT produced a significantly greater decrease in pain intensity (effect size 0.6; 95% CI 0.1-1.1).

1++

B Spinal manipulation therapy should be considered in patients with cervicogenic headache.

Migraine

A Cochrane systematic review identified three studies of effectiveness of spinal manipulation in migraine compared with amitriptyline, spinal mobilisation and placebo electrotherapy.²⁴⁹ The studies were too dissimilar for results to be pooled and the evidence of effectiveness is too limited to lead to recommendation.

1++

Tension-type headache

Two studies of SMT in patients with chronic tension-type headache were included in a Cochrane systematic review.²⁴⁹ In one study SMT was inferior to amitriptyline for effect on pain intensity during six weeks of treatment, although this was reversed at four weeks post-treatment. The second study examined the immediate effects of a single treatment and found more pain reduction in the SMT group than in a no-treatment control group.

1++

A systematic review of a range of manual therapies for pain reduction in tension-type headache found no rigorous positive effect of manual therapies.²⁵⁰

1+

A small single blind RCT (n = 26) found that three osteopathic treatments, one each week for three weeks, plus relaxation exercises, increased the number of headache free days per week in patients with TTH compared with relaxation exercises alone (0.21 days to 1.79 days, p = 0.016).²⁵¹

1+

An RCT in a mixed group of patients with episodic and chronic TTH compared a craniocervical training programme combined with physiotherapy with physiotherapy alone. There was a positive and clinically relevant effect on headache frequency at six months following a six week programme. 85% of patients in the treatment group (n = 39) experienced a reduction of ≥ 50% in their headache frequency at six months compared to 35% in the control group.²⁵²

1+

13.2 MASSAGE

For patients with episodic TTH the benefit of massage as part of soft tissue manipulation is inconclusive.²⁵⁰ | 1++

As part of a multidisciplinary intervention for patients with migraine massage appears effective with statistically significant reductions in frequency, intensity and duration of pain, and improved quality of life compared to controls which is maintained three months post-intervention.²⁴¹ The separate effect of massage is not clear. | 1+

There is insufficient evidence to make a recommendation on the use of massage in the treatment of patients with headache.

13.3 TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

A Cochrane review identified two trials where transcutaneous electrical nerve stimulation (TENS) was used as part of a combined physical therapies intervention.²⁴⁹ In a single RCT in patients with transformed migraine (MOH), TENS resulted in a statistically significant reduction in number of headache days per month, 21 days at baseline versus 11 days one month after TENS, ($p < 0.05$) but this benefit was not evident at four months.²⁵³ | 1++
| 1+

There is insufficient evidence to make a recommendation on the use of TENS in the treatment of patients with headache.

13.4 ACUPUNCTURE

Interpretation of the evidence base for acupuncture is complicated by the lack of standardisation of interventions, the choice of control and comparison groups and the range of outcome measures employed. In addition to difficulties in blinding and concealment, trials very often have high drop-out rates (> 10%). A review examining the methodology of 13 studies noted that the majority of studies of acupuncture in patients with migraine are of poor quality, with conflicting results.²⁵⁴ | 1+

A Cochrane systematic review of 26 studies found that the majority of trials had methodological and/or reporting shortcomings and suggested there was no conclusive evidence for the use of acupuncture in patients with migraine or TTH, although trends were towards benefit.²⁵⁵ | 1++

In a large ($n = 401$), well conducted RCT in patients with chronic headache disorder, predominantly migraine, headache scores at 12 months were significantly reduced in patients having acupuncture compared to usual care.²⁵⁶ | 1+

A number of RCTs in patients with a range of chronic headache types found that sham acupuncture (eg needling superficially at points distant from the segments of true treatment points) was as effective as real acupuncture. This may be mediated through generation of non-specific physiological effects.²⁵⁷⁻²⁶⁰ | 1+
| 1-

B Acupuncture should be considered for preventive management in patients with migraine.

13.5 ORAL REHABILITATION

No good quality evidence was found to determine whether the use of acrylic splints is effective for patients with migraine.

Temporomandibular disorders (TMD) include symptoms such as joint clicking, facial pain and limitation of mandibular movement. Headache is included as one of the diagnostic criteria for TMD (but is not diagnostic alone). There is inconsistency in criteria between studies and headache type may not be defined.^{261,262} A Cochrane review found no evidence from RCTs that occlusal adjustment treats or prevents headache in patients with temporomandibular disorders.²⁶²

1++

One study showed that occlusal splint therapy may be effective for headache as part of TMD but there are concerns about cases of aspiration of small splints and changes in tooth positions.²⁶³

1+

B Occlusal adjustment is not recommended for treatment of patients with headache associated with temporomandibular disorders.

14 Complementary therapies

14.1 HOMEOPATHY

A systematic review of four randomised placebo-controlled double blind trials concluded that homeopathy is not effective in the prophylaxis of migraine beyond a placebo effect.²⁶⁴

1⁺

14.2 REFLEXOLOGY

No evidence was identified for the effectiveness of reflexology in reducing the frequency and severity of headaches.

14.3 MINERALS, VITAMINS AND HERBS

A Cochrane review concluded that there is insufficient evidence that feverfew is efficacious beyond placebo for preventing migraine. In four trials of acceptable size two showed that the frequency of migraine reduced with feverfew while two trials did not.²⁶⁵ A CO₂ extract of feverfew was shown to reduce the migraine frequency by 1.9 attacks per month as compared to 1.3 attacks in the placebo group (p=0.0456).²⁶⁶

1⁺⁺
1⁻

A Feverfew is not recommended for preventive treatment of patients with migraine.

Petasites hybridus root (butterbur) in a dose of 75 mg per day has been shown to reduce migraine attack frequency by 48% over four months as compared to a 28% reduction with placebo (p=0.0012).²⁶⁷

1⁻

In a small study coenzyme Q10 was shown to be superior to placebo for attack frequency, headache days, and days with nausea. The responder rate for attack frequency was 14.4% for placebo and 47.6% for CoQ10 (NNT = 3).²⁶⁸

1⁻

Niacin (oral or intravenous) may have beneficial effects for patients with migraine and tension-type headaches.²⁶⁹

4

Intravenous magnesium has an analgesic effect similar to IV metoclopramide and to placebo when administered for the treatment of patients with an acute migraine attack.²⁷⁰ A double blind RCT found no significant difference between the group receiving placebo or magnesium. The patients receiving magnesium had significantly more (p=0.03) side effects as compared to placebo.²⁷¹

1⁺

B Intravenous magnesium is not recommended as treatment in patients with acute migraine attack.

Riboflavin in a dose of 200 mg per day has been compared to placebo and found to have a responder rate of 56% versus 9% for attack frequency and 59% versus 15% for the number of migraine days.²⁷²

1⁻

A combination of riboflavin 400 mg, magnesium 300 mg and feverfew 100 mg was not found to be more effective than placebo containing riboflavin 25 mg.²⁷³

1⁻

15 Information provision

15.1 FREQUENTLY ASKED QUESTIONS

These frequently asked questions and suggested answers are intended as a prompt for discussion between healthcare professionals and patients with headache concerns. They are not designed for direct distribution to patients, but might be incorporated into locally developed patient information materials. General patient information leaflets and further patient information is available from the organisations listed in section 15.2.

What is the difference between headache and migraine?

There are many different types of headache. The most common is tension-type headache which causes mild to moderate pain on both sides of the head.

Migraine usually causes moderate to severe pain on one side of the head and many people also feel or are sick. They may feel uncomfortable with bright light or noise. Sometimes people with migraine experience 'aura' which can cause changes to their sight, such as flashing lights or spots, and numbness or 'pins and needles' in their hands and face.

Is a brain tumour causing my headache?

Most common headaches are not caused by tumours. It is very unusual for headache to be the sole symptom of a brain tumour.

Is it going to go away?

People have different experiences of how often headaches and migraines occur, and how long they last. There are treatments which can help to prevent headaches occurring as frequently and which can help reduce the severity of the pain. Keeping a headache diary may help as it can show whether there are any patterns in your headaches.

Why me?

A tendency to troublesome headaches often runs in families. Many headache disorders are genetically linked. Headaches affect over 90% of the population in the UK at some time in their life, although some people experience much worse or more frequent headaches than others.

When should I consult my GP?

If you experience new severe headache, sudden headache, prolonged headache or a change in your usual headache pattern you should see your doctor.

If you have been prescribed medication and your headaches continue you should go back to your GP to discuss trying different treatment, and to make sure that the medicine itself is not causing more headaches (known as medication overuse headache).

What treatments are available?

There are many medicines available without prescription which can relieve headache and migraine, such as aspirin, paracetamol and ibuprofen.

If your headaches are more severe or occur frequently your GP can prescribe drugs to reduce the pain or prevent headaches occurring so often. If your treatment is not helping, go back to your GP as there may be another treatment which will work better for you.

Other therapies, such as acupuncture, or a combined programme of relaxation and exercise, may also help to reduce the frequency of your headaches.

Are there any problems with taking medicines for headache?

Taking medication too frequently can cause headaches known as medication overuse headache. Medicines for immediate pain relief should not generally be taken on more than 10 days per month. You should consult your GP if you are worried that your medication is causing more headaches or any side effects.

Women who are pregnant are advised to discuss headache medication with their pharmacist or GP.

15.2 SOURCES OF FURTHER INFORMATION

The British Association for the Study of Headache

www.bash.org.uk/

BASH is the United Kingdom national society member of the International Headache Society and the European Headache Federation. It is open to all healthcare professionals with an interest in headache.

The British Pain Society

Third Floor, Churchill House
35 Red Lion Square
London, WC1R 4SG
Tel: 020 7269 7840 • Fax: 020 7831 0859

Email: info@britishpainsociety.org

The British Pain Society has published a number of booklets aimed specifically for patients. Each publication is available to download free of charge, in PDF format.

The Migraine Action Association

27 East Street
Leicester, LE1 6NB
Tel: 0116 275 8317 • Fax: 0116 254 2023
Email: info@migraine.org.uk • Website: www.migraine.org.uk/

The Migraine Action Association provides information for healthcare professionals and patients on the causes, diagnosis and treatment of migraine.

Migraine in Primary Care Advisers

www.mipca.org.uk/

MIPCA is a UK society dedicated to the management of headache in primary care, and has strong links with the Migraine Action Association (the UK patient support group), academic societies and governmental groups. It runs three special interest groups, on research, education and how to set up a headache clinic.

The Migraine Trust

55-56 Russell Square
London, WC1B 4HP
Tel: 020 7436 1336 • Helpline: 020 7462 6601, Monday to Friday 10am - 5pm
Fax: 020 7436 2880
Email: info@migrainetrust.org • www.migrainetrust.org/

The Migraine Trust is a medical research and patient support charity for the condition. It supports sufferers and their families by funding and promoting research, providing information and raising awareness of migraine as a significant public health problem.

Organisation for the Understanding of Cluster Headache

OUCH (UK), Pyramid House
956 High Road
London, N12 9RX
Helpline: 01646 651 979
www.ouchuk.org

Provides support, information and advice on coping with cluster headaches. Can assist with supply of and contacts for appropriate equipment for oxygen treatment.

Pain Association Scotland

Cramond House

Cramond Glebe Road

Edinburgh, EH4 6NS

Tel (Enquiries only): 0800 783 6059 • Tel (Office): 0131 312 7955 • Fax: 0131 312 6007

www.chronicpaininfo.org

Runs local support groups for people with chronic pain.

Pain Concern

PO Box 13256

Haddington, EH41 4YD

Tel: 01620 822572 • Fax: 01620 829138

Email: info@painconcern.org.uk • www.painconcern.org.uk

Provides information and support for pain sufferers and their carers, factsheets and leaflets to help manage pain and a helpline.

16 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

16.1 RESOURCE IMPLICATIONS

The guideline development group did not identify any significant resource implications associated with implementing the recommendations.

16.2 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

16.2.1 PRIMARY CARE

GPs should review all patients who are prescribed 12 or more triptans a month to consider the diagnosis of medication overuse headache. Reducing triptan use may help to reduce headache frequency.

Audit how often patient information leaflets are given to patients. Patient understanding of headache improves management of the headache.

16.2.2 SECONDARY CARE

Review all patients with admission for thunderclap headache and audit how many have had an LP if the CT scan is negative.

The number of patients in the health board area with cluster headache that are known to the specialist headache services.

16.3 ADVICE TO NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM

The SMC has approved certain formulations of sumatriptan.

Frovatriptan has been accepted for the treatment of patients during the headache phase of migraine attacks with or without aura.

Topiramate is accepted for restricted use within NHSScotland for the prophylaxis of migraine headache in adults.

Further information is available from the SMC website, www.scottishmedicines.org.uk/

There are no MTAs relevant to this guideline.

17 The evidence base

17.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using search strategies devised by a SIGN information specialist. Databases searched include Medline, Embase, CINAHL, PsycINFO, and the Cochrane Library. For most searches, the year range covered was 2001-2007. Internet searches were carried out on various websites including the US National Guideline Clearinghouse, NLH Guidelines Finder, and Guidelines International Network (G-I-N). The Medline version of the database search strategies for each key question can be found on the SIGN website in the section covering supplementary guideline material (www.sign.ac.uk/guidelines/published/support/). The main searches were supplemented by material identified by individual members of the guideline development group.

17.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline. The following areas for further research have been identified:

- Comparison of acute versus gradual withdrawal of overused medications in medication overuse headache. Which is the best strategy for use in primary care?
- Does education on headache diagnosis and management change GPs' pattern of referral to secondary care neurological and headache services? What is appropriate headache education?
- Does open access to CT brain scanning change GPs' pattern of referral to secondary care neurological and headache services?
- Does the use of headache diaries by GPs in routine clinical practice improve diagnostic accuracy of headache type?

17.3 REVIEW AND UPDATING

This guideline was issued in 2008 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk

18 Development of the guideline

18.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. The views and interests of NHS Quality Improvement Scotland as the funding body have not influenced any aspect of guideline development, including the final recommendations. Further details about SIGN and the guideline development methodology are contained in "SIGN 50: A Guideline Developer's Handbook", available at www.sign.ac.uk

18.2 THE GUIDELINE DEVELOPMENT GROUP

Dr David P B Watson (Chair)	<i>General Practitioner, Hamilton Medical Group, Aberdeen</i>
Dr Anne Coker (Secretary)	<i>General Practitioner, Dundee</i>
Ms Arlene Coulson	<i>Principal Clinical Pharmacist, Ninewells Hospital, Dundee</i>
Dr Roger Cull	<i>Honorary Consultant Neurologist, Western General Hospital, Edinburgh</i>
Dr Callum Duncan	<i>Consultant Neurologist, Aberdeen Royal Infirmary</i>
Ms Helen Duncan	<i>Lay representative, Haddington</i>
Dr Murray Fleming	<i>General Practitioner, Clydebank Health Centre</i>
Ms Penelope Fraser	<i>Lead Clinician/Consultant Clinical Psychologist, Ninewells Hospital, Dundee</i>
Mrs Suzie Harrold	<i>Senior Physiotherapist, Glasgow Royal Infirmary</i>
Ms Michele Hilton Boon	<i>Information Officer, SIGN</i>
Dr Gillian Smith	<i>Oral Medicine Consultant, Glasgow Dental Hospital</i>
Ms Ailsa Stein	<i>Programme Manager, SIGN</i>
Dr Lorna Thompson	<i>Programme Manager, SIGN</i>
Dr Alok Tyagi	<i>Consultant Neurologist, Southern General Hospital, Glasgow</i>
Ms Heather Wallace	<i>Chairman, Pain Concern, Haddington</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

18.3 CONSULTATION AND PEER REVIEW

18.3.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 5 September 2007 and was attended by 123 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

18.3.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

Dr Anish Bahra	<i>Consultant Neurologist, National Hospital for Neurology and Neurosurgery, London</i>
Mr Richard Bowen	<i>Patient representative, Lanarkshire</i>
Dr Rodney Burnham	<i>Registrar, Royal College of Physicians, London</i>
Dr Richard Coleman	<i>Consultant Neurologist, Aberdeen Royal Infirmary</i>
Dr Richard J Davenport	<i>Consultant Neurologist, Western General Hospital, Edinburgh</i>
Dr Paul Davies	<i>Consultant Neurologist, Northampton General Hospital</i>
Mrs Ruth M Edwards	<i>Lecturer in Pharmacy Practice, The Robert Gordon University, Aberdeen</i>
Dr John Gibson	<i>Consultant in Oral Medicine, Dundee Dental Hospital and School</i>
Mr David Gill	<i>Head of Pharmacy, Angus Community Health Partnership</i>
Professor Donald M Hadley	<i>Consultant Neuroradiologist and Professor in Radiology, Southern General Hospital, Glasgow</i>
Dr Chris Isles	<i>Consultant Physician, Dumfries and Galloway Royal Infirmary</i>
Dr Avinash Kanodia	<i>Consultant Radiologist, Perth Royal Infirmary</i>
Dr E Anne MacGregor	<i>Honorary Research Director, The City of London Migraine Clinic</i>
Dr Alan Merry	<i>General Practitioner, Ardrossan</i>
Ms Lesley Murray	<i>Senior Clinical Pharmacist, Southern General Hospital, Glasgow</i>
Dr Christian Neumann	<i>Consultant Neurologist, Falkirk and District Royal Infirmary</i>
Dr John Olson	<i>Consultant in Medical Ophthalmology, Aberdeen Royal Infirmary</i>
Mr David Paul	<i>Patient representative, Bearsden</i>
Dr Richard C Peatfield	<i>Consultant Neurologist, Charing Cross Hospital, London</i>
Dr Philip Rutledge	<i>Consultant in Medicines Management, Lothian NHS Board</i>
Dr Rani Sinnak	<i>Consultant Clinical (Neuro and Health) Psychologist, Ayrshire Central Hospital</i>
Ms Cathy Stillman-Lowe	<i>Independent Oral Health Promotion Adviser, Reading</i>
Dr Tom Whitmarsh	<i>Consultant Physician, Glasgow Homeopathic Hospital</i>
Professor Joanna M Zakrzewska	<i>Consultant in Oral Medicine, Eastman Dental Hospital, London</i>

18.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Dr Keith Brown	<i>Chair of SIGN; Co-Editor</i>
Dr John Gillies	<i>Royal College of General Practitioners</i>
Ms Fiona McMillan	<i>Royal Pharmaceutical Society of Great Britain</i>
Dr Safia Qureshi	<i>SIGN Programme Director; Co-Editor</i>
Dr Graeme Simpson	<i>Royal College of Physicians of Edinburgh</i>

Abbreviations

CAT	Computerised adaptive testing
CH	Cluster headache
CI	Confidence interval
CNS	Central nervous system
COCP	Combined oral contraceptive pill
CPH	Chronic paroxysmal hemicrania
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computerised tomography
CTTH	Chronic tension-type headache
DSM-IV	Diagnostic and Statistical Manual, 4 th edition
ESR	Erythrocyte sedimentation rate
ETTH	Episodic tension-type headache
GCA	Giant cell arteritis
GP	General practitioner
HIT	Headache impact test
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
LP	Lumbar puncture
MIDAS	Migraine Disability Assessment Questionnaire
MOH	Medication overuse headache
MRI	Magnetic resonance imaging
MTA	Multiple technology appraisal
NDPH	New daily-persistent headache
NHS QIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
NSAIDS	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PH	Paroxysmal hemicrania
PPV	Positive predictive value
RCT	Randomised controlled trial
RR	Relative risk
SAH	Subarachnoid haemorrhage

SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMT	Spinal manipulation therapy
SSRI	Selective serotonin reuptake inhibitor
SUNA	Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms
SUNCT	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
TA	Temporal arteritis
TAC	Trigeminal autonomic cephalalgia
TENS	Transcutaneous electrical nerve stimulation
TMD	Temporomandibular disorder
TTH	Tension-type headache
UK	United Kingdom
WHO	World Health Organisation

Annex 1

Key questions used to develop the guideline

DIAGNOSIS AND INVESTIGATION	
Key question	See guideline section
1. In patients > 18 yrs presenting with primary or secondary headache what are the critical signs and symptoms that help determine headache diagnosis and which patients should be referred?	3, 9.1
2. In patients with migraine or chronic headache, what tools are most effective in assessing headache severity, frequency and social and economic impact? Include: MIDAS (migraine disability and assessment score) HIT (headache impact test) SF36	4
3. In patients presenting with headache what is the evidence that the following investigations are effective in confirming diagnosis? a) CT scan b) MRI c) X-ray of the cervical spine d) full blood count e) ESR/CRP/plasma viscosity f) lumbar puncture	5
MANAGEMENT	
4. In patients with the following types of headache: Migraine with or without aura Tension headache Cluster headache and its variants (trigeminal autonomic cephalalgia, paroxysmal hemicrania, hemicrania continua) Jolts and jabs (primary stabbing headache) Medication overuse Cervicogenic – secondary headache Low pressure headache Oromandibular Benign intracranial hypertension / idiopathic intracranial hypertension what lifestyle factors have been shown to be effective in reducing frequency and severity of acute and chronic headache? a) diet b) exercise c) sleep d) stress management e) trigger avoidance	11

<p>5. In patients with the following types of headache:</p> <ul style="list-style-type: none"> Migraine with or without aura Tension headache Cluster headache and its variants (trigeminal autonomic cephalalgia, paroxysmal hemicrania, hemicrania continua) Jolts and jabs (primary stabbing headache) Medication overuse Cervicogenic – secondary headache Low pressure headache Oromandibular Benign intracranial hypertension/idiopathic intracranial hypertension <p>which pharmacological therapies for acute attack are the most effective for immediate pain freedom or pain freedom at 24 hours?</p> <ul style="list-style-type: none"> a) aspirin b) paracetamol c) NSAIDs d) COX-2 inhibitors e) anti-emetics f) corticosteroids g) triptans h) oxygen i) intranasal lidocaine j) indomethacin k) ergotamine l) opiates m) caffeine <p>Outcomes: Scale used is 0 1 2 3 where 0 = no headache 1 = mild headache 2 = moderate headache 3 = severe headache</p> <p>pain free is score down to 0 pain relief is 2 or 3 headache to 1</p> <p>[consider comorbidities]</p>	<p>6.1, 7.1, 8.1, 8.3, 9.2</p>
---	--------------------------------

<p>6. In patients with the following types of headache: Migraine with or without aura Tension headache Cluster headache and its variants (trigeminal autonomic cephalalgia, paroxysmal hemicrania, hemicrania continua Jolts and jabs (primary stabbing headache) Medication overuse Cervicogenic – secondary headache Low pressure headache Oromandibular Benign intracranial hypertension/idiopathic intracranial hypertension</p> <p>which prophylactic pharmacological therapies are most effective in reducing frequency and severity of headaches?</p> <ol style="list-style-type: none"> beta blockers antiepileptics serotonin antagonists (pizotifen, methysergide, cyproheptadine) antidepressants ACE inhibitors angiotensin-II receptor antagonists low-dose aspirin lithium verapamil and other calcium channel blockers indomethacin and other NSAIDs corticosteroids ergotamine <p>Outcomes: Scale used is 0 1 2 3 where 0 = no headache 1 = mild headache 2 = moderate headache 3 = severe headache</p> <p>pain free is score down to 0 pain relief is 2 or 3 headache to 1</p> <p>[consider comorbidities]</p>	<p>6.2, 7.2, 8.2, 9.2</p>
<p>7. In patients with chronic headache are psychological therapies effective in reducing frequency and severity of headaches? Consider:</p> <ol style="list-style-type: none"> cognitive behavioural therapy (CBT) biofeedback and relaxation stress management hypnotherapy 	<p>12</p>

<p>8. In patients with chronic headache are physical therapies effective in reducing frequency and severity of headaches? Consider:</p> <ul style="list-style-type: none"> a) cervical manual therapy (manipulation or mobilisation) b) osteopathy c) chiropracty d) physiotherapy e) massage f) transcutaneous electrical nerve stimulation (TENS) g) postural or exercise advice h) acupuncture i) occlusal splint therapy/oral rehabilitation 	13
<p>9. In patients with chronic headache are complementary therapies effective in reducing frequency and severity of headaches? Consider:</p> <ul style="list-style-type: none"> a) homeopathy b) reflexology c) minerals, vitamins and herbs d) magnesium e) riboflavin f) butterbur g) feverfew h) coenzyme Q 	14
<p>10. In patients with medication overuse headache what management strategies are effective?</p>	9
<p>HORMONAL HEADACHE AND HEADACHE IN PREGNANCY</p>	
<p>11. In women experiencing predominantly menstrual migraine what drugs are safe and effective in reducing the frequency and severity of headaches?</p> <ul style="list-style-type: none"> a) combined oral contraceptives b) progesterone c) oestrogen supplementation d) long-acting implantable contraceptives e) triptans f) mefenamic acid and other NSAIDs 	10.3
<p>12. In women who are menopausal and experiencing migraine is hormone replacement therapy (HRT) safe and effective in reducing the frequency and severity of headaches?</p>	10.4

<p>13. In pregnant women with headache what is the safety of the following treatments:</p> <ul style="list-style-type: none"> a) aspirin b) paracetamol c) NSAIDs d) COX-2 inhibitors e) anti-emetics f) corticosteroids g) triptans h) oxygen i) intranasal lidocaine j) indomethacin k) ergotamine l) opiates m) caffeine n) beta blockers o) antiepileptics p) serotonin antagonists (pizotifen, methysergide, cyproheptadine) q) tricyclic antidepressants r) SSRIS s) ace inhibitors t) angiotensin-II receptor antagonists u) low-dose aspirin v) lithium w) verapamil and other calcium channel blockers 	<p>10.1</p>
--	-------------

Annex 2

Selected Diagnostic Criteria from International Headache Society Classification (ICHD-II)^{*16,27}

1 Migraine

1.1 Migraine without aura

Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

- A. At least 5 attacks, 1 fulfilling criteria B–D
- B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
 - 1. unilateral location
 - 2. pulsating quality
 - 3. moderate or severe pain intensity
 - 4. aggravation by or causing avoidance of routine physical activity (eg walking or climbing stairs)
- D. During headache at least one of the following:
 - 1. nausea and/or vomiting
 - 2. photophobia and phonophobia
- E. Not attributed to another disorder

1.2 Migraine with aura

Description: Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criterion B
- B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1–1.2.6
- C. Not attributed to another disorder

*Cited from International Headache Society. The International classification of headache disorders, 2nd edition. Cephalgia 2004;24 (Supp 1): 8-160.

1.2.1 *Typical aura with migraine headache*

Diagnostic criteria:

- A. At least 2 attacks fulfilling criteria B–D
- B. Aura consisting of at least one of the following, but no motor weakness:
 - 1. fully reversible visual symptoms including positive features (eg flickering lights, spots or lines) and/or negative features (ie loss of vision)
 - 2. fully reversible sensory symptoms including positive features (ie pins and needles) and/or negative features (ie numbness)
 - 3. fully reversible dysphasic speech disturbance
- C. At least two of the following:
 - 1. homonymous visual symptoms¹ and/or unilateral sensory symptoms
 - 2. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 - 3. each symptom lasts ≥ 5 and < 60 minutes
- D. Headache fulfilling criteria B–D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder

1.5.1 *Chronic migraine*

- A. Headache (tension-type and/or migraine) on ≥ 15 days per month for at least 3 months*
- B. Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 Migraine without aura
- C. On ≥ 8 days per month for at least 3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura
 - 1. Has at least two of a–d
 - (a) unilateral location
 - (b) pulsating quality
 - (c) moderate or severe pain intensity
 - (d) aggravation by or causing avoidance of routine physical activity (eg walking or climbing stairs)
 - and at least one of a or b
 - (a) nausea and/or vomiting
 - (b) photophobia and phonophobia
 - 2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above
- D. No medication overuse and not attributed to another causative disorder

2 Tension-type headache

2.1 Infrequent episodic tension-type headache

Description: Infrequent episodes of headache lasting minutes to days. The pain is typically bilateral, pressing or tightening in quality and of mild to moderate intensity, and it does not worsen with routine physical activity. There is no nausea but photophobia or phonophobia may be present.

Diagnostic criteria:

- A. At least 10 episodes occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B–D
 - B. Headache lasting from 30 minutes to 7 days
 - C. Headache has at least two of the following characteristics:
 1. bilateral location
 2. pressing/tightening (non-pulsating) quality
 3. mild or moderate intensity
 4. not aggravated by routine physical activity such as walking or climbing stairs
 - D. Both of the following:
 1. no nausea or vomiting (anorexia may occur)
 2. no more than one of photophobia or phonophobia
 - E. Not attributed to another disorder
- ± Increased pericranial tenderness on manual palpation

2.2 Frequent episodic tension-type headache

Diagnostic criteria:

As for 2.1 Infrequent episodic tension-type headache except:

- A. At least 10 episodes occurring on ≥ 1 but <15 days per month for at least 3 months (≥ 12 and <180 days per year) and fulfilling criteria B–D (2.1)

2.3 Chronic tension-type headache

Diagnostic criteria:

As for 2.1 Infrequent episodic tension-type headache except:

- A. Headache occurring on ≥ 15 days per month on average for >3 months (≥ 180 days per year) and fulfilling criteria B–D (2.1)

3 Cluster headache and other trigeminal autonomic cephalalgias

3.1 Cluster headache

Description: Attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15–180 minutes and occurring from once every other day to 8 times a day. The attacks are associated with one or more of the following, all of which are ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, eyelid oedema. Most patients are restless or agitated during an attack.

Diagnostic criteria:

- A. At least 5 attacks fulfilling criteria B–D
- B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes if untreated
- C. Headache is accompanied by at least one of the following:
 1. ipsilateral conjunctival injection and/or lacrimation
 2. ipsilateral nasal congestion and/or rhinorrhoea
 3. ipsilateral eyelid oedema
 4. ipsilateral forehead and facial sweating
 5. ipsilateral miosis and/or ptosis
 6. a sense of restlessness or agitation
- D. Attacks have a frequency from one every other day to 8 per day
- E. Not attributed to another disorder

3.1.1 Episodic cluster headache

At least two cluster periods lasting 7–365 days and separated by pain-free remission periods of ≥ 1 month

3.1.2 Chronic cluster headache

Attacks recur over > 1 year without remission periods or with remission periods lasting < 1 month

3.2 Paroxysmal hemicrania

Description: Attacks with similar characteristics of pain and associated symptoms and signs to those of cluster headache, but they are shorter-lasting, more frequent, occur more commonly in females and respond absolutely to indometacin.

Diagnostic criteria:

- A. At least 20 attacks fulfilling criteria B–D
- B. Attacks of severe unilateral orbital, supraorbital or temporal pain lasting 2–30 minutes
- C. Headache is accompanied by at least one of the following:
 1. ipsilateral conjunctival injection and/or lacrimation
 2. ipsilateral nasal congestion and/or rhinorrhoea
 3. ipsilateral eyelid oedema
 4. ipsilateral forehead and facial sweating
 5. ipsilateral miosis and/or ptosis

- D. Attacks have a frequency above 5 per day for more than half of the time, although periods with lower frequency may occur
- E. Attacks are prevented completely by therapeutic doses of indometacin
- F. Not attributed to another disorder

3.2.1 Episodic paroxysmal hemicrania

At least two attack periods lasting 7–365 days and separated by pain-free remission periods of ≥ 1 month

3.2.2 *Chronic paroxysmal hemicrania (CPH)*

Attacks recur over > 1 year without remission periods or with remission periods lasting < 1 month

3.3 Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT)

Description: This syndrome is characterised by short-lasting attacks of unilateral pain that are much briefer than those seen in any other TAC and very often accompanied by prominent lacrimation and redness of the ipsilateral eye.

Diagnostic criteria:

- A. At least 20 attacks fulfilling criteria B–D
- B. Attacks of unilateral orbital, supraorbital or temporal stabbing or pulsating pain lasting 5–240 seconds
- C. Pain is accompanied by ipsilateral conjunctival injection and lacrimation
- D. Attacks occur with a frequency from 3 to 200 per day
- E. Not attributed to another disorder

Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms (SUNA)

Description: This syndrome is characterised by short-lasting attacks of unilateral pain that are much briefer than those seen in any other TAC and very often accompanied by prominent cranial autonomic features.

Diagnostic criteria:

- A. At least 20 attacks fulfilling criteria B–D
- B. Attacks of unilateral orbital, supraorbital or temporal stabbing or pulsating pain lasting from 2 seconds to 10 minutes
- C. Pain is accompanied by one of:
 1. conjunctival injection and/or lacrimation
 2. nasal congestion and/or rhinorrhoea
 3. eyelid oedema
- D. Attacks occur with a frequency of > 1 per day for more than half the time
- E. No refractory period follows attacks triggered from trigger areas
- F. Not attributed to another disorder

4 Other primary headaches

4.1 Primary stabbing headache

Description: Transient and localised stabs of pain in the head that occur spontaneously in the absence of organic disease of underlying structures or of the cranial nerves.

Diagnostic criteria:

- A. Head pain occurring as a single stab or a series of stabs and fulfilling criteria B–D
- B. Exclusively or predominantly felt in the distribution of the first division of the trigeminal nerve (orbit, temple and parietal area)
- C. Stabs last for up to a few seconds and recur with irregular frequency ranging from one to many per day
- D. No accompanying symptoms
- E. Not attributed to another disorder

4.2 Primary cough headache

Description: Headache precipitated by coughing or straining in the absence of any intracranial disorder.

Diagnostic criteria:

- A. Headache fulfilling B and C
- B. Sudden onset, lasting from one second to 30 minutes
- C. Brought on by and occurring only in association with coughing, straining and/or valsalva manoeuvre
- D. Not attributable to another disorder

4.3 Primary exertional headache

Description: Headache precipitated by any form of exercise.

Diagnostic criteria:

- A. Pulsating headache fulfilling criteria B and C
- B. Lasting from five minutes to 48 hours
- C. Brought on by and occurring only during or after physical exertion
- D. Not attributed to another disorder

4.4 Primary headache associated with sexual activity

Description: Headache precipitated by sexual activity, usually starting as a dull bilateral ache as sexual excitement increases and suddenly becoming intense at orgasm, in the absence of any intracranial disorder.

4.4.1 Preorgasmic headache

Diagnostic criteria:

- A. Dull ache in the head and neck associated with awareness of neck and/or jaw muscle contraction and fulfilling criterion B
- B. Occurs during sexual activity and increases with sexual excitement
- C. Not attributed to another disorder

4.4.2 Orgasmic headache

Diagnostic criteria:

- A. Sudden severe headache fulfilling criterion B
- B. Occurs at orgasm
- C. Not attributed to another disorder

4.5 Hypnic headache

Description: Attacks of dull headache that always awaken the patient from asleep.

Diagnostic criteria:

- A. Dull headache fulfilling criteria B–D
- B. Develops only during sleep, and awakens patient
- C. At least two of the following characteristics:
 - 1. occurs > 15 times per month
 - 2. lasts \geq 15 minutes after waking
 - 3. first occurs after age of 50 years
- D. No autonomic symptoms and no more than one of nausea, photophobia or phonophobia
- E. Not attributed to another disorder

4.6 Primary thunderclap headache

Description: High-intensity headache of abrupt onset mimicking that of ruptured cerebral aneurysm.

Diagnostic criteria:

- A. Severe head pain fulfilling criteria B and C
- B. Both of the following characteristics:
 - 1. sudden onset, reaching maximum intensity in < 1 minute
 - 2. lasting from 1 hour to 10 days
- C. Does not recur regularly over subsequent weeks or months
- D. Not attributed to another disorder

4.7 Hemicrania continua

Description: Persistent strictly unilateral headache responsive to indometacin.

Diagnostic criteria:

- A. Headache for > 3 months fulfilling criteria B–D
- B. All of the following characteristics:
 - 1. unilateral pain without side-shift
 - 2. daily and continuous, without pain-free periods
 - 3. moderate intensity, but with exacerbations of severe pain

- C. At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain:
 1. conjunctival injection and/or lacrimation
 2. nasal congestion and/or rhinorrhoea
 3. ptosis and/or miosis
- D. Complete response to therapeutic doses of indometacin
- E. Not attributed to another disorder

4.8 New daily-persistent headache (NDPH)

Description: Headache that is daily and unremitting from very soon after onset (within 3 days at most). The pain is typically bilateral, pressing or tightening in quality and of mild to moderate intensity. There may be photophobia, phonophobia or mild nausea.

Diagnostic criteria:

- A. Headache for > 3 months fulfilling criteria B–D
- B. Headache is daily and unremitting from onset or from < 3 days from onset
- C. At least two of the following pain characteristics:
 1. bilateral location
 2. pressing/tightening (non-pulsating) quality
 3. mild or moderate intensity
 4. not aggravated by routine physical activity such as walking or climbing stairs
- D. Both of the following:
 1. no more than one of photophobia, phonophobia or mild nausea
 2. neither moderate or severe nausea nor vomiting
- E. Not attributed to another disorder

Secondary Headaches

8.2 Medication overuse headache

Diagnostic criteria:

- A. Headache present on ≥ 15 days/month
- B. Regular overuse for > 3 months of one or more acute/symptomatic treatment drugs as defined under sub forms of 8.2.
 1. Ergotamine, triptans, opioids, or combination analgesic medications on ≥ 10 days/month on a regular basis for > 3 months
 2. Simple analgesics or any combination of ergotamine, triptans, analgesics opioids on ≥ 15 days/month on a regular basis for > 3 months without overuse of any single class alone
- C. Headache has developed or markedly worsened during medication overuse

11.2.1 Cervicogenic Headache

Diagnostic Criteria:

- A. Pain referred from a source in the neck and perceived in one or more regions of the head and/or face, fulfilling criteria C & D
- B. Clinical, laboratory &/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache
- C. Evidence that the pain can be attributed to the neck disorder or lesion based on at least one of the following
 - 1. Demonstration of clinical signs that implicate a source of pain in the neck
 - 2. Abolition of headache following diagnostic blockade of a cervical structure or its nerve supply using placebo or other adequate control
- D. Pain resolves in 3 months after successful treatment of the causative disorder or lesion.

11.7 Headache or facial pain attributed to temporomandibular joint (TMJ) disorder

Diagnostic Criteria:

- A. Recurrent pain in one or more regions of the head and/or face fulfilling criteria C and D
- B. X-ray, MRI and/or bone scintigraphy demonstrate TMJ disorder
- C. Evidence that pain can be attributed to the TMJ disorder, based on at least one of the following:
 - 1. pain is precipitated by jaw movements and/or chewing of hard or tough food
 - 2. reduced range of or irregular jaw opening
 - 3. noise from one or both TMJs during jaw movements
 - 4. tenderness of the joint capsule(s) of one or both TMJs
- D. Headache resolves within 3 months, and does not recur, after successful treatment of the TMJ disorder

Annex 3

Differentiation between trigeminal autonomic cephalalgias

The following differentiate trigeminal autonomic cephalalgias from each other:^{32, 33, 274}

- Gender: CH is more common in men (M:F 3.5-7:1); PH is more common in women (M:F 1:2.13-2.36); SUNCT is more common in men (M:F 2:1)
- Duration: CH 15min-3hr; PH 2-45min; SUNCT 2-250s
- Frequency: CH 1 every other day – 8/day; PH 1-40/day; SUNCT 1/day – 30/hour
- Restlessness during an attack: 100% in cluster headache, 50% in paroxysmal hemicrania, 50% in SUNCT
- Episodic form predominates in CH, Chronic form predominates in PH
- Response to indometacin is absolute in paroxysmal hemicrania, but indometacin is ineffective in CH or SUNCT
- Alcohol frequently triggers CH, occasionally triggers PH and does not trigger SUNCT.

3
4

Differentiation from trigeminal neuralgia

The following differentiate trigeminal autonomic cephalalgias from trigeminal neuralgia:^{23,32,33}

- Trigeminal neuralgia may coexist with cluster headache and paroxysmal hemicrania (cluster-tic, and paroxysmal hemicrania-tic syndromes)
- Location: Orbital, supra-orbital, temporal in TACs; in trigeminal neuralgia the pain occurs in the maxillary and mandibular divisions of the trigeminal nerve in 90%, when present in the ophthalmic division it has usually been in the other two divisions for many years
- Duration: In trigeminal neuralgia pain duration is brief (few seconds) easily distinguishing it from CH and PH
- Autonomic symptoms are not prominent in trigeminal neuralgia and when present the disorder has usually been established for many years, distinguishing it from SUNCT where autonomic features are very prominent.

3
4

Annex 4

Headache history¹¹

1. How many different headache types does the patient experience?

Separate histories are necessary for each. It is reasonable to concentrate on the most bothersome to the patient but others should always attract some enquiry in case they are clinically important.

2. Time questions

- a) Why consulting now?
- b) How recent in onset?
- c) How frequent, and what temporal pattern (especially distinguishing between episodic and daily or unremitting)?
- d) How long lasting?

3. Character questions

- a) Intensity of pain
- b) Nature and quality of pain
- c) Site and spread of pain
- d) Associated symptoms

4. Cause questions

- a) Predisposing and/or trigger factors
- b) Aggravating and/or relieving factors
- c) Family history of similar headache

5. Response questions

- a) What does the patient do during the headache?
- b) How much is activity (function) limited or prevented?
- c) What medication has been and is used, and in what manner?

6. State of health between attacks

- a) Completely well, or residual or persisting symptoms?
- b) Concerns, anxieties, fears about recurrent attacks, and/or their cause

Annex 5

Weekly Headache Diary

WEEK 1	Please score the pain of your headache out of 10 and indicate if you have any other symptoms as listed.						
	Sun	Mon	Tue	Wed	Thur	Fri	Sat
Headache (0 = none 10 = worse)							
Feeling sick (Yes/No)							
Vomiting (Yes/No)							
Other symptoms (Yes/No)							
Duration of attack (hours)							
Had to lie down (Yes/No)							
Time away from normal activities (hours)							
Number of tablets of medicine taken:							
Prescribed							
Over the counter							
Menstruation (Yes/No)							

Annex 6

Drug licensing status

All the drugs recommended in this guideline are licensed for the indication in the recommendation with the following exceptions:

Section	Drug
6.1.2	Sumatriptan/naproxen sodium fixed combination is not licensed for the treatment of acute migraine.
6.2.1	Atenolol is not licensed for the prophylaxis of patients with migraine.
6.2.2	Gabapentin and sodium valproate are not licensed for the treatment of migraine.
6.2.3	Amitriptyline and venlafaxine are not licensed for the prophylaxis of migraine.
7.2.3	Tricyclic antidepressants are not licensed for the prophylaxis of tension-type headache.
8.1.3	Lidocaine is not licensed for the treatment of headache.
8.2.1	Verapamil is not licensed for the prophylaxis of cluster headache.

References

- Boardman HF, Thomas E, Croft PR, Millson DS. Epidemiology of headache in an English district. *Cephalalgia* 2003;23(2):129-37.
- Latinovic R, Gulliford M, Ridsdale L. Headache and migraine in primary care: consultation, prescription, and referral rates in a large population. *J Neurol Neurosurg Psychiatry* 2006;77(3):385-7.
- Larner AJ. Guidelines for primary headache disorders in primary care: an "intervention" study. *Headache Care* 2006;3(1):1-2.
- Patterson VH, Esmonde TF. Comparison of the handling of neurological outpatient referrals by general physicians and a neurologist. *J Neurol Neurosurg Psychiatry* 1993;56(7):830.
- Martin V, Elkind A. Diagnosis and classification of primary headache disorders. In: *Standards of care for headache diagnosis and treatment*. Chicago (IL): National Headache Foundation; 2004. p.4-18.
- Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia* 2003;23(7):519-27.
- World Health Organisation. *The world health report 2001 - mental health: new understanding, new hope*. Geneva: World Health Organisation; 2001.
- Anon. *Migraine: costs and consequences*. Bandolier 1999;6(9):5-6.
- BMJ Clinical Evidence. *Headache (chronic tension-type)*. [cited 16 Oct 2008]. Available from url: <http://clinicalevidence.bmj.com/ceweb/conditions/nud/1205/1205.jsp>
- Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007;27(3):193-210.
- British Association for the Study of Headache. *Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache*, 3rd edition. Hull; 2007.
- US Headache Consortium, Frishberg BM, Rosenberg JH, Matchar DB, McCrory DC, Pietrzak MP, et al. Evidence based guidelines in the primary care setting: neuroimaging in patients with non-acute headache. [cited 16 Oct 2008]. Available from url: <http://www.aan.com/professionals/practice/pdfs/gl0088.pdf>
- Dowson AJ, Lipscombe S, Sender J, Rees T, Watson D, MIPCA Migraine Guidelines Development Group, et al. New guidelines for the management of migraine in primary care. *Curr Med Res Opin* 2002;18(7):414-39.
- Edmeads J, Láinez JM, Brandes JL, Schoenen J, Freitag F. Potential of the Migraine Disability Assessment (MIDAS) Questionnaire as a public health initiative and in clinical practice. *Neurology* 2001;56(6 Suppl 1):S29-34.
- MacGregor EA, Brandes J, Eikermann A. Migraine prevalence and treatment patterns: the global Migraine and Zolmitriptan Evaluation survey. *Headache* 2003;43(1):19-26.
- International Headache Society. *The international classification of headache disorders*, 2nd edition. *Cephalalgia* 2004;24(Suppl 1):8-160.
- Diamond ML. The role of concomitant headache types and non-headache co-morbidities in the underdiagnosis of migraine. *Neurology* 2002;58(9 Suppl 6):S3-9.
- Lipton RB, Stewart WF, Celentano DD, Reed ML. Undiagnosed migraine headaches. A comparison of symptom-based and reported physician diagnosis. *Arch Intern Med* 1992;152(6):1273-8.
- Lipton RB, Cady RK, Stewart WF, Wilks K, Hall C. Diagnostic lessons from the spectrum study. *Neurology* 2002;58(9 Suppl 6):S27-31.
- Tepper SJ, Dahlof CG, Dowson A, Newman L, Mansbach H, Jones M, et al. Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. *Headache* 2004;44(9):856-64.
- Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al. Incidental findings on brain MRI in the general population. *N Engl J Med* 2007;357(18):1821-8.
- Weber F, Knopf H. Incidental findings in magnetic resonance imaging of the brains of healthy young men. *J Neurol Sci* 2006;240(1-2):81-4.
- Smetana GW. The diagnostic value of historical features in primary headache syndromes: a comprehensive review. *Arch Intern Med* 2000;160(18):2729-37.
- Dodick DW. Diagnosing headache: clinical clues and clinical rules. *Adv Stud Med* 2003;3(2):87-92.
- Fisher CM. Late-life migraine accompaniments—further experience. *Stroke* 1986;17(5):1033-42.
- Lipton RB, Goadsby PJ, Sawyer JPC, Blakeborough P, Stewart WF. Migraine: diagnosis and assessment of disability. *Rev Contemp Pharmacother* 2000;11(2):63-73.
- Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 2006;26(6):742-6.
- Lipton RB, Dodick D, Sadovsky R, Kolodner K, Endicott J, Hettiarachchi J, et al. A self-administered screener for migraine in primary care: the ID Migraine-super(TM) Validation Study. *Neurology* 2003;61(3):375-82.
- Maizels M, Burchette R. Rapid and sensitive paradigm for screening patients with headache in primary care settings. *Headache* 2003;43(5):441-50.
- Mulleners WM, Aurora SK, Chronicle EP, Stewart R, Gopal S, Koehler PJ. Self-reported photophobic symptoms in migraineurs and controls are reliable and predict diagnostic category accurately. *Headache* 2001;41(1):31-9.
- Russell MB, Fenger K, Olesen J. The family history of migraine. Direct versus indirect information. *Cephalalgia* 1996;16(3):156-60.
- Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003;63(16):1637-77.
- Cohen AS, Matharu MS, Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA) - a prospective clinical study of SUNCT and SUNA. *Brain* 2006;129(10):2746-60.
- Goadsby PJ, Boes C. New daily persistent headache. *J Neurol Neurosurg Psychiatry* 2002;72(Suppl II):ii6-ii9.
- Landtblom AM, Fridriksson S, Boivie J, Hillman J, Johansson G, Johansson I. Sudden onset headache: a prospective study of features, incidence and causes. *Cephalalgia* 2002;22(5):354-60.
- Locker TE, Thompson C, Rylance J, Mason SM. The utility of clinical features in patients presenting with nontraumatic headache: an investigation of adult patients attending an emergency department. *Headache* 2006;46(6):954-61.
- Maggioni F, Dainese F, Mainardi F, Lisotto C, Zanchin G. Intermittent angle-closure glaucoma in the presence of a white eye, posing as retinal migraine. *Cephalalgia* 2005;25(8):622-6.
- American College for Emergency Physicians (ACEP). Critical issues in the evaluation and management of patients presenting to the emergency department with acute headache. *Ann Emerg Med* 2002;39:108-22.
- Aygun D, Bildik F. Clinical warning criteria in evaluation by computed tomography the secondary neurological headaches in adults. *Eur J Neurol* 2003;10:437-42.
- Shibata T, Kubo M, Kuwayama N, Hirashima Y, Endo S. Warning headache of subarachnoid hemorrhage and infarction due to vertebralbasilar artery dissection. *Clin J Pain* 2006;22(2):193-6.
- Linn FH, Rinkel GJ, Algra A, van Gijn J. Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. *J Neurol Neurosurg Psychiatry* 1998;65(5):791-3.
- Agostoni E. Headache in cerebral venous thrombosis. *Neurol Sci* 2004;25(3 Suppl Oct):S206-10.
- Joseph R, Cook GE, Steiner TJ, Clifford Rose F. Intracranial space-occupying lesions in patients attending a migraine clinic. *Practitioner* 1985;229(1403):477-81.
- Schievink WJ. Misdiagnosis of spontaneous intracranial hypotension. *Arch Neurol* 2003;60(12):1713-8.
- Skau M, Brennum J, Gjerris F, Jensen R. What is new about idiopathic intracranial hypertension? An updated review of mechanism and treatment. *Cephalalgia* 2006;26(4):384-99.
- Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. *J Neurol Neurosurg Psychiatry* 2005;76(8):1084-7.
- Iurlaro S, Beghi E, Masetto N, Guccione A, Autunno M, Colombo B, et al. Does headache represent a clinical marker in early diagnosis of cerebral venous thrombosis? A prospective multicentric study. *Neurol Sci* 2004;25(Suppl 3):S298-9.
- Smetana GW, Shmerling RH. Does this patient have temporal arteritis? *JAMA* 2002;287(1):92-101.
- van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *New Engl J Med* 2004;351(18):1849-59.
- Al-Shahi R, White PM, Davenport RJ, Lindsay KW. Subarachnoid haemorrhage. *BMJ* 2006;333(7561):235-40.

51. Zito G, Jull G, Story I. Clinical tests of musculoskeletal dysfunction in the diagnosis of cervicogenic headache. *Man Ther* 2006;11(2):118-29.
52. Sjaastad O, Fredriksen TA, Pfaffenrath V. Cervicogenic headache: diagnostic criteria. The Cervicogenic Headache International Study Group. *Headache* 1998;38(6):442-5.
53. Grant R. Overview: brain tumour diagnosis and management/Royal College of Physicians guidelines. *J Neurol Neurosurg Psychiatry* 2004;75(Suppl 2):ii18-23.
54. Hamilton W, Kernick D. Clinical features of primary brain tumours: a case-control study using electronic primary care records. *Br J Gen Pract* 2007;57(542):695-9.
55. Coleman AL. Glaucoma. *Lancet* 1999;354(9192):1803-10.
56. Holmes WF, MacGregor EA, Sawyer JP, Lipton RB. Information about migraine disability influences physicians' perceptions of illness severity and treatment needs. *Headache* 2001;41(4):343-50.
57. Coeytaux RR, Kaufman JS, Chao R, Mann JD, Devellis RF. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. *J Clin Epidemiol* 2006;59(4):374-80.
58. Kosinski M, Bayliss MS, Bjorner JB, Ware JE, Jr., Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res* 2003;12(8):963-74.
59. Bayliss MS, Dewey JE, Dunlap I, Batenhorst AS, Cady R, Diamond ML, et al. A study of the feasibility of Internet administration of a computerized health survey: the headache impact test (HIT). *Qual Life Res* 2003;12(8):953-61.
60. De Diego EV, Lanteri-Minet M. Recognition and management of migraine in primary care: influence of functional impact measured by the headache impact test (HIT). *Cephalalgia* 2005;25(3):184-90.
61. Kilminster SG, Dowson A, Bundy M. The Headache Impact Test 1 and the Short Pain Inventory: outcome measures compared. *Int J Pharmaceutical Med* 2003;17(1):23-32.
62. Bjorner JB, Kosinski M, Ware JE, Jr. Calibration of an item pool for assessing the burden of headaches: an application of item response theory to the headache impact test (HIT). *Qual Life Res* 2003;12(8):913-33.
63. Ware JE, Jr., Kosinski M, Bjorner JB, Bayliss MS, Batenhorst A, Dahlof CG, et al. Applications of computerized adaptive testing (CAT) to the assessment of headache impact. *Qual Life Res* 2003;12(8):935-52.
64. Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: the Migraine Disability Assessment (MIDAS) questionnaire. *Headache* 2001;41(9):854-61.
65. Dowson AJ. Assessing the impact of migraine. *Curr Med Res Opin* 2001;17(4):298-309.
66. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia* 1999;19(2):107-14.
67. Stewart WF, Lipton RB, Whyte J, Dowson A, Kolodner K, Liberman JN, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology* 1999;53(5):988-94.
68. Stewart WF, Lipton R. Need for care and perceptions of MIDAS among headache sufferers study. *CNS Drugs* 2002;16(Suppl 1):5-11.
69. Bigal ME, Rapoport AM, Lipton RB, Tepper SJ, Sheftell FD. Assessment of migraine disability using the migraine disability assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine. *Headache* 2003;43(4):336-42.
70. Stewart WF, Lipton RB, Kolodner K. Migraine disability assessment (MIDAS) score: relation to headache frequency, pain intensity, and headache symptoms. *Headache* 2003;43(3):258-65.
71. US Headache Consortium. Evidence-based guidelines in the primary care setting: neuroimaging in patients with nonacute headache. [cited 16 Oct 2008]. Available from url: <http://www.americanheadachesociety.org/professionalresources/USHeadacheConsortiumGuidelines.asp>
72. Sempere AP, Porta-Etessam J, Medrano V, Garcia-Morales I, Concepcion L, Ramos A, et al. Neuroimaging in the evaluation of patients with non-acute headache. *Cephalalgia* 2005;25(1):30-5.
73. Wang HZ, Simonson TM, Greco WR, Yuh WTC. Brain MR imaging in the evaluation of chronic headache in patients without other neurologic symptoms. *Acad Radiol* 2001;8(5):405-8.
74. Tsushima Y, Endo K. MR imaging in the evaluation of chronic or recurrent headache. *Radiology* 2005;235(2):575-9.
75. 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.
76. Evers S, Afra J, Frese A, Goadsby, PJ, Linde M, May, A and Sandor, PS. EFNS guideline on the drug treatment of migraine – report of an EFNS task force. *Eur J Neurol* 2006;13(6):560-72.
77. Cutrer MF, Boes CJ. Cough, exertional, and sex headaches. *Neurol Clin N Am* 2004;22:133-49.
78. Favier I, van Vliet JA, Roon KI. Trigeminal autonomic cephalgias due to structural lesions: a review of 31 cases. *Arch Neurol* 2007;64(1):25-31.
79. Pascual J, Iglesias F, Oterino A, Vázquez-Barquero A, Berciano J. Cough, exertional, and sexual headaches: an analysis of 72 benign and symptomatic cases. *Neurology* 1996;46(6):1520-24.
80. Yousry I, Forderreuther S, Moriggl B, Holtmannspotter M, Naidich TP, Straube A, et al. Cervical MR imaging in postural headache: MR signs and pathophysiological implications. *ANJR Am J Neuroradiol* 2001;22(7):1239-50.
81. Moayeri NN, Henson JW, Schaefer PW, Zervas NT. Spinal dural enhancement on magnetic resonance imaging associated with spontaneous intracranial hypotension. Report of three cases and review of the literature. *J Neurosurg* 1998;88(5):912-8.
82. Pannullo SC, Reich JB, Krol G, Deck MD, Posner JB. MRI changes in intracranial hypotension. *Neurology* 1993;43(5):919-26.
83. Rabin BM, Roychowdhury S, Meyer JR, Cohen BA, LaPat KD, Russell EJ. Spontaneous intracranial hypotension: spinal MR findings. *ANJR Am J Neuroradiol* 1998;19(6):1034-9.
84. Detsky ME, McDonald DR, Baerlocher MO, Tomlinson GA, McCrory DC, Booth CM. Does this patient with headache have a migraine or need neuroimaging? *JAMA* 2006;296(10):1274-83.
85. O'Neill J, McLaggan S, Gibson R. Acute headache and subarachnoid haemorrhage: a retrospective review of CT and lumbar puncture findings. *Scott Med J* 2005;50(4):151-3.
86. Webb S, Bone I, Lindsay K. The investigation of acute severe headache suggestive of probable subarachnoid haemorrhage: a hospital-based study. *Br J Neurosurg* 2003;17(6):580-4.
87. Davenport R. Sudden headache in the emergency department. *Pract Neurol* 2005;5:132-43.
88. Hayreh SS, Podhajsky PA, Raman R, Zimmerman B. Giant cell arteritis: validity and reliability of various diagnostic criteria. *Am J Ophthalmol* 1997;123(3):285-96.
89. Ferrari MD. Current perspectives on effective migraine treatments: are small clinical differences important for patients? *Drugs Today* 2003;39:37-41.
90. British National Formulary. 56th ed. London: BMJ Publishing; 2008.
91. Diener HC, Bussone G, de Liano H, Eikermann A, Englert R, Floeter T, et al. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalalgia* 2004;24(11):947-54.
92. Lipton RB, Goldstein J, Baggish JS, Yataco AR, Sorrentino JV, Quiring JN. Aspirin is efficacious for the treatment of acute migraine. *Headache* 2005;45(4):283-92.
93. MacGregor EA, Dowson A, Davies PT. Mouth-dispersible aspirin in the treatment of migraine: a placebo-controlled study. *Headache* 2002;42(4):249-55.
94. Goldstein J, Silberstein SD, Saper JR, Elkind AH, Smith TR, Gallagher RM, et al. Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the early treatment of migraine: results from the ASSET trial. *Headache* 2005;45(8):973-82.
95. Codispoti JR, Prior MJ, Fu M, Harte CM, Nelson EB. Efficacy of nonprescription doses of ibuprofen for treating migraine headache. A randomized controlled trial. *Headache* 2001;41(7):665-79.
96. Dib M, Massiou H, Weber M, Henry P, Garcia-Acosta S, Bousser MG, et al. Efficacy of oral ketoprofen in acute migraine: a double-blind randomized clinical trial. *Neurology* 2002;58(11):1660-5.
97. Electronic medicines compendium. [cited 16 Oct 2008]. Available from url: <http://www.emc.medicines.org.uk/>
98. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med* 2000;160(22):3486-92.
99. Belsey J. The clinical and financial impact of oral triptans in the management of migraine in the UK: a systematic review. *J Med Economics* 2000;3:35-47.
100. Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ, et al. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison. *Eur Neurol* 2002;47(2):99-107.

101. Edmeads J. Defining response in migraine: which endpoints are important? *Eur Neurol* 2005;1:22-8.
102. Loder E. Fixed drug combinations for the acute treatment of migraine: place in therapy. *CNS Drugs* 2005;19(9):769-84.
103. Mannix LK. Effect of triptans on the quality of life of patients with migraine. *Headache Q* 2002;13(3):11-21.
104. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT_{1B/1D} agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 2002;22(8):633-58.
105. Pascual J, Mateos V, Roig C, Sanchez-Del-Rio M, Jimenez D. Marketed oral triptans in the acute treatment of migraine: a systematic review on efficacy and tolerability. *Headache* 2007;47(8):1152-68.
106. Poolsup N, Leelasangaluk V, Jittangtrong J, Rithlamlert C, Ratanapantamane N, Khanthong M. Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther* 2005;30(6):521-32.
107. Diener HC. Efficacy of almotriptan 12.5 mg in achieving migraine-related composite endpoints: a double-blind, randomized, placebo-controlled study in patients with previous poor response to sumatriptan 50 mg. *Curr Med Res Opin* 2005;21(10):1603-10.
108. Brandes JL, Kudrow D, Stark SR, O'Carroll CP, Adelman JU, O'Donnell FJ, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007;297(13):1443-54.
109. Chabriot H, Dancho J, Hugues FC, Joire JE. Combined aspirin and metoclopramide in the acute treatment of migraine attacks: a review. *Headache Q* 1997;8(2):118-21.
110. Dowson A, Ball K, Haworth D. Comparison of a fixed combination of domperidone and paracetamol (Domperamol) with sumatriptan 50 mg in moderate to severe migraine: a randomised UK primary care study. *Curr Med Res Opin* 2000;16(3):190-7.
111. Colman I, Brown MD, Innes GD, Grafstein E, Roberts TE, Rowe BH. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ* 2004;329(7479):1369-72.
112. Honkaniemi J, Liimatainen S, Rainesalo S, Sulavuori S. Haloperidol in the acute treatment of migraine: a randomized, double-blind, placebo-controlled study. *Headache* 2006;46(5):781-7.
113. Katsarava Z, Schneeweiss S, Kurth T, Kroener U, Fritsche G, Eikermann A, et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. *Neurology* 2004;62(5):788-90.
114. Diener HC, Agosti R, Allais G, Bergmans P, Bussone G, Davies B, et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2007;6(12):1054-62.
115. US Headache Consortium, Ramadan NM, Silberstein SD, Freitag F, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. [cited 16 Oct 2008]. Available from url: <http://www.aan.com/professionals/practice/pdfs/gl0090.pdf>
116. Linde K, Rosnagel K. Propranolol for migraine prophylaxis (Cochrane Review). In: *The Cochrane Library*, Issue 1. London: Wiley; 2006.
117. Chronicle E, Mulleners W. Anticonvulsant drugs for migraine prophylaxis (Cochrane Review). In: *The Cochrane Library*, Issue 3. London: Wiley; 2004.
118. Mei D, Ferraro D, Zelano G, Capuano A, Vollono C, Gabriele C, et al. Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. *Clin Neuropharmacol* 2006;29(5):269-75.
119. Edwards KR, Potter DL, Wu SC, Kamin M, Hulihan J. Topiramate in the preventive treatment of episodic migraine: a combined analysis from pilot, double-blind, placebo-controlled trials. *CNS spectrums* 2003;8(6):428-32.
120. Nadin C. Topiramate: the evidence for its therapeutic value in the prevention of migraine. *Core Evidence* 2005;1(2):103-24.
121. Silberstein SD, Loder E, Forde G, Papadopoulos G, Fairclough D, Greenberg S. The impact of migraine on daily activities: effect of topiramate compared with placebo. *Curr Med Res Opin* 2006;22(6):1021-9.
122. Diener HC, Tfelt-Hansen P, Dahlof C, Lainez MJ, Sandrini G, Wang SJ, et al. Topiramate in migraine prophylaxis—results from a placebo-controlled trial with propranolol as an active control. *J Neurol* 2004;251(8):943-50.
123. Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007;47(2):170-80.
124. Limmroth V, Biondi D, Pfeil J, Schwalen S. Topiramate in patients with episodic migraine: reducing the risk for chronic forms of headache. *Headache* 2007;47(1):13-21.
125. Diamond M, Dahl AC, Papadopoulos G, Neto W, Wu SC. Topiramate improves health-related quality of life when used to prevent migraine. *Headache Care* 2005;45(8):1023-30.
126. Bartolini M, Silvestrini M, Taffi R, Lanciotti C, Luconi R, Capecci M, et al. Efficacy of topiramate and valproate in chronic migraine. *Clin Neuropharmacol* 2005;28(6):277-9.
127. Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V. Comparison of the effect of topiramate and sodium valproate in migraine prevention: a randomized blinded crossover study. *Headache* 2006;46(4):642-48.
128. Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, et al. Efficacy of gabapentin in migraine prophylaxis. *Headache* 2001;41(2):119-28.
129. Tomkins GE, Jackson JL, O'Malley PG, Balden E, Santoro JE. Treatment of chronic headache with antidepressants: a meta-analysis. *Am J Med* 2001;111(1):54-63.
130. Moja PL, Cusi C, Sterzi RR, Canepari C. Selective serotonin reuptake inhibitors (SSRIs) for preventing migraine and tension-type headaches (Cochrane Review). In: *The Cochrane Library*, Issue 3. London: Wiley; 2005.
131. Ozyalcin SN, Talu GK, Kiziltan E, Yucel B, Ertaş M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005;45(2):144-52.
132. Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungen B. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. *Clin Neurol Neurosurg* 2004;107(1):44-8.
133. Cleland PG, Barnes D, Elrington GM, Loizou LA, Rawes GD. Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. *Eur Neurol* 1997;38(1):31-8.
134. Diener HC, Matias-Guiu J, Hartung E, Pfaffenrath V, Ludin HP, Nappi G, et al. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. *Cephalalgia* 2002;22(3):209-21.
135. Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C, et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. *Cephalalgia* 2007;27(6):492-503.
136. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003;289(1):65-9.
137. Bensenor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE. Low-dose aspirin for migraine prophylaxis in women. *Cephalalgia* 2001;21(3):175-83.
138. Brandes JL, Visser WH, Farmer MV, Schuhl AL, Malbecq W, Vrijens F, et al. Montelukast for migraine prophylaxis: a randomized, double-blind, placebo-controlled study. *Headache Care* 2004;44(6):581-6.
139. Vahedi K, Taupin P, Djombly R, El-Amrani M, Lutz G, Filipetti V, et al. Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial. *J Neurol* 2002;249(2):206-11.
140. Eftedal OS, Lydersen S, Helde G, White L, Brubakk AO, Stovner LJ. A randomized, double blind study of the prophylactic effect of hyperbaric oxygen therapy on migraine. *Cephalalgia* 2004;24(8):639-44.
141. Goldstein DJ, Offen WW, Klein EG, Phebus LA, Hipskind P, Johnson KW, et al. Lanepitant, an NK-1 antagonist, in migraine prevention. *Cephalalgia* 2001;21(2):102-6.
142. Lee ST, Park JH, Kim M. Efficacy of the 5-HT_{1A} agonist, buspirone hydrochloride, in migraineurs with anxiety: a randomized, prospective, parallel group, double-blind, placebo-controlled study. *Headache* 2005;45(8):1004-11.
143. Steiner TJ, Lange R, Voelker M. Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. *Cephalalgia* 2003;23(1):59-66.
144. Law M, Morris JK, Jordan R, Wald N. Headaches and the treatment of blood pressure: results from a meta-analysis of 94 randomized placebo-controlled trials with 24,000 participants. *Circulation* 2005;112(15):2301-6.
145. Etmann M, Levine MA, Tomlinson G, Rochon PA. Efficacy of angiotensin II receptor antagonists in preventing headache: a systematic overview and meta-analysis. *Am J Med* 2002;112(8):642-6.
146. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001;322(7277):19-22.

147. Spira PJ, Beran RG, Australian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. *Neurology* 2003;61(12):1753-9.
148. Bendtsen L, Jensen R. Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache. *Neurology* 2004;62(10):1706-11.
149. Singh NN, Misra S. Sertraline in chronic tension-type headache. *J Assoc Physicians India* 2002;50:873-8.
150. Zisis NP, Harmoussi S, Vlaikidis N, Mitsikostas D, Thomaidis T, Georgiadis G, et al. A randomized, double-blind, placebo-controlled study of venlafaxine XR in out-patients with tension-type headache. *Cephalalgia* 2007;27(4):15-24.
151. Silberstein SD, Gobel H, Jensen R, Elkind AH, DeGryse R, Walcott JM, et al. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. *Cephalalgia* 2006;26(7):790-800.
152. Sycha T, Kranz G, Auff E, Schnider P. Botulinum toxin in the treatment of rare head and neck pain syndromes: a systematic review of the literature. *J Neurol* 2004;251(Suppl 1):19-30.
153. Saper JR, Lake IA, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002;42(6):470-82.
154. Ekblom K. Treatment of cluster headache: clinical trials, design and results. *Cephalalgia* 1995;15(Suppl):33-6.
155. Ekblom K, Krabbe A, Miciceli G, Prusinski A, Cole JA, Pilgrim AJ, et al. Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). Sumatriptan Cluster Headache Long-term Study Group. *Cephalalgia* 1995;15(3):230-6.
156. Ekblom K, Monstad I, Prusinski A, Cole JA, Pilgrim AJ, Noronha D. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. The Sumatriptan Cluster Headache Study Group. *Acta Neurol Scand* 1993;88(1):63-9.
157. Ekblom K, Waldenlind E, Levi R, Andersson B, Boivie J, Dizdar N, et al. Treatment of acute cluster headache with sumatriptan. *New Engl J Med* 1991;325(5):322-6.
158. Gobel H, Lindner V, Heinze A, Ribbat M, Deuschl G. Acute therapy for cluster headache with sumatriptan: findings of a one-year long-term study. *Neurology* 1998;51(3):908-11.
159. van Vliet JA, Bahra A, Martin V, Ramadan N, Aurora SK, Mathew NT, et al. Intranasal sumatriptan in cluster headache: randomized placebo-controlled double-blind study. *Neurology* 2003;60(4):630-3.
160. Rapoport AM, Mathew NT, Silberstein SD, Dodick D, Tepper SJ, Sheftell FD, et al. Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology* 2007;69(9):821-6.
161. Bahra A, Gawel MJ, Hardebo JE, Millson D, Breen SA, Goadsby PJ. Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000;54(9):1832-9.
162. Fogan L. Treatment of cluster headache. A double-blind comparison of oxygen v air inhalation. *Arch Neurol* 1985;42(4):362-3.
163. Kudrow L. Response of cluster headache attacks to oxygen inhalation. *Headache* 1981;21(1):1-4.
164. Nilsson Remahl AI, Ansjon R, Lind F, Waldenlind E. Hyperbaric oxygen treatment of active cluster headache: a double-blind placebo-controlled cross-over study. *Cephalalgia* 2002;22(9):730-9.
165. Di Sabato F, Rocco M, Martelletti P, Giacobozzo M. Hyperbaric oxygen in chronic cluster headache: influence on serotonergic pathways. *Undersea Hyperb Med* 1997;24(2):117-22.
166. Costa A, Pucci E, Antonaci F, Sances G, Granella F, Broich G, et al. The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache. *Cephalalgia* 2000;20(2):85-91.
167. Leone M, D'Amico D, Frediani F, Moschiano F, Grazi L, Attanasio A, et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000;54(6):1382-5.
168. May A, Leone M, Afra J, Linde M, Sandor PS, Evers S, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol* 2006;13(10):1066-77.
169. Steiner TJ, Hering R, Couturier EG, Davies PT, Whitmarsh TE. Double-blind placebo-controlled trial of lithium in episodic cluster headache. *Cephalalgia* 1997;17(6):673-5.
170. Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia* 1996;16(7):494-96.
171. El Amrani M, Massiou H, Bousser MG. A negative trial of sodium valproate in cluster headache: methodological issues. *Cephalalgia* 2002;22(3):205-8.
172. Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. *Pain* 2005;118(1-2):92-6.
173. Silberstein SD, Olesen J, Bousser MG, Diener HC, Dodick D, First M, et al. The International Classification of Headache Disorders, 2nd Edition (ICHD-II)--revision of criteria for 8.2 Medication-overuse headache. *Cephalalgia* 2005;25(6):460-5.
174. Bahra A, Walsh M, Menon S, Goadsby PJ. Does chronic daily headache arise de novo in association with regular use of analgesics? *Headache* 2003;43(3):179-90.
175. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology* 2002;59(7):1011-4.
176. Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ. Medication-overuse headache in patients with cluster headache. *Neurology* 2006;67(1):109-13.
177. Paemeleire K, Crevits L, Goadsby PJ, Kaube H. Practical management of medication-overuse headache. *Acta Neurol Belg* 2006;106(2):43-51.
178. Zwart JA, Dyb G, Hagen K, Svebak S, Holmen J. Analgesic use: a predictor of chronic pain and medication overuse headache: the Head-HUNT Study. *Neurology* 2003;61(2):160-4.
179. Williams D, Cahill T, Dowson A, Fearon H, Lipscombe S, O'Sullivan E, et al. Usage of triptans among migraine patients: an audit in nine GP practices. *Curr Med Res Opin* 2002;18(1):1-9.
180. Atasoy HT, Atasoy N, Unal AE, Emre U, Sumer M. Psychiatric comorbidity in medication overuse headache patients with pre-existing headache type of episodic tension-type headache. *Eur J Pain* 2005;9(3):285-91.
181. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001;57(9):1694-8.
182. Krymchantowski AV, Moreira PF. Out-patient detoxification in chronic migraine: comparison of strategies. *Cephalalgia* 2003;23(10):982-93.
183. Rossi P, Di Lorenzo C, Faroni J, Cesarino F, Nappi G. Advice alone vs. structured detoxification programmes for medication overuse headache: a prospective, randomized, open-label trial in transformed migraine patients with low medical needs. *Cephalalgia* 2006;26(9):1097-105.
184. Zed PJ, Loewen PS, Robinson G. Medication-induced headache: overview and systematic review of therapeutic approaches. *Ann Pharmacother* 1999;33:61-72.
185. Zeeberg P, Olesen J, Jensen R. Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. *Cephalalgia* 2006;26(10):1192-8.
186. Zeeberg P, Olesen J, Jensen R. Probable medication-overuse headache: the effect of a 2-month drug-free period. *Neurology* 2006;66(12):1894-8.
187. Katsarava Z, Limmroth V, Finke M, Diener HC, Fritsche G. Rates and predictors for relapse in medication overuse headache: a 1-year prospective study. *Neurology* 2003;60(10):1682-3.
188. Andrasik F, Grazi L, Usai S, D'Amico D, Kass S, Bussone G. Disability in chronic migraine with medication overuse: treatment effects at 3 years. *Headache* 2007;47(9):1277-81.
189. Boe MG, Mygland A, Salvesen R. Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. *Neurology* 2007;69(1):26-31.
190. Pageler L, Katsarava Z, Diener HC, Limmroth V. Prednisone vs. placebo in withdrawal therapy following medication overuse headache. *Cephalalgia* 2008;28(2):152-6.
191. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007;27(7):814-23.
192. Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L. Topiramate in the treatment of chronic migraine. *Cephalalgia* 2003;23(8):820-4.
193. Descombes S, Brefel-Courbon C, Thalamos C, Albucher JF, Rascol O, Montastruc JL, et al. Amitriptyline treatment in chronic drug-induced headache: a double-blind comparative pilot study. *Headache* 2001;41(2):178-82.
194. Briggs G, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2005.
195. Lee A, Inch S, Finnigan D, editors. *Therapeutics in pregnancy and lactation*. Abingdon: Radcliffe Medical Press; 2000.
196. Rubin P, editor. *Prescribing in pregnancy*. 3rd ed. London: BMJ Publishing; 2000.

197. Schaefer D, editor. *Drugs during pregnancy and lactation*. 1st ed. Amsterdam: Elsevier Science B.V.; 2001.
198. Fox AW, Chambers CD, Anderson PO, Diamond ML, Spierings ELH. Evidence-based assessment of pregnancy outcome after sumatriptan exposure. *Headache* 2002;42(1):8-15.
199. Hilaire ML, Cross LB, Eichner SF. Treatment of migraine headaches with sumatriptan in pregnancy. *Ann Pharmacother* 2004;38:1726-30.
200. Loder E. Safety of sumatriptan in pregnancy: a review of the data so far. *CNS Drugs* 2003;17(1):1-7.
201. Buse DC, Loder EW, Golub JR. Use of oral contraceptives in women with migraine. *Headache Care* 2005;2(3):183-94.
202. MacGregor EA. Migraine and use of combined hormonal contraceptives: a clinical review. *J Fam Plann Reprod Health Care* 2007;33(3):159-69.
203. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *BMJ* 1999;318(7175):13-8.
204. Etmnan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ* 2005;330(7482):63-5.
205. Mendizabal JE, Herbert DE. Risk of ischemic stroke in migraineurs: a meta-analysis. *Headache & Pain: Diagnostic Challenges, Current Therapy* 2004;15(4):197-200.
206. Curtis KM, Mohllajee AP, Peterson HB. Use of combined oral contraceptives among women with migraine and nonmigrainous headaches: a systematic review. *Contraception* 2006;73(2):189-94.
207. Faculty of Family Planning and Reproductive Health Care. UK medical eligibility criteria for contraceptive use 2005/2006. [cited 17 Oct 2008]. Available from url: http://www.ffprhc.org.uk/admin/uploads/298_UKMEC_200506.pdf
208. Brandes JL. The influence of estrogen on migraine: a systematic review. *JAMA* 2006;295(15):1824-30.
209. Burke BE, Olson RD, Cusack BJ. Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine. *Biomed Pharmacother* 2002;56(6):283-8.
210. Ferrante F, Fusco E, Calabresi P, Cupini LM. Phyto-oestrogens in the prophylaxis of menstrual migraine. *Clin Neuropharmacol* 2004;27(3):137-40.
211. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. *Neurology* 2006;67(12):2159-63.
212. Martin V, Wernke S, Mandell K, Zoma W, Bean J, Pinney S, et al. Medical oophorectomy with and without estrogen add-back therapy in the prevention of migraine headache. *Headache* 2003;43(4):309-21.
213. MacGregor EA. Menstrual migraine: a clinical review. *J Fam Plann Reprod Health Care* 2007;33(1):36-47.
214. Silberstein SD, Armellino JJ, Hoffman HD, Battikha JP, Hamelsky SW, Stewart WF, et al. Treatment of menstruation-associated migraine with the nonprescription combination of acetaminophen, aspirin, and caffeine: results from three randomized, placebo-controlled studies. *Clin Ther* 1999;21(3):475-91.
215. Al-Waili NS. Treatment of menstrual migraine with prostaglandin synthesis inhibitor mefenamic acid: double-blind study with placebo. *Eur J Med Res* 2000;5(4):176-82.
216. Loder E, Silberstein SD, Abu-Shakra S, Mueller L, Smith T. Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: a randomized, prospective, parallel-group, double-blind, placebo-controlled study. *Headache* 2004;44(2):120-30.
217. Massiou H, Jamin C, Hinzelin G, Bidaut-Mazel C, The French Naramig Collaborative Study Group. Efficacy of oral naratriptan in the treatment of menstrually related migraine. *Eur J Neurol* 2005;12(10):774-81.
218. Nett R, Landy S, Shackelford S, Richardson MS, Ames M, Lener M. Pain-free efficacy after treatment with sumatriptan in the mild pain phase of menstrually associated migraine. *Obstet Gynecol* 2003;102(4):835-42.
219. Silberstein SD, Massiou H, McCarroll KA, Lines CR. Further evaluation of rizatriptan in menstrual migraine: retrospective analysis of long-term data. *Headache* 2002;42(9):917-23.
220. Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headaches: evidence-based review. *Neurology* 2008;70(17):1555-63.
221. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 2004;63(2):261-9.
222. Newman L, Mannix LK, Landy S, Silberstein S, Lipton RB, Putnam DG, et al. Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. *Headache* 2001;41(3):248-56.
223. Ashkenazi A, Silberstein SD. Hormone-related headache: pathophysiology and treatment. *CNS Drugs* 2006;20(2):125-41.
224. MacGregor EA, Barnes D. Migraine in a specialist menopause clinic. *Climacteric* 1999;2(3):218-23.
225. Misakian AL, Langer RD, Bensenor IM, Cook NR, Manson JE, Buring JE, et al. Postmenopausal hormone therapy and migraine headache. *J Womens Health (Larchmt)* 2003;12(10):1027-36.
226. Wang SJ, Fuh JL, Lu SR, Juang KD, Wang PH. Migraine prevalence during menopausal transition. *Headache* 2003;43(5):470-8.
227. Neri I, Granella F, Nappi R, Manzoni GC, Facchinetti F, Genazzani AR. Characteristics of headache at menopause: a clinico-epidemiologic study. *Maturitas* 1993;17(1):31-7.
228. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288(3):321-33.
229. Kittner SJ, Bousser MG. Post-menopausal hormone replacement therapy and stroke risk. *Cephalalgia* 2000;20:208-13.
230. Tzourio C, Iglesias S, Hubert JB, Visy JM, Alperovitch A, Tehindrazanarivelo A, et al. Migraine and risk of ischaemic stroke: a case-control study. *BMJ* 1993;307(6899):289-92.
231. MacGregor EA. Migraine and the menopause. *J Br Menopause Soc* 2006;12:104-8.
232. Silberstein SD. Headache and female hormones: what you need to know. *Curr Opin Neurol* 2001;14(3):323-33.
233. Nappi RE, Cagnacci A, Granella F, Piccinini F, Polatti F, Facchinetti F. Course of primary headaches during hormone replacement therapy. *Maturitas* 2001;38(2):157-63.
234. Crawford P, Simmons M. What dietary modifications are indicated for migraines? *J Fam Pract* 2006;55(1):62-6.
235. Wober C, Holzhammer J, Zeitlhofer J, Wessely P, Wober-Bingol C. Trigger factors of migraine and tension-type headache: experience and knowledge of the patients. *J Headache Pain* 2006;7(4):188-95.
236. Wober C, Brannath W, Schmidt K, Kapitan M, Rudel E, Wessely P, et al. Prospective analysis of factors related to migraine attacks: the PAMINA study. *Cephalalgia* 2007;27(4):304-14.
237. Pradalier A, Bakouche P, Baudesson G, Delage A, Cornaille-Lafage G, Launay JM, et al. Failure of omega-3 polyunsaturated fatty acids in prevention of migraine: a double-blind study versus placebo. *Cephalalgia* 2001;21(8):818-22.
238. Boardman HF, Thomas E, Millson DS, Croft PR. The natural history of headache: predictors of onset and recovery. *Cephalalgia* 2006;26(9):1080-8.
239. Jull G, Trott P, Potter H, Zito G, Niere K, Shirley D, et al. A randomized controlled trial of exercise and manipulative therapy for cervicogenic headache. *Spine* 2002;27(17):1835-43.
240. Stanton WR, Jull GA. Cervicogenic headache: locus of control and success of treatment. *Headache* 2003;43(9):956-61.
241. Lemstra M, Stewart B, Olszynski WP. Effectiveness of multidisciplinary intervention in the treatment of migraine: a randomized clinical trial. *Headache* 2002;42(9):845-54.
242. Nobre ME, Leal AJ, Filho PM. Investigation into sleep disturbance of patients suffering from cluster headache. *Cephalalgia* 2005;25(7):488-92.
243. Sand T, Hagen K, Schrader H. Sleep apnoea and chronic headache. *Cephalalgia* 2003;23(2):90-5.
244. Vos J, Passchier J. Reduced impact of migraine in everyday life: an observational study in the Dutch Society of Headache Patients. *Headache* 2003;43(6):645-50.
245. Holroyd KA, O'Donnell FJ, Stensland M, Lipchik GL, Cordingley GE, Carlson BW. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA* 2001;285(17):2208-15.
246. Symvoulakis EK, Clark LV, Dowson AJ, Jones R, Ridsdale L. Headache: a 'suitable case' for behavioural treatment in primary care? *Br J Gen Pract* 2007;57(536):231-7.
247. Andrasik F. What does the evidence show? Efficacy of behavioural treatments for recurrent headaches in adults. *Neurol Sci* 2007;28 Suppl 2:570-7.
248. US Headache Consortium. Evidence-based guidelines for migraine headache: behavioral and physical treatments. [cited 17 Oct 2008]. Available from url: <http://www.aan.com/professionals/practice/pdfs/g10089.pdf>

249. Bronfort G, Nilsson N, Haas M, Evans R, Goldsmith CH, Assendelft WJ, et al. Non-invasive physical treatments for chronic/recurrent headache (Cochrane Review). In: *The Cochrane Library*, Issue 3. London: Wiley; 2004.
250. Fernandez-de-Las-Penas C, Alonso-Blanco C, Cuadrado ML, Miangolarra JC, Barriga FJ, Pareja JA. Are manual therapies effective in reducing pain from tension-type headache?: a systematic review. *Clin J Pain* 2006;22(3):278-85.
251. Anderson RE, Seniscal C. A comparison of selected osteopathic treatment and relaxation for tension-type headaches. *Headache* 2006;46(8):1273-80.
252. van Ettehoven H, Lucas C. Efficacy of physiotherapy including a craniocervical training programme for tension-type headache; a randomized clinical trial. *Cephalalgia* 2006;26(8):983-91.
253. Allais G, De Lorenzo C, Quirico PE, Lupi G, Airola G, Mana O, et al. Non-pharmacological approaches to chronic headaches: transcutaneous electrical nerve stimulation, lasertherapy and acupuncture in transformed migraine treatment. *Neurol Sci* 2003;24 Suppl 2:S138-42.
254. Griggs C, Jensen J. Effectiveness of acupuncture for migraine: critical literature review. *J Adv Nurs* 2006;54(4):491-501.
255. Melchart D, Linde K, Berman B, White A, Vickers A, Allais G, et al. Acupuncture for idiopathic headache (Cochrane Review). In: *The Cochrane Library*, Issue 1. London: Wiley; 2001.
256. Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, et al. Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis. *Health Technol Assess* 2004;8(48):1-50.
257. Alecrim-Andrade J, Maciel-Junior JA, Cladellas XC, Correa-Filho HR, Machado HC. Acupuncture in migraine prophylaxis: a randomized sham-controlled trial. *Cephalalgia* 2006;26(5):520-9.
258. Diener HC, Kronfeld K, Boewing G, Lungenhausen M, Maier C, Molsberger A, et al. Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. *Lancet Neurol* 2006;5(4):310-6.
259. Karst M, Reinhard M, Thum P, Wiese B, Rollnik J, Fink M. Needle acupuncture in tension-type headache: a randomized, placebo-controlled study. *Cephalalgia* 2001;21(6):637-42.
260. Melchart D, Streng A, Hoppe A, Brinkhaus B, Witt C, Wagenpfeil S, et al. Acupuncture in patients with tension-type headache: randomised controlled trial. *BMJ* 2005;331(7513):376-82.
261. Al-Ani MZ, Davies SJ, Gray RJ, Sloan P, Glenny AM. Stabilisation splint therapy for temporomandibular pain dysfunction syndrome (Cochrane Review). In: *The Cochrane Library*, Issue 1. London: Wiley; 2004.
262. Koh H, Robinson PG. Occlusal adjustment for treating and preventing temporomandibular joint disorders (Cochrane Review). In: *The Cochrane Library*, Issue 1. London: Wiley; 2003.
263. Jokstad A, Mo A, Krogstad BS. Clinical comparison between two different splint designs for temporomandibular disorder therapy. *Acta Odontol Scand* 2005;63(4):218-26.
264. Ernst E. Homeopathic prophylaxis of headaches and migraine: a systematic review. *J Pain Symptom Manage* 1999;18:353-7.
265. Pittler MH, Ernst E. Feverfew for preventing migraine (Cochrane Review). In: *The Cochrane Library*, Issue 1. London: Wiley; 2004.
266. Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-von Zepelin HH. Efficacy and safety of 6.25 mg t.i.d. feverfew CO₂-extract (MIG-99) in migraine prevention—a randomized, double-blind, multicentre, placebo-controlled study. *Cephalalgia* 2005;25(11):1031-41.
267. Lipton RB, Göbel H, Einhüpl KM, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004;63(12):2240-4.
268. Sándor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. *Neurology* 2005;64(4):713-5.
269. Prousky J, Seely D. The treatment of migraines and tension-type headaches with intravenous and oral niacin (nicotinic acid): systematic review of the literature. *Nutrition J* 2005;4:3.
270. Cete Y, Dora B, Ertan C, Ozdemir C, Oktay C. A randomized prospective placebo-controlled study of intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the emergency department. *Cephalalgia* 2005;25(3):199-204.
271. Frank LR, Olson CM, Shuler KB, Gharib SF. Intravenous magnesium for acute benign headache in the emergency department: a randomized double-blind placebo-controlled trial. *Can J Emerg Med* 2004;6(5):327-32.
272. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology* 1998;50(2):466-70.
273. Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. *Headache* 2004;44(9):885-90.
274. Zidverc-Trajkovic J, Pavlovic AM, Mijajlovic M, Jovanovic Z, Sternic N, Kostic VS. Cluster headache and paroxysmal hemicrania: differential diagnosis. *Cephalalgia* 2005;25(4):244-8.

ISBN 978 1 905813 39 1

Scottish Intercollegiate Guidelines Network

Elliott House
8 -10 Hillside Crescent
Edinburgh EH7 5EA

www.sign.ac.uk

