Healthcare Improvement Scotland | SIGN Evidence-based clinical guidelines

See information at https://www.sign.ac.uk/our-guidelines/pharmacological-management-of-migraine/ for updated MHRA advice on introduction of new safety measures including a Pregnancy Prevention Programme

SIGN 155

Pharmacological management of migraine

A national clinical guideline

First published February 2018
Revised March 2023

NHS SCOTLAND

Key to evidence statements and 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

Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence; and the balance of benefits and harms of the options.

R For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that '**should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

R For '**conditional**' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for **most** patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-practice points

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

NICE has accredited the process used by Scottish Intercollegiate Guidelines Network to produce clinical guidelines. The accreditation term is valid until 31 March 2025 and is applicable to guidance produced using the processes described in SIGN 50: a guideline developer's handbook, 2019 edition (https://www.sign.ac.uk/assets/sign50_2019.pdf). More information on accreditation can be viewed at www.nice.org.uk/accreditation

Scottish Intercollegiate Guidelines Network

Pharmacological management of migraine

A national clinical guideline

First published February 2018
Revised March 2023

Scottish Intercollegiate Guidelines Network
Gyle Square, 1 South Gyle Crescent
Edinburgh EH12 9EB

www.sign.ac.uk

First published February 2018
Revised March 2023

ISBN 978 1 909103 62 7

Citation text

Scottish Intercollegiate Guidelines Network (SIGN).
Pharmacological management of migraine. Edinburgh: SIGN; 2023.
(SIGN publication no. 155). [March 2023]. Available from URL: http://www.sign.ac.uk

Contents

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 care and 30% of neurology outpatient consultations.[1-4] Headache disorders are classified as either primary or secondary.[5] 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. Medication-overuse headache (MOH) is increasingly recognised as a problem and affects around 1% of the population worldwide, but can vary significantly between countries (0.5% to 2.6%).[6,7] In patients with MOH, migraine is the most common underlying headache disorder (approximately 80%).

Migraine is the most common severe form of primary headache with a global prevalence of around one in seven people.[8] The Global Burden of Disease study ranks migraine as the seventh most common cause of disability worldwide, rising to the third most common cause in the under 50s.[9] It is estimated that migraine costs the UK around £3 billion a year in direct and indirect costs, taking into consideration the costs of healthcare, lost productivity and disability.[10]

Twice as many women as men are affected.[11] This is considered to be due to changes in hormone levels during the menstrual cycle, which can be more pronounced at puberty and perimenopause. Before puberty migraine frequency is the same in boys and girls.[11] Following the menopause migraine often improves.[11,12]

Migraine is often underdiagnosed, misdiagnosed (eg as sinusitis) and undertreated in both primary and secondary care.[13] In a multicentre primary care-based study more than 90% of patients presenting to primary care with headache had migraine.[14]

In recent years there have been advances in the diagnosis and treatment of migraine. There are new therapies on the horizon for both acute and preventative treatment of patients with migraine. Botulinum toxin A was approved for restricted use in Scotland by the Scottish Medicines Consortium (SMC) in February 2017 (*see section 8.4*). A number of devices are now available for the treatment of migraine that could potentially avoid the need for medication. There is, therefore, a need to update the evidence on existing treatments and evaluate the evidence for new treatments.

1.1.1 PATIENT PERSPECTIVE

Patients may have different perspectives on healthcare processes and outcomes from those of healthcare professionals. The involvement of patients in guideline development is therefore important to ensure that guidelines reflect their needs and concerns and address issues that matter to them.

Common concerns raised by patient groups and through research include:

- quality of life issues around coping with pain, sleep disturbance and restriction on daily activities, education, working and social life, and the impact it has on the family
- concerns around side effects of pharmacological therapies, medication overuse and feeling dependent on prophylactic therapies
- the need for clear information on the use of preventer medication.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the acute and prophylactic management of adults with migraine using pharmacological therapies or devices. The focus is on adults with acute migraine and preventative treatment in patients with episodic or chronic migraine and medication-overuse headache. Studies of children with migraine were not included, however the recommendations could be considered for treating adolescents with migraine.

The guideline excludes complementary, physical and psychological therapies, and specialist surgical interventions.

This guideline updates and replaces section 6 of SIGN 107: Diagnosis and management of headache in adults.

1.2.2 COMMON COMORBIDITIES AND HEALTH ISSUES TO CONSIDER WHEN PRESCRIBING

Common comorbidities and coexisting health issues which have been considered when reviewing the evidence for this guideline are:

- asthma
- chronic pain
- fibromyalgia
- depression
- hypertension, cardiovascular and cerebrovascular risk
- obesity
- obstructive sleep apnoea
- women's hormonal and fertility issues (use of contraception, menopause, preconception, pregnancy).

Migraine with aura increases the risk of stroke. Combined oral contraception (COC) also increases the risk of stroke. The prescribing of hormonal contraception for women with migraine should follow Faculty of Sexual and Reproductive Healthcare guidance.[15]

1.2.3 DEFINITIONS

The international classification of headache disorders (ICHD) was first published in 1988 and updated in 2003. An updated version (ICHD Beta 3) was published in 2013 as a document open for comment *(see Annex 2)*.[5]

Migraine is subdivided into migraine with and without aura. It is defined as episodic and chronic.

Episodic migraine

Episodic migraine occurs on less than 15 days per month and can be further subdivided into low frequency (1–9 days per month) and high frequency (10–14 days per month).[5]

Chronic migraine

Chronic migraine occurs on 15 or more days per month.[5] In the first two versions of ICHD patients had to have 15 or more migraines per month. This group of patients is very small and it was increasingly recognised that this definition did not represent the majority of patients with chronic headache evolving from episodic migraine. The majority of patients with chronic migraine have background headache with superimposed migraine attacks. A consensus statement was produced in 2007 with a new definition of chronic migraine and this has been used in all subsequent studies on chronic migraine.[16] Chronic migraine is now defined as headache on 15 or more days per month with superimposed migraine on eight or more days per month, for more than three months. This has been further refined in the ICHD beta 3 edition to allow migraine attacks to be with and without aura and also to include attacks that the patient believes are migraine and respond to acute treatment for migraine.[5]

Medication-overuse headache is defined as headache on 15 or more days per month that has evolved along with the frequent use of acute medication, for more than three months.[5] In the majority of patients this is a complication of migraine and patients with MOH often have a chronic migraine pattern *(see section 5)*. Importantly, not all patients with chronic migraine frequently using acute treatment have MOH; some have poorly-treated migraine. For triptans, opioids and combination analgesics 10 or more days use per month is considered sufficient to cause MOH, and for simple analgesics (eg aspirin, ibuprofen and paracetamol) 15 days per month.[5] When prescribing acute treatment for migraine, patients should be counselled about the risk of MOH.

The majority of studies in this guideline use the ICHD-2 2003 definitions except for those on chronic migraine where the 2007 consensus statement is used.

The ICHD Beta 3 diagnostic criteria for migraine and MOH are listed in Annex 2.

1.2.4 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to healthcare professionals in primary and secondary care, including general practitioners (GPs), headache nurses, neurologists, out-of-hours clinicians, pharmacists, and patients with migraine.

1.2.5 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, www.sign.ac.uk.

1.3 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 through a process of shared decision making 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 documented in the patient's medical records at the time the relevant decision is taken.

1.3.1 INFLUENCE OF FINANCIAL AND OTHER INTERESTS

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at www.sign.ac.uk.

1.3.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[17]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability."[17]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:[18]

- be satisfied that there is no suitably licensed medicine that will meet the patient's need.
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy.
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so.
- Make a clear, accurate and legible record of all medicines prescribed and, when not following common practice, the reasons for prescribing an unlicensed medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[19]

1.3.3 ADDITIONAL ADVICE FOR NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

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, all new formulations of existing medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

SMC advice relevant to this guideline is summarised in section 8.4.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

Medical treatment is subdivided into acute and preventative. Acute treatment should be taken as early as possible in the headache phase with the aim of aborting an attack. It is given once, with the option of repeating after two hours (with the same or different treatment) if there is an inadequate response. Preventative treatment is taken continuously in order to reduce the frequency and severity of migraine attacks. Often a combination of acute and preventative treatment is needed.

For treatment to be effective, it is crucial that the correct diagnosis has been made. Diagnostic criteria for migraine and MOH are listed in Annex 2. Choice of treatment should take account of severity and frequency of attacks, other symptoms, patient preference, history of treatment and comorbid conditions.

Patients have a variable response to triptans and it is worth sequencing through the triptans to find the most effective treatment. When starting a preventative treatment a low dose should be used and treatment dose gradually increased. The minimum effective dose should be used and this may vary between patients. The need for ongoing prophylaxis should be considered after six to 12 months.

2.1 ACUTE TREATMENT

R **Aspirin** (900 mg) **is recommended as first-line treatment for patients with acute migraine.**

R **Ibuprofen** (400 mg) **is recommended as first-line treatment for patients with acute migraine. If ineffective, the dose should be increased to 600 mg.**

R **Triptans are recommended as first-line treatment for patients with acute migraine. The first choice is sumatriptan** (50–100 mg)**, but others should be offered if sumatriptan fails.**

R **Combination therapy using sumatriptan** (50–85 mg) **and naproxen** (500 mg) **should be considered for the treatment of patients with acute migraine.**

2.2 PREVENTION OF MIGRAINE

R **Propranolol** (80–160 mg daily) **is recommended as a first-line prophylactic treatment for patients with episodic or chronic migraine.**

R **Topiramate** (50–100 mg daily) **is recommended as a prophylactic treatment for patients with episodic or chronic migraine.**

R **Amitriptyline** (25–150 mg at night) **should be considered as a prophylactic treatment for patients with episodic or chronic migraine.**

R **Candesartan** (16 mg daily) **can be considered as a prophylactic treatment for patients with episodic or chronic migraine.**

R **Botulinum toxin A is recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments.**

R **Erenumab, fremanezumab, galcanezumab and eptinezumab are recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.**

R **Fremanezumab, galcenezumab and eptinezumab can be considered for the prophylactic treatment of patients with episodic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.**

See section 1.2.3 and Annex 2 for the definitions of chronic and episodic migraine.

2.3 MEDICATION-OVERUSE HEADACHE

R **In patients overusing acute treatment, medication overuse should be addressed.**

✓ When starting acute treatment, healthcare professionals should warn patients about the risk of developing medication-overuse headache.

3 Treatment for patients with acute migraine

3.1 INTRODUCTION

Acute treatment is used either to abort an attack of migraine or to significantly reduce the severity of the headache and other symptoms. Acute treatment should be taken as soon as the patient knows they are developing a migraine headache.[20] In patients who have aura, it is recommended that triptans are taken at the start of the headache and not at the start of the aura (unless the aura and headache start at the same time).[20] It is given once, with the option of repeating after two hours (with the same or different treatment) if there is an inadequate response.

Treatment response is measured as pain free at two hours and sustained pain free at 24 hours. In addition, pain relief or headache relief (from severe/moderate to mild or no pain) is reported in some studies. A table of numbers needed to treat (NNTs) to achieve pain free at two hours for some acute therapies can be found in section 3.9.

Treatment can either be stepped or stratified.[20] In stepped treatment high-dose aspirin or ibuprofen is given first and, if not successful over three headaches, treatment is stepped up to triptans. In stratified treatment patients might, for example, use high dose aspirin for a milder headache and a triptan for a more severe headache. The strategy used should be tailored to patient preference.[20] Patients have a variable response to individual triptans and it is worth sequencing through different triptans to find the most effective one. Acute treatment will not always work for every migraine. Patients should be offered appropriate rescue medication for this situation, for example subcutaneous sumatriptan may be appropriate in some patients who don't respond to oral or nasal triptan. The risk of MOH should be discussed with every patient started on acute treatment.

It should be noted that all orodispersible (dissolve in the mouth) triptans are gastrically absorbed. In patients who vomit early in a migraine attack, nasal and subcutaneous triptans should be considered.[20] A significant proportion of the nasal dose is still gastrically absorbed. Antiemetics should be considered in patients with nausea or vomiting.

In patients with moderate to severe attacks combining a triptan with aspirin or a non-steroidal anti-inflammatory drug (NSAID) may be beneficial. Nasal or subcutaneous triptans should also be considered.[20]

A treatment algorithm outlining good practice in acute treatment can be found in Annex 3.

✓ When starting acute treatment, healthcare professionals should warn patients about the risk of developing medication-overuse headache.

3.2 ASPIRIN

A Cochrane review of 13 studies (4,222 participants) reported that aspirin 900 mg and aspirin 1,000 mg were effective in achieving pain free at two hours compared to placebo (NNT=8.1). For sustained pain relief at 24 hours aspirin 1,000 mg had an NNT of 6.6 compared to placebo.[21] **1++**

Aspirin alone had similar efficacy to sumatriptan 50 mg, and sumatriptan 100 mg was superior to aspirin and metoclopramide combined.[21] **1++**

Associated symptoms of nausea, vomiting, photophobia (NNT=7.7) and phonophobia (NNT=6.6) were reduced by aspirin when compared to placebo. The addition of metoclopramide further reduced nausea (NNT=2.6) and vomiting.[21] **1++**

Aspirin is a potential gastrointestinal irritant and may cause ulcers or gastrointestinal bleeding, however adverse effects from short-term use are mostly mild and transient.[21] Aspirin should not be used in patients under 16 years of age due to the risk of Reye's syndrome.[17] The use of aspirin during pregnancy, especially of intermittent high doses, should be avoided.[22] Aspirin is contraindicated during the third trimester of pregnancy.[17] **1++**

R **Aspirin** (900 mg) **is recommended as first-line treatment for patients with acute migraine.**

✓ Aspirin, in doses for migraine, is not an analgesic of choice during pregnancy and should not be used in the third trimester of pregnancy.[17]

3.3 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

A Cochrane review found ibuprofen to be superior to placebo in all doses between 200 mg and 600 mg for pain free at two hours and sustained pain relief at 24 hours for patients with acute migraine with moderate to severe baseline pain. The NNT for achieving the outcome of pain free at two hours was 9.7 for 200 mg and 7.2 for 400 mg.[23] **1++**

Naproxen has also been found to be effective for two hour pain relief compared to placebo for patients with acute migraine. The NNT for pain free at two hours was 11. Results did not vary for doses of 500 mg and 825 mg.[24] **1++**

Diclofenac potassium 50 mg is reported to have a relative benefit over placebo, relative risk (RR) 2.0 (95% confidence interval (CI) 1.6 to 2.6), NNT=8.9, for pain free at two hours in patients with acute migraine.[25] **1++**

Naproxen and ibuprofen were also effective in relieving migraine-associated symptoms of nausea, photophobia, phonophobia and functional disability compared to placebo.[23,24] **1++**

No serious adverse events were reported in the trials.[23-25] NSAIDs can cause gastrointestinal problems with long-term use.[17] They should also be used with caution in patients with asthma as NSAIDs may worsen the condition.[17] **1++**

In pregnancy, ibuprofen is the anti-inflammatory agent of first choice until gestational week 28. After 28 weeks of gestation, repeated use of ibuprofen should be avoided.[26] **4**

Ibuprofen is the only NSAID which is licensed for patients with acute migraine.

R **Ibuprofen** (400 mg) **is recommended as first-line treatment for patients with acute migraine. If ineffective, the dose should be increased to 600 mg.**

3.4 PARACETAMOL

A Cochrane review identified three studies (717 participants) and reported a relative benefit of paracetamol 1,000 mg in achieving pain free at two hours as 1.8 (95% CI, 1.2 to 2.6), NNT=12, compared to placebo in patients with moderate or severe acute migraine.[27] **1++**

In two studies including 1,140 patients with acute migraine, a combination of paracetamol 1,000 mg plus metoclopramide 10 mg had similar efficacy to sumatriptan 100 mg for headache relief at two hours (39% of participants reported relief using paracetamol and metoclopramide versus 42% for sumatriptan).[27] **1++**

For pain free and sustained headache relief at 24 hours, paracetamol was more effective than placebo, but not compared to rizatriptan.[27] **1++**

No serious adverse events were reported in the trials. Paracetamol is better tolerated than NSAIDs or triptans.[27] **1++**

Paracetamol is commonly used in all trimesters of pregnancy although routine use should be avoided.[22,26]

R **Paracetamol** (1,000 mg) **can be considered for treatment of patients with acute migraine who are unable to take other acute therapies.**

✓ Due to its safety profile, paracetamol is first choice for the short-term relief of mild to moderate headache during any trimester of pregnancy.[22,26]

3.5 ANTIEMETICS

Metoclopramide 10 mg (oral) in combination with aspirin 900 mg had similar efficacy to 100 mg sumatriptan in achieving the outcome of pain free at two hours.[21] Similar results were found for paracetamol 1,000 mg combined with metoclopramide 10 mg versus sumatriptan.[27] However, aspirin and metoclopramide provided significantly better relief of associated symptoms, with an NNT of 2.6 (95% CI 2.1 to 3.1). It was particularly beneficial in reducing vomiting, NNT=2.1 (95% CI 1.5 to 3.7).[21] **1++**

A randomised controlled trial (RCT) comparing different doses of metoclopramide found that all doses provided an improvement in pain response, measured using an 11-point numerical rating score for pain (NRS). Most patients improved by more than 50%. Individual improvement with metoclopramide was 4.7 NRS units for 10 mg, 4.9 for 20 mg and 5.3 for 40 mg.[28] **1+**

A meta-analysis found that phenothiazines are superior to placebo for complete headache relief up to one hour after treatment (odds ratio (OR) 15.02, 95% CI 7.57 to 29.82). There was no significant difference in efficacy for complete headache relief when compared to metoclopramide.[29] **1+**

Both prochlorperazine 10 mg and metoclopramide 20 mg (both coadministered with diphenhydramine and given intravenously) were found to be effective for pain relief at one hour for patients with acute migraine, as recorded on the NRS scale. At two hours the NRS for pain after treatment with prochlorperazine was 6.4 from a baseline NRS of 8.4, and for metoclopramide 5.9 from a baseline NRS of 8.8. The overall difference was 0.6 (95% CI -0.6 to 1.8), with an NNT of 17 for pain free at two hours.[30] **1+**

Reporting of side effects was inconsistent amongst trials.[21,29] Most side effects were minor.[21] Akathisia was reported in trials of metoclopramide and prochlorperazine in 5–9% of participants.[28,30] Drowsiness and dizziness was also noted. More dropouts were noted as the dose of metoclopramide increased.[28] **1+**

R **Metoclopramide** (10 mg) **or prochlorperazine** (10 mg) **can be considered in the treatment of headache in patients with acute migraine. They can be used either as an oral or parenteral formulation depending on presentation and setting.**

R **Metoclopramide** (10 mg) **or prochlorperazine** (10 mg) **should be considered for patients presenting with migraine-associated symptoms of nausea or vomiting. They can be used either as an oral or parenteral formulation depending on presentation and setting.**

✓ Metoclopramide should not be used regularly due to the risk of extrapyramidal side effects.

3.6 TRIPTANS

For patients experiencing acute migraine, triptans are superior to placebo, for pain relief, pain free within two hours and sustained pain relief at 24 hours.[31-35] **1++** **1+** **2++**

An overview of Cochrane reviews reported that sumatriptan is an effective abortive treatment for acute migraine episodes.[33] The subcutaneous route is the most effective in terms of pain relief at two hours from moderate to severe baseline pain, with an NNT of 2.5 for 4 mg and 2.3 for a 6 mg dose. Efficacy was significantly improved if treatment was taken early, while pain was mild. For oral sumatriptan 50 mg the NNT for pain free at two hours was 6.1 for moderate to severe baseline pain and 4.4 for mild baseline pain. For 100 mg sumatriptan the NNT was 4.7 for pain free at two hours for moderate to severe pain and 2.4 for mild pain. Intranasal sumatriptan is also effective for pain free at two hours (NNT=3.1).[33] **1++**

In studies comparing sumatriptan to other triptans, zolmitriptan and almotriptan showed similar efficacy.[33] Rizatriptan 10 mg was superior to all doses of sumatriptan for achieving pain free at two hours. Rizatriptan 5 mg had similar efficacy to sumatriptan 50 mg. Eletriptan 40 mg and 80 mg was superior to both doses of sumatriptan for the outcome of pain free at two hours and was associated with reduced need for rescue medication.[33] **1++**

Compared to other therapies, sumatriptan 100 mg was superior for achieving pain free at two hours than aspirin 900 mg with metoclopramide 10 mg, or paracetamol 1,000 mg and metoclopramide 10 mg.[33] Sumatriptan was superior to effervescent aspirin 1,000 mg for headache relief at two hours.[33] **1++**

For patients with menstrually-related migraine (MRM), sumatriptan resulted in a therapeutic gain with 25% of patients pain free at two hours with 50 mg and 34% with 100 mg compared to placebo.[35] Rizatriptan, frovatriptan and zolmitriptan were also reported to provide benefit for acute treatment of patients with MRM.[34,35] **1++** **1+**

Adverse events reported in the trials were described as mild to moderate. Serious adverse events were rare.[33 31] **1++**

Patients using rizatriptan and propranolol should be given a maximum dose of 5 mg rizatriptan due to the risk of interactions and rizatriptan should not be taken within two hours of taking propranolol.[17]

One study of cardiovascular outcomes with triptan use reported an OR of 0.86 (95% CI 0.52 to 1.43), for a serious cardiovascular event.[36] Triptans are contraindicated in patients with uncontrolled hypertension and in symptomatic cardiovascular and cerebrovascular disease.[17] Trials of triptans have focused on a population aged 18–65 years. There is therefore no information on triptan use in the over 65s. Hypertension, cardiovascular disease and cerebrovascular disease are all more common in older people. Age is not a contraindication to use of triptans but age and vascular risk factors should be taken into account before prescribing triptans in the over 65s.[17] **2++**

The United States Food and Drug Administration (FDA) issued a warning following a small number of case reports of serotonin syndrome in patients whilst taking triptans and selective serotonin reuptake inhibitors (SSRIs). This has been reviewed and a consensus statement produced by the American Headache Society. Clinical information in the FDA report was lacking and it was concluded that there is insufficient information to determine whether there is an increased risk of serotonin syndrome in patients taking triptans and SSRIs together compared with patients taking SSRIs alone. Given the frequency of coprescribing any risk is very small. It is therefore reasonable to prescribe triptans in patients on SSRIs.[37] **4**

Registry data has given increasing confidence in the use of triptans in pregnancy. A meta-analysis on the use of triptans, in particular sumatriptan, at all stages of pregnancy compared with women with migraine who did not use triptans showed that the use of triptans in pregnancy is not associated with an increased risk of major congenital malformation or prematurity.[38] This is supported by an additional cohort study.[39] The risk of spontaneous abortion rates was reported to be higher (OR 1.41, 95% CI 1.11 to 1.80) in the meta-analysis, but this was not assessed in all of the studies and was based on a small number of patients.[38] A more recent, larger cohort study (432 women) reported there was no increased risk of spontaneous abortion with triptan use.[39] **2++**

A further cohort study, where women completed validated questionnaires about their child at 18 and 36 months, suggested that prenatal triptan use (primarily in the first trimester) may be associated with externalising behaviour problems (1.36-fold risk).[40] The evidence is subject to possible confounders and should be interpreted with caution. **2+**

Sumatriptran is the preferred triptan based on efficacy, safety profile and cost. For patients with early vomiting, a nasal or subcutaneous triptan may be more effective. Nasal zolmitriptan 5 mg and sumatriptan 6 mg subcutaneous are effective (*see Table 1, section 3.9*). Where treatment with paracetamol (all trimesters) or ibuprofen (first and second trimester only) fail, the use of triptans, in particular sumatriptan, in all stages of pregnancy can be considered. None of the triptans are classed as non-teratogenic.

R **Triptans are recommended as first-line treatment for patients with acute migraine. The first choice is sumatriptan** (50–100 mg)**, but others should be offered if sumatriptan fails.**

R **In patients with severe acute migraine or early vomiting, nasal zolmitriptan or subcutaneous sumatriptan should be considered.**

R **Triptans are recommended for the treatment of patients with acute migraine associated with menstruation.**

R **Sumatriptan can be considered for treatment of acute migraine in pregnant women in all stages of pregnancy. The risks associated with use should be discussed before commencing treatment.**

3.7 COMBINED THERAPIES

A combination of sumatriptan 50–85 mg and naproxen 500 mg is better than placebo or monotherapy with active comparators in patients with acute migraine.[41] Fifty percent of patients with mild pain were pain free at two hours with combination therapy compared to 18% in the placebo group (NNT=3.1, 95% CI 2.9 to 3.5). When baseline pain was moderate to severe the NNT was 4.9 (95% CI 4.3 to 5.7) compared to placebo.[41] The associated features of nausea, photophobia, phonophobia and functional disability were also better managed when combination therapy was used compared to placebo or monotherapy.[41] **1**$^{++}$

The relative benefit of combination therapy when compared to sumatriptan alone was 1.4 with a NNT of 10. However, compared to naproxen alone combination therapy was clearly superior, with a relative benefit of 2.0, NNT=6.1.[41] **1**$^{++}$

Adverse effects were more common with combination therapy than placebo or naproxen alone, but were reported to be mild.[41] **1**$^{++}$

R **Combination therapy using sumatriptan** (50–85 mg) **and naproxen** (500 mg) **should be considered for the treatment of patients with acute migraine.**

3.8 STEROIDS

Two meta-analyses reported that use of steroids (prednisolone or dexamethasone) in addition to other acute treatments provided a small benefit in reducing the rate of moderate or severe headache at 24–72 hours (NNT=10).[42,43] The studies included in the meta-analyses were small and some reported no statistical difference to placebo. There was also heterogeneity in the additional acute therapies used. Pooled data from six studies reporting a secondary outcome of totally resolved migraine showed no significant benefit from steroids compared to placebo.[43] **1**$^{+}$

Adverse events were mild and transient.[42,43] In all but one study steroids were delivered intravenously to patients presenting to the emergency department. Intravenous steroids are not a viable option in routine practice. **1**$^{+}$

No evidence was identified on the use of prednisolone as a tapered treatment in patients with prolonged migraine (>3 days).

3.9 COMPARISON OF THERAPIES

Table 1 lists the NNTs for therapies to achieve the outcome of pain free at two hours from a baseline of moderate to severe pain, collated from the Cochrane reviews discussed in sections 3.2 to 3.8. It is not an exhaustive list of available therapies. Other triptans are effective (*see section 3.6 for details*), but were not measured against placebo so NNTs could not be calculated for comparison. A treatment algorithm outlining good practice in acute treatment can be found in Annex 3.

Table 1: Calculated numbers needed to treat for acute migraine therapies for an outcome of pain free at two hours in patients with moderate to severe pain, compared to placebo

Therapy	NNT
Simple analgesics	
Aspirin 900 mg or 1,000 mg[21]	8.1
Diclofenac potassium 50 mg[25]	8.9
Ibuprofen 400 mg[23]	7.2
Ibuprofen 200 mg[23]	9.7
Naproxen 500 mg or 825 mg[24]	11
Paracetamol 1,000 mg[27]	12
Oral triptans	
Sumatriptan 50 mg[33]	6.1
Sumatriptan 100 mg[33]	4.7
Zolmitriptan 5 mg[31]	4.8
Zolmitriptan 2.5 mg[31]	5.0
Nasal sprays	
Sumatriptan 20 mg[33]	4.7
Zolmitriptan 5 mg[31]	3.0
Subcutaneous injection	
Sumatriptan 6 mg[33]	2.3
Combination therapy	
Sumatriptan 50–85 mg and naproxen 500 mg[41]	4.9

4 Pharmacological prevention of migraine

4.1 INTRODUCTION

This section considers the preventative treatment options for patients with episodic and chronic migraine. Most of the available evidence is based on studies of a patient population with episodic migraine rather than chronic migraine *(for definitions, see section 1.2.3*). There is limited data to make specific treatment recommendations for patients with chronic migraine. Recommendations are therefore based on the premise that chronic migraine and episodic migraine are on a spectrum of the same condition and patients with chronic migraine may benefit from the therapies found to be effective for prophylaxis of episodic migraine.

Migraine can have considerable impact on quality of life and daily function. Modest improvements in the frequency or severity of migraine headaches may provide considerable benefits to an individual. Within trials, a reduction in migraine headache severity and/or frequency of 30–50% is regarded as a successful outcome. The decision about when to start migraine prophylaxis is best guided by establishing the impact of migraine on each patient, rather than just focusing on the absolute number of headaches or migraines per month. For example, a few severe incapacitating migraines per month may warrant prophylactic treatment whereas more frequent but milder migraines that have little impact on daily function may not warrant treatment. Overusing acute medication can limit the effectiveness of preventative medication and medication overuse should also be assessed and addressed.[44] Prophylactic treatment should be used for at least three months at the maximum tolerated dose before deciding if it is effective or not. In many patients prophylactic medication can be successfully phased out again and the need for ongoing prophylaxis should be considered after six to 12 months.[45]

An algorithm of a suggested treatment pathway can be found in Annex 3. The decision regarding which medication to try first is dependent on evidence of effectiveness, patient comorbidities, other risk factors, drug interactions and patient preference. It is important to ensure adequate contraception whilst on preventative therapies as some have risks of teratogenicity and others can potentially cause harm to unborn babies. Given that migraine without aura often improves during pregnancy women should aim to stop migraine prophylactic treatments before pregnancy.[12] Migraine with aura often continues unchanged.[12] Before commencing treatment, potential harmful effects of therapies need to be discussed with women who are, or may become, pregnant. No evidence was identified on which to base recommendations on preventative treatments for women during pregnancy.

4.2 BETA BLOCKERS

A well-conducted systematic review identified a large number of trials on the use of beta blockers for prophylaxis of migraine, mostly from the 1980s. The individual trials were rated as low quality and of short duration (<3 months).[46] Propranolol (80–160 mg) reduced the frequency of episodic migraine by ≥50% compared to placebo (NNT=4, 95% CI 3 to 7).[46] Metoprolol (200 mg daily, slow release) reduced migraine severity, but no consistent benefits in reduction of migraine frequency or use of acute analgesics was shown.[46] Atenolol 50–200 mg daily was reported to reduce frequency of episodic migraine and use of acute therapies.[46] **1++**

Direct comparative trials of the effectiveness of propranolol with other medications used for migraine prevention in patients with episodic and chronic migraine were of low quality due to risk of bias and failure to analyse data according to intention-to-treat principles. Within these constraints the likelihood of a 50% reduction in headache frequency did not differ between propranolol and topiramate. Propranolol was better than nifedipine but there was no clear evidence to suggest it was better than other beta blockers such as metoprolol and timolol. Similarly there was no difference when compared to amitriptyline or nortriptyline. The use of combined tricyclic antidepressant and propranolol was no better than propranolol monotherapy.[46] **1++**

Propranolol use led to treatment side effects more commonly than placebo and specific adverse events leading to discontinuation included nausea (43 per 1,000 treated) and diarrhoea (89 per 1,000 treated).[46] However, it is a well-established therapy and is widely used in NHSScotland. Beta blockers should be used **1++**

with caution if the patient has a history of asthma.[17] Patients using rizatriptan and propranolol should be given a maximum dose of 5 mg rizatriptan as propranolol increases the plasma concentration of rizatriptan. Rizatriptan should not be taken within two hours of taking propranolol.[17] 1++

R **Propranolol** (80–160 mg daily) **is recommended as a first-line prophylactic treatment for patients with episodic or chronic migraine.**

4.3 TOPIRAMATE

Three systematic reviews reported on the efficacy of topiramate compared to placebo in patients with episodic and chronic migraine.[46-48] Pooled analysis from nine RCTs (1,700 patients; treatment duration 4–52 weeks) comparing topiramate to placebo reported use of topiramate resulted in twice as many patients reporting a ≥50% reduction in headache frequency (RR 2.02, 95% CI 1.57 to 2.60; NNT=4, 95% CI 3 to 6), one less headache per 28 days and an improvement in quality of life outcomes.[48] In patients with chronic migraine, low-quality evidence suggests that topiramate reduces monthly migraine days, frequency of associated symptoms and is more effective in reducing monthly migraine attacks by 25% when compared to placebo.[46] Topiramate also improved quality of life and migraine-related disability scores.[46] 1++

Topiramate at doses of 50–200 mg daily is effective in reducing monthly migraine frequency and monthly migraine days by 50% or more (absolute reduction of five migraine days/month for topiramate at a dose of 100 mg/day).[46] Meta-analysis of three trials that used multiple doses of topiramate demonstrated that 200 mg daily is no more effective than 100 mg daily.[48] Improvement in quality of life measures, general health status, self-reported vitality and use of acute drugs was also reported.[46] 1++

In seven trials of topiramate versus active comparators (amitriptyline, flunarizine, propranolol, sodium valproate and relaxation) topiramate was found to be no better than any comparator except for a small, but significant, benefit over sodium valproate. However, these trials were underpowered and further evidence is needed to confirm these findings.[48] 1++

Topiramate 100 mg daily was associated with a higher rate of adverse events than placebo, although these were mild to moderate.[47,48] Adverse effects include nausea, paraesthesia, anorexia and weight loss.[47-49] Cognitive adverse effects are common, vary in severity, tend to be dose related and often define drug tolerability.[50] As depression is also a common side effect, topiramate should be used with caution in patients with depression.[17] Exposure to topiramate during the first trimester of pregnancy has an increased risk of abnormal oral cleft development in infants (OR 6.2, 95% CI 3.13 to 12.51).[51] Children exposed to topiramate in utero are at high risk of serious developmental disorders (HR 3.53, 95% CI 1.42 to 8.74 for risk of developing intellectual disability, and HR 2.73, 95% CI 1.34 to 5.57 for autism spectrum disorder).[147] It should not be used by women who are breast feeding as it can be present in breast milk.[17] Patients who are using topiramate and who may become pregnant should therefore use highly-effective contraception. Advice on contraception is available from the Royal College of the Obstetricians and Gynaecologists Faculty of Sexual and Reproductive Healthcare, https://www.fsrh.org/standards-and-guidance/fsrh-guidelines-and-statements/. 1++ 1+ 2++

R **Topiramate** (50–100 mg daily) **is recommended as a prophylactic treatment for patients with episodic or chronic migraine.**

R **Before commencing treatment women should be informed of:**

- **the risks associated with taking topiramate during pregnancy**
- **the risk that potentially harmful exposure to topiramate may occur before a women is aware she is pregnant**
- **the need to use highly-effective contraception**
- **the need to seek further advice on migraine prophylaxis if pregnant or planning a pregnancy.**

4.4 TRICYCLIC ANTIDEPRESSANTS

A systematic review reported patients with episodic migraine (on average 4.7 migraines per month) treated with tricyclic antidepressants (TCAs) experienced a reduction of 1.4 headaches per month.[52] Study duration varied from four to 24 weeks and the studies were rated as having a high risk of bias.[52] The average dose of TCA used was 50% of the maximum dose (eg the dose range for amitriptyline was 10 mg to 150 mg with a pooled mean dose of 80 mg). In most studies doses were titrated. There was some evidence that higher doses resulted in greater benefit but the difference between higher and lower doses was not significant. Patients with episodic migraine taking TCAs had an 80% chance of a 50% improvement in headaches (RR 1.80, 95% CI 1.24 to 2.62) compared to placebo. There was a small ongoing reduction in headache frequency with continued treatment with TCAs.[52] **1++**

A further meta-analysis found that amitriptyline (100 mg) was more effective than placebo in achieving a ≥50% reduction in headache frequency but more so in those with higher headache frequencies. This was based on low-quality evidence.[46] **1++**

In comparative trials, low-dose (eg an average amitriptyline dose of 50 mg) TCAs were more likely to produce at least a 50% improvement in episodic migraine headache frequency than SSRIs. Studies comparing beta blockers and TCAs, amitriptyline and topiramate, and amitriptyline and flunarizine found no difference in the likelihood of gaining a 50% reduction in headache attacks. However there are relatively few trials and most were underpowered to assess clinical equivalence.[46] **1++**

Across 37 studies of various TCAs, only dry mouth and drowsiness were reported as more frequent in the TCA group than the placebo group. Some TCAs are less sedating than others.[17] Withdrawal from treatment due to an adverse event was similar between patients taking placebo or TCA.[52] TCAs are unlicensed for the treatment of patients with migraine (*see section 1.3.2*). **1+**

R **Amitriptyline** (25–150 mg at night) **should be considered as a prophylactic treatment for patients with episodic or chronic migraine.**

R **In patients who cannot tolerate amitriptyline a less sedating tricyclic antidepressant should be considered.**

4.5 CANDESARTAN

A systematic review identified two small RCTs of moderate quality that demonstrated the efficacy of candesartan (16 mg).[53] One of the studies reported a relative reduction of 26% in headache days.[54] In the other study, candesartan had similar efficacy to propranolol 160 mg for the secondary outcome of ≥50% reduction in migraine days (proportion of responders: 43% for candesartan, 40% for propranolol and 23% for placebo).[55] Candesartan is usually well tolerated and early trial data suggested no increase in the rate of adverse events compared to the placebo rate.[54] Due to teratogenic effects, it is advised that candesartan should be avoided during pregnancy and breastfeeding.[146] **1+** **4**

The evidence base for candesartan is small and further trials are unlikely to be conducted. However, candesartan is a widely used and inexpensive drug with a good side-effect profile, and no potential cognitive effects.

R **Candesartan** (16 mg daily) **can be considered as a prophylactic treatment for patients with episodic or chronic migraine.**

R **Use of candesartan should be avoided during pregnancy and breastfeeding. Women using candesartan who are planning to become pregnant, or who are pregnant, should seek advice from their healthcare professional on switching to another therapy.**

4.6 SODIUM VALPROATE

For patients with episodic migraine, sodium valproate is more effective than placebo providing a ≥50% reduction in headache frequency over eight to twelve weeks (RR 2.83, 95% CI 1.27 to 6.31; NNT=3, 95% CI 2 to 9) in pooled data from two small trials (n=63), using doses ranging from 400–1500 mg daily.[56] There was no difference in efficacy when compared to flunarizine, and sodium valproate 500 mg was not as effective as high-dose topiramate (400 mg) in pooled analysis of two small trials.[56] **1++**

There was variable reporting on adverse effects in the trials included in the Cochrane review. Those reported were mild but common and included fatigue, dizziness, tremor and weight gain.[56] **1++**

Children exposed to sodium valproate in utero are at high risk of serious developmental disorders and congenital malformations. It should therefore not be used during pregnancy. There is also a risk of transient impaired fertility in men. The Commission on Human Medicines recommends that no patients (male or female) under the age of 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment. For patients under 55 years currently receiving valproate, two specialists should independently consider and document that there is no other effective or tolerated treatment or the risks do not apply.[57] Sources of further advice for prescribing sodium valproate for women who may become pregnant are available in section 7.2 and the MHRA patient information card and checklist can be found in Annex 4. Sodium valproate is unlicensed for the treatment of patients with migraine *(see section 1.3.2)*.

R **Sodium valproate** (400–1,500 mg daily) **can be considered as a prophylactic treatment for patients over the age of 55 with episodic or chronic migraine.**

✓ Although valproate is not recommended for those under the age of 55 for those who remain on it and who fulfil MHRA requirements, the safety advice is to inform the patient of the risks to children exposed to valproate in utero and the need to use effective contraception (see www.fsrh.org/standards-and-guidance/fsrh-guidelines-and-statements).

✓ If prescribing sodium valproate check the MHRA website for current advice, www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency.

4.7 CALCIUM CHANNEL BLOCKERS

Low-quality studies, mostly from the 1980s and of variable design and size, reported some, but not consistent, benefit from verapamil, nimodipine, nifedipine or nicardipine over placebo in patients with episodic or chronic migraine.[46,53] **1++** **1+**

Meta-analysis of seven trials of flunarazine at a dose of 10 mg daily reported a moderate benefit in patients with episodic migraine compared to placebo. The standardised mean difference (SMD) for reduction in headache frequency was -0.60 (95% CI -1.2 to 0.005) at eight weeks and -0.84 (95% CI -1.3 to 0.34) at 12 weeks. No significant benefit was found at four weeks.[53] The trials included in the meta-analysis were small. **1+**

Comparative trial data was limited, but there is some evidence that flunarazine has similar efficacy to propranolol, topiramate and sodium valproate.[53,58] **1++**

Flunarazine is often well tolerated.[58] Depression is a possible side effect, so it should be used with caution in patients with depression.[58,59] Expert opinion recommends flunarizine should be avoided during pregnancy.[148]

Flunarizine is not licensed for use in the UK. Provision is normally via hospital prescription by a specialist headache service. Clinicians should be familiar with the side-effect profile.[59]

R **Flunarizine** (10 mg daily) **should be considered as a prophylactic treatment for patients with episodic or chronic migraine.**

✓ Use of flunarazine should be avoided during pregnancy and breastfeeding. Women using flunarazine who are planning to become pregnant, or who are pregnant, should seek advice from their healthcare professional on switching to another therapy.

4.8 PIZOTIFEN

Pizotifen is a long-established, licensed prophylactic agent and is commonly used in the UK. Most of the studies on pizotifen were conducted in the 1970s, using doses ranging from 1.5–6 mg daily. Between 30% and 50% of patients have reported that using pizotifen reduces migraine frequency.[60] **1⁻**

Two multicentre studies, one a double blind placebo-controlled trial (study 1) and the other an open study (study 2) were conducted to assess if pizotifen prophylaxis (in doses of 1.5 mg per day) reduced the frequency of migraine. The median of the monthly migraine rate was lower in patients receiving pizotifen and sumatriptan than in those receiving placebo and sumatriptan (study 1; 3.5 versus 3.9), or sumatriptan alone (study 2; 2.9 versus 3.2). The authors concluded that pizotifen may be better reserved for those patients who have four or more migraines per month.[60] **1⁻**

There is insufficient evidence to support a recommendation, but it is a well-established therapy which is widely used.

4.9 GABAPENTIN AND PREGABALIN

There is limited evidence from two small trials of gabapentin that high doses (1,800–2,400 mg) are significantly superior to placebo for patients with episodic migraine, but the pooled data from six trials of gabapentin (1,000 patients) suggest no consistent benefit over placebo in the prophylaxis of adults with episodic migraine at any dose.[61] **1⁺⁺**

Adverse effects were common, particularly with high doses of gabapentin, including fatigue, dizziness, flu-like symptoms, somnolence and cognitive disturbance.[61] **1⁺⁺**

There is a lack of evidence on the use of pregabalin in patients with episodic migraine.[61] **1⁺⁺**

If migraine is part of a chronic pain syndrome, further advice on the use of pregabalin is available in SIGN 136: Management of chronic pain.[62]

Use of gabapentin or pregabalin is associated with increased risk of addiction.[63] **4**

R **Gabapentin should not be considered as a prophylactic treatment for patients with episodic or chronic migraine.**

4.10 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

A systematic review identified one trial of 60 patients with episodic migraine (with or without hypertension), where 12 weeks of treatment with lisinopril was better than placebo in reducing migraine days/severity and body pain, but did not reduce use of acute therapies.[46] Another small RCT (n=24) found captopril reduced headache and improved depression over 32 weeks.[46] **1⁺⁺**

4.11 SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS

A Cochrane review identified 11 RCTs of the use of SSRIs and one RCT of venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI) for the management of patients with migraine.[64] Most of the studies were considered poor in quality, due to incomplete reporting of adverse events, lack of adequate follow up, lack of power and inconsistent use of outcome events. Overall, there was a lack of evidence to support the use of SSRIs or venlafaxine for migraine prophylaxis. One trial suggested that venlafaxine had similar efficacy to amitriptyline but was better tolerated.[64] **1⁺⁺**

4.12 OTHER ANTIEPILEPTICS

A Cochrane review found no consistent evidence of efficacy in patients with episodic migraine for acetazolamide, lamotrigine, clonazepam, oxcarbazepine, vigabatrin or zonisamide when compared to placebo.[65] Levetiracetam 1,000 mg daily was superior to placebo in reducing headache frequency and in the proportion of headache responders, but was not superior to topiramate 100 mg daily in reducing headache frequency. Further trials are needed to determine its efficacy. Carbamazepine was superior to placebo in the proportion of responders, which was deemed clinically significant, but high rates of adverse events were noted.[65] **1++**

4.13 BOTULINUM TOXIN A

Systematic reviews on the efficacy of botulinum toxin A are based mainly on two large multicentre RCTs, the Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and PREEMPT 2. Both trials were conducted in patients with chronic migraine over 24 weeks. Patients received two sets of injections at 12 week intervals, followed by an open label phase.[46,66,67]

In PREEMPT 1 the primary endpoint of reduction in headache episodes from baseline compared to placebo was negative. However, there was significant reduction in secondary endpoints of headache days with botulinum toxin A versus placebo (-7.8 *v* -6.4; p=0.006) and migraine days (-7.6 *v* -6.1; p=0.002).[68]

In PREEMPT 2 the primary endpoint was changed (prior to completion of the trial and before analysis) to reduction in headache days. It was stated that this was a better measure than headache episodes in patients with chronic migraine due to the prolonged, continuous nature of their headaches. There was a significant reduction in both headache days for botulinum toxin A versus placebo (-9.0 *v* -6.7; p<0.001) and migraine days (-8.7 *v* -6.3; p<0.001) compared with baseline. There was also a significant reduction in headache episodes in PREEMPT 2 for botulinum toxin A versus placebo (-5.3 *v* -4.6; p=0.003).[69] **1++** **1+**

Post hoc analysis of pooled data from both trials of those patients who had previously used three or more migraine preventatives reported a bigger difference, compared to placebo, in headache days and migraine days for botulinum toxin A (-7.4 *v* -4.7; p<0.001) and migraine days (-7.1 *v* -4.3; p<0.001) compared with baseline.[70]

In both PREEMPT trials about two thirds of the patients overused abortive treatments. In such patients MOH should be addressed first (*see section 5*). However, in patients where treatment of MOH has been unsuccessful, botulinum toxin A should still be considered.

A meta-analysis of trials of patients with episodic migraine or tension-type headache found no difference in efficacy compared to placebo.[66] **1+**

Five individual RCTs provided low-strength evidence about the comparative effectiveness of botulinum toxin A versus other drugs for chronic migraine prevention in 350 adults ages 18–65 with 12–24 migraine days per month. No significant differences in likelihood of migraine prevention or improvement in migraine disability assessment were found for botulinum toxin A compared to topiramate. Absolute scores of the Headache Impact Test were significantly better with topiramate than botulinum toxin A, however, the need for acute drugs did not differ between the two. A single RCT examined the comparative effectiveness of botulinum toxin A versus divalproex sodium and found no differences between the two drugs for migraine prevention, migraine-related disability, or quality of life.[46] **1++**

Adverse events were slightly more common in patients injected with botulinum toxin A compared to placebo (RR 1.25, 95% CI, 1.14 to1.36), although they were not more likely to withdraw from the study as a result. Adverse events included ptosis, muscle weakness, neck pain and stiffness, paraesthesia and skin tightness.[46,66] **1++** **1+**

Botulinum toxin A (Botox®) has been accepted with restricted use in NHSScotland for adults with chronic migraine (headaches on at least 15 days per month of which at least eight days are with migraine) whose condition has failed to respond to ≥3 prior oral prophylactic treatments, where medication overuse has been appropriately managed.[70] This was based on clinical effectiveness and a cost-utility analysis (Markov model) which compared botulinum toxin A to best supportive care, over a three-year time horizon. The analysis reported that botulinum toxin A resulted in an incremental cost-effectiveness ratio (ICER) of £10,816 and quality-adjusted life year (QALY) gain of 0.12.[70] Botulinum toxin A is required to be administered by appropriately trained personnel in hospital specialist centres, which may have implications for service delivery.

R **Botulinum toxin A is not recommended for the prophylactic treatment of patients with episodic migraine.**

R **Botulinum toxin A is recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments.**

✓ Botulinum toxin A should only be administered by appropriately trained individuals under the supervision of a headache clinic or the local neurology service.

4.14 CALCITONIN GENE-RELATED PEPTIDE MONOCLONAL ANTIBODIES

Four calcitonin-gene-related peptide (CGRP) monoclonal antibodies are available for use in NHSScotland. Erenumab targets the CGRP receptor. Fremanezumab, galcanezumab and eptinezumab target the CGRP ligand. Erenumab, fremanezumab and galcanezumab are provided by monthly subcutaneous injections. Fremanezumab can also be given quarterly. Eptinezumab is only available as a quarterly intravenous infusion.

Meta-analyses have demonstrated the effectiveness of CGRP monoclonal antibodies, with significant reductions in monthly migraine days (MMDs) compared to placebo in patients with episodic and chronic migraine.[114-118] The meta-analyses included RCTs of each therapy as described below. Studies of the three CGRP monoclonal antibodies available in NHSScotland varied in the number of preventives participants were allowed to have tried prior to inclusion in the trial *(see Table 2)*. **1++**

Table 2: Reduction in monthly migraine days with treatment and placebo

Treatment study	Migraine frequency	Number of prior classes of treatment failure	Baseline MMD (treatment/ placebo groups)	Reduction in MMD with treatment	Reduction in MMDs with placebo	Difference* (95% CI)
Erenumab						
STRIVE[119] 70 mg	EM	<3	8.3/8.2	-3.2	-1.8	-1.4 (-1.9 to -0.9)
STRIVE[119] 140 mg	EM	<3	8.3/8.2	-3.7	-1.8	-1.9 (-2.3 to -1.4)
ARISE[120] 70 mg	EM	<3	8.1/8.4	-2.9	-1.8	-1.0 (-1.6 to -0.5)
LIBERTY[121] 140 mg	EM	2–4	9.2/9.3	-1.8	-0.2	-1.6 (-2.7 to -0.5)

Treatment study	Migraine frequency	Number of prior classes of treatment failure	Baseline MMD (treatment/ placebo groups)	Reduction in MMD with treatment	Reduction in MMDs with placebo	Difference* (95% CI)
Fremanezumab						
HALO[123] monthly 225 mg	EM	<3	8.9/9.1	-3.7	-2.2	-1.5 (-2.01 to -0.93)
HALO[123] quarterly 625 mg	EM	<3	9.3/9.1	-3.4	-2.2	-1.3 (-1.79 to -0.72)
HALO[124] monthly 225 mg	CM	<2	16/16.4	-5	-3.2	-1.8 ± SE 0.4
HALO[124] quarterly 625mg	CM	<2	16.2/16.4	-4.9	-3.2	-1.7 ± SE 0.4
FOCUS[124] monthly 225 mg	EM and CM	2–4	14.1/14.3	-4.1	-0.6	-3.5 (-4.2 to -2.8)
FOCUS[125] quarterly 625 mg	EM and CM	2–4	14.1/14.3	-3.7	-0.6	-3.1 (-3.8 to -2.4)
Galcanezumab						
EVOLVE 1[126] 120 mg†	EM	<3	9.2/9.1	-4.7	-2.8	-1.9 (-2.5 to -1.4)
EVOLVE 1[126] 240 mg	EM	<3	9.1/9.1	-4.6	-2.8	-1.8 (-2.3 to -1.2)
EVOLVE 2[127] 120 mg†	EM	<3	9.07/9.2	-4.3	-2.3	-2.0 (-2.6 to -1.5)
EVOLVE 2[127] 240 mg	EM	<3	9.06/9.2	-4.2	-2.3	-1.9 (-2.4 to -1.4)
REGAIN[128] 120 mg†	CM	<4	19.4/19.6	-4.8	-2.7	-2.1 (-2.9 to -1.3)
REGAIN[128] 240 mg	CM	<4	19.2/19.6	-4.6	-2.7	-1.9 (-2.7 to -1.1)
CONQUER[129] 120 mg†	EM	2–4	9.5/9.2	-2.9	-0.3	-2.6 (-3.4 to -1.7)
CONQUER[129] 120 mg†	CM	2–4	19.2/18.2	-6.0	-2.2	-3.7 (-5.2 to -2.2)

Treatment study	Migraine frequency	Number of prior classes of treatment failure	Baseline MMD (treatment/ placebo groups)	Reduction in MMD with treatment	Reduction in MMDs with placebo	Difference* (95% CI)
Eptinezumab						
PROMISE 1[149] 30 mg	EM	Not reported	8.7/8.4	-4.0	-3.2	-0.82 (-1.39 to -0.25)
PROMISE 1[149] 100 mg	EM	Not reported	8.7/8.4	-3.9	-3.2	-0.69 (-1.25 to -0.12)
PROMISE 1[149] 300 mg	EM	Not reported	8.6/8.4	-4.3	-3.2	-1.11 (-1.68 to -0.54)
PROMISE 2[150] 100 mg	CM	Not reported	16.1/16.2	-7.6	-5.7	-2.0 (-2.9 to -1.2)
PROMISE 2[150] 300 mg	CM	Not reported	16.1/16.2	-8.2	-5.7	-2.6 (-3.4 to -1.7)
DELIVER 100 mg[151]	EM and CM	2–4	13.8/13.9	-4.8	-2.1	-2.7 (-3.4 to -2.0)
DELIVER 300 mg[151]	EM and CM	2–4	13.7/13.9	-5.3	-2.1	-3.2 (-3.9 to -2.5)

*Data for reduction in monthly migraine days are least means squared. *Differences in MMD are expressed with (95% confidence intervals unless otherwise stated. †Patients receiving 120 mg galcanezumab received 240 mg loading dose. CM – chronic migraine; EM – episodic migraine.*

Two RCTs assessed the efficacy of erenumab in patients with episodic migraine: STRIVE and ARISE.[119,120] A further RCT, LIBERTY, assessed its efficacy in patients with harder-to-treat episodic migraine (defined as prior failure of 2–4 migraine preventive agents).[121] The majority of participants in these RCTs had a higher frequency of episodic migraine (8–14 days per month). There was a significant reduction in MMDs compared to placebo at 12 weeks in both STRIVE (-3.2 with 70 mg vs -3.7 with 140 mg vs -1.8 with placebo p<0.001) and ARISE (-2.9 with 70 mg vs -1.8 with placebo p<0.001).[119,120] There was a ≥50% reduction in MMDs in 43.3% of participants with 70 mg and in 50% with 140 mg in STRIVE, and in 39.7% in ARISE.[119,120] In the harder-to-treat population (LIBERTY) the reduction in MMDs with 140 mg at 12 weeks was lower (-1.8), but there was a much smaller placebo rate (-0.2), p=0.004. A ≥50% reduction in MMDs was reported in 30% of participants with 140 mg compared to 14% with placebo.[121] **1++**

In patients with chronic migraine, a high-quality phase 2 RCT of erenumab reported a significant reduction in MMDs compared to placebo at 12 weeks (-6.6 with 70 mg vs -6.6 with 140 mg vs -4.2 with placebo, p<0.001) from a baseline of 18 MMDs.[122] There was a ≥50% reduction in MMDs in 40% of participants with 70 mg and in 41% with 140 mg. Forty-one percent of patients enrolled in the study overused abortive treatments, reflecting clinical experience where medication overuse headache remains common in patients presenting with chronic migraine *(see section 5)*. **1++**

A follow-up study of a phase 2 RCT in patients with episodic migraine showed that reductions in MMDs were sustained.[130,131] Those in the placebo group were transferred onto 70 mg erenumab monthly and achieved a similar reduction in MMDs by week 16 compared to the group originally randomised to 70 mg. The 70 mg dose was continued to week 64 and then increased to 140 mg. The mean change in MMDs from a baseline of 8.7 MMDs was -5.3 at 5 years and a ≥50% reduction was achieved in 71% of paticipants.[130] **2++**

The HALO episodic migraine trial compared monthly doses of fremanezumab (225 mg) to quarterly doses (675 mg) or placebo. The baseline number of migraine days was 8.9±2.6 for the cohort receiving a monthly dose and 9.3±2.7 for the quarterly cohort, indicating that the majority of participants had a higher frequency of episodic migraine. There was a significant reduction in MMDs (-3.7 in the group who received monthly fremanezumab (225 mg) vs -3.4 with quarterly fremanezumab (675 mg), vs -2.2 with placebo (p<0.001)).[123] In the open-label extension study, which included episodic migraine, chronic migraine and new enrollees, this increased to -5.1 MMDs with the monthly dose and -5.2 with the quarterly dose at 12 months in the episodic migraine cohort.[132] There was a ≥50% reduction in MMDs in 41% of participants with the monthly dose and in 44.4% with the quarterly dose, which increased to 68% and 66% respectively at 12 months.[123,132] **1++** **2++**

In the chronic migraine cohort of the HALO trial there was a significant reduction in MMDs compared to placebo at 12 weeks (-5.0 in the group who received monthly fremanezumab (675 mg loading and 225 mg monthly thereafter) vs -4.9 with quarterly fremanezumab (675 mg) vs -3.2 with placebo p<0.001).[124] This increased to -8.0 for the monthly dose and -7.2 with the quarterly dose in the open-label extension study.[132] There was a ≥50% reduction in MMDs in 47.7% with the monthly dose and 38% with the quarterly dose, which increased to 57% and 53% respectively at 12 months.[124,132] The dose of 675 mg then a monthly dose of 225 mg used in the trial differs from the licensed monthly dose of 225 mg monthly or 675 mg quarterly. **1++** **2++**

In a study, FOCUS, of patients who had had treatment failure with up to four previous therapies, in which 60% of the patients had chronic migraine and 40% had episodic, the reduction in MMDs at 12 weeks was -4.1 with monthly fremanezumab (225 mg), and -3.7 with quarterly fremanezumab (675 mg). The 50% responder rate was 34% for both regimens.[125] **1++**

In the EVOLVE 1 and EVOLVE 2 RCTs of galcanezumab in patients with episodic migraine, there was a significant reduction in monthly migraine headache days (MHD) compared to placebo at 12 weeks (EVOLVE 1: -4.7 with 120 mg vs -4.6 with 240 mg vs -2.8 with placebo p<0.001, and EVOLVE 2: -4.3 with 120 mg vs -4.2 with 240 mg vs -2.3 with placebo p<0.001).[126,127] There was a ≥50% reduction in monthly MHDs in 62.3% of participants with 120 mg and in 60.9% with 240 mg in EVOLVE 1, and in 59.3% with 120 mg and in 56.5% with 240 mg in EVOLVE 2. The baseline number of migraine days in EVOLVE 1 was 9.2±3.1 with 120 mg and 9.1±2.9 with 240 mg, and in EVOLVE 2 it was 9.07±2.9 with 120 mg and 9.06±2.9 with 240 mg, indicating that the trial cohort had higher frequency episodic migraine. **1++**

An RCT, REGAIN, of galcanezumab in patients with chronic migraine (64% of whom overused abortive treatments) reported a significant reduction in monthly MHDs compared to placebo at 12 weeks (-4.8 with 120 mg vs -4.6 with 240 mg vs -2.7 with placebo, p<0.001, from a baseline of 19.4 monthly MHDs).[128] There was a ≥50% reduction in monthly MHDs in 27.6% of participants with 120 mg and in 27.5% with 240 mg. Ninety-nine percent of patients entered the open-label extension with 81% completing 12 months of treatment. Patients remained blinded as per their original allocation. At month three all patients were given a 240 mg loading dose and then maintained on 120 mg monthly (with the option of a 120 mg top up at the discretion of the treating clinician). At 12 months the reduction in monthly MHDs improved to -9.0 in the previous 120 mg group, -8.0 in the previous 240 mg group and -8.5 in the previous placebo group.[133] **1++**

In the CONQUER RCT in patients with harder-to-treat migraine, participants received galcanezumab 120 mg or placebo.[129] This included a loading dose of either 2 x 120 mg galcanezumab or 2 x placebo injections. At 12 weeks the reduction in monthly MHDs was -2.9 with 120 mg vs -0.3 with placebo in patients with episodic migraine (p<0.0001), 48.1% had a ≥50% reduction in monthly MHDs. For patients with chronic migraine the reduction was -6.0 with 120 mg galcanezumab vs -2.2 with placebo (p<0.0001), and 32% had a ≥50% reduction in monthly MHDs.[129] All except two patients who completed the double-blind phase entered the open-label phase and 96% of these completed the study.[134] All patients previously in the placebo group had a 240 mg loading dose at month three (2 x 120mg in the placebo group and 1 x 120mg and 1 x placebo in the 120 mg group). At 6 months the reduction in monthly MHDs was -3.8 for the previous 120 mg group versus -4.5 for the previous placebo group in patients with episodic migraine and -8.2 for the previous 120 mg group vs -6.5 for the previous placebo group in patients with chronic migraine.[134] **1++** **2++**

In the PROMISE 1 RCT of eptinezumab in patients with episodic migraine there was a significant reduction of MMDs compared to placebo at 12 weeks with 100 mg and 300 mg (-4.0 with 30 mg (p=0.0046) versus -3.9 with 100 mg (p=0.0182) versus -4.3 with 300 mg (p=0.0001) versus -3.2 with placebo).[149] There was a >50% reduction in MMDs in 48.9% of participants with 100 mg and 56.3% with 300 mg, and a >75% reduction in MMDs in 22.2% of participants with 100 mg and 29.7% with 300 mg. There was an observed preventative effect on the first day after dosing (percentage of patients with migraine on day 1 was 14.8% with 100 mg versus 13.9% with 300 mg versus 22.5% with placebo). The baseline number of migraine days was 8.7 with 100 mg and 8.6 with 300 mg and 8.4 with placebo.[149] **1+**

In the PROMISE 2 RCT of eptinezumab in patients with chronic migraine there was a significant reduction of MMDs compared to placebo at 12 weeks with 100 mg and 300 mg (-7.6 with 100 mg versus -8.2 with 300 mg versus -5.7 with placebo p<0.0001).[150] There was a >50% reduction in MMDs in 57.6% of participants with 100 mg and 61.4% with 300 mg, and a >75% reduction in MMDs in 26.7% of participants with 100 mg and 33.1% with 300 mg. There was an observed preventative effect on the first day after dosing (percentage of patients with migraine on day 1 was 28.6% with 100 mg versus 27.8% with 300 mg versus 42.3% with placebo). The baseline number of migraine days was 16.1 with 100 mg and 300 mg and 16.2 with placebo.[150] **1+**

The number of prior preventative treatments used is not reported in either PROMISE 1 or PROMISE 2. The study, DELIVER, of patients who had treatment failure with up to four previous preventative treatments, enrolled participants with both episodic and chronic migraine.[151] In the 100 mg group 13% had low-frequency episodic migraine (≤14 monthly headache days including 4–7 monthly migraine days), 41% had high-frequency episodic migraine (≤14 monthly headache days including 8–14 monthly migraine days), 46% had chronic migraine and 13% met criteria for MOH. The percentages were comparable in the 300 mg and placebo groups. Results for episodic and chronic migraine were not analysed separately. The mean MMDs was 13.8 with 100 mg, 13.7 with 300 mg and 13.9 with placebo. There was a significant reduction in mean MMDs compared to placebo at 12 weeks with 100 mg and 300 mg (-4.8 with 100 mg versus -5.3 with 300 mg versus -2.1 with placebo p<0.0001). This was sustained at 24 weeks (-5.4 with 100 mg versus -6.1 with 300 mg versus -2.4 with placebo p<0.0001). There was a >50% reduction in mean MMDs in 42% of participants with 100 mg and 49% with 300 mg, and a >75% reduction in mean MMDs in 16% of participants with 100 mg and 17% with 300 mg at 12 weeks. **1++**

When compared to topiramate in an RCT, erenumab was more effective in reducing MMDs (-5.86 erenumab vs -4.02 topiramate). There was a ≥50% reduction in MMDs in 55.4% of participants in the erenumab group compared with 31.2% in the topiramate group. Erenumab was significantly better tolerated than topiramate (used at standard doses); 10.6% of the erenumab cohort discontinued treatment compared to 38.9% on topiramate.[135] Results from a network meta-analysis comparing CGRP monoclonal antibodies to topiramate or botulinum toxin A are limited.[136] More head-to-head trials are needed before a recommendation can be made. The primary endpoint for CGRP trials is MMDs, whereas trials of botulinum toxin A used MHD therefore they are not directly comparable. **1+**

Subgroup analyses of patients with migraine and concomitant medication overuse in trials of erenumab, fremanezumab and galcanezumab demonstrated similar efficacy to those without medication overuse.[137-139] These subgroup analyses also demonstrated that the CGRP monoclonal antibodies reduced the use of acute medications. In the parent studies, medication overuse was defined as simple analgesia (eg paracetamol or NSAIDs) taken on 15 days per month, triptans on 10 days per month, and combination analgesics (including those with simple analgesia and opioids) taken on 10 days per month. Although inclusion criteria varied between studies, all of the parent studies had some restriction on the intake of opioid and/or barbiturate containing medications. **2++**

There are very limited data, in two small case series, describing outcomes of switching to a second CGRP monoclonal antibody if the first is ineffective.[140,141] Further evidence is needed before a recommendation can be made. **3**

All four CGRP monoclonal antibodies are well tolerated. Limited side effects were seen in the RCTs, and these were similar between the treatment and placebo groups.[114-118] Injection site reactions were the most common adverse event reported for the subcutaneous medications.[114-118] No increased rate of adverse event was reported in the extension studies.[130,132,133] A small number of patients in the eptinezumab studies were noted to have hypersensitivity reactions, coded as mild or moderate.[149-151] However, two patients receiving eptinezumab 300 mg in the DELIVER study suffered an anaphylactic reaction judged to be related to the study drug.[151] **1++**

Patients at high risk of ischaemic cardiovascular disease were excluded from the trials. In pooled analyses of the RCTs, 8% of participants included in the fremanezumab studies had hypertension, 17.2% of participants in galcanezumab trials were defined as having a cardiovascular risk, and in the erenumab trials between 6.6% and 9.9% had a history of vascular disorder, most commonly hypertension.[142-144] Increased risk of hypertension with erenumab use was not identified in pooled analysis of clinical trials, however, since then hypertension has been identified in a small number of patients using erenumab and the United States prescribing information has been adjusted to reflect this.[145]

There is limited evidence on the safety of use of CGRP monoclonal antibodies during pregnancy and breast feeding.[146] Until further information is available CGRP monoclonal antibodies should not be used during pregnancy or breast feeding. A washout period of 6 months is advised before trying for a pregnancy.

Prescribing CGRP monoclonal antibodies may have workload implications for service delivery. Initiation should be under the guidance of neurology or headache specialist services, and patients being treated with CGRP monoclonal antibodies will require education and monitoring. For the subcutaneous formulations, patients (or their carers) will need to have the facilities to store the medications appropriately, and administer the injection themselves. Patients will require a hospital admission (or a suitable alternative) to receive intravenous eptinezumab.

Fremanezumab, galcanezumab and eptinezumab are accepted by the SMC for use in Scotland for patients with episodic or chronic migraine (at least four headaches per month) who have had prior failure on at least three or more migraine preventative treatments. Erenumab is accepted for use with the same conditions for patients with chronic migraine, but not episodic, following economic analysis (see section 8.4).

R **Erenumab, fremanezumab, galcanezumab and eptinezumab are recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.**

R **Fremanezumab, galcenezumab and eptinezumab can be considered for the prophylactic treatment of patients with episodic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.**

✓ Use of CGRP monoclonal antibodies should only be initiated following consultation with a neurologist or headache specialist.

✓ There should be careful consideration of potential risks and benefits to patients at high risk of ischaemic cardiovascular disease before prescribing CGRP monoclonal antibodies.

✓ Use of CGRP monoclonal antibodies should be avoided during pregnancy and breastfeeding. A washout period of 6 months is advised before trying for a pregnancy.

✓ Medication overuse headache should be addressed before treatment with CGRPs *(see section 5)*. However, in patients where treatment of MOH has been unsuccessful, CGRP monoclonal antibodies should still be considered.

4.15 OCCIPITAL NERVE BLOCK

Four small RCTs measured short-term benefit (one week up to 28 days) of greater occipital nerve (GON) blocks. Each trial used different regimens. Three of the trials reported a reduction in headache frequency compared to placebo.[71-73] The other trial reported no difference, however this could have been due to the placebo group receiving a small dose of lidocaine.[74] Although they are used in headache clinics in Scotland further evidence is required before recommendations for use can be made.

1+
1-

4.16 MENSTRUAL MIGRAINE PROPHYLAXIS

The drop in oestrogen just prior to menstruation is a known trigger for migraine and in women migraine is more frequent, more severe and harder to treat just before and during menstruation.[11,12] In some women migraine only occurs (pure menstrual migraine) or predominantly occurs (menstrually-related migraine) from two days before the start of bleeding until three days after. In these women perimenstrual strategies may be used instead of, or in addition to, standard, continuous prophylaxis. The menstrual cycle has to be regular for treatment to be effective.

4.16.1 TRIPTANS

A meta-analysis found that triptans reduce the occurrence of menstrual migraine (both menstrually-related migraine and pure menstrual migraine) compared to placebo. Table 2 shows the numbers needed to treat for reduction of menstrual migraine with triptans.[34]

Table 3: Numbers needed to treat for reduction of menstrual migraine with triptans[34]

Triptan	NNT	Number of patients
Frovatriptan 2.5 mg daily	7.22	633
Frovatriptan 2.5 mg twice daily	3.90	584
Naratriptan 1 mg twice daily*	7.99	392
Zolmitriptan 2.5 mg twice daily	4.98	80
Zolmitriptan 2.5 mg 3 times daily	2.52	83
*1 mg twice daily naratriptan is not available in the UK. NNT for 2.5 mg daily was not available		

Frovatriptan once daily and twice daily was also effective in reducing the secondary outcomes of migraine severity and rescue medication needed. Drug-related adverse events were low and similar to placebo for both doses. Zolmitriptan 2.5 mg twice and three-times daily also reduced the need for rescue medication and drug-related adverse events were similar for treatment and placebo in two small trials.[34]

1+

A pilot open-label study which assessed frovatriptan versus transdermal oestrogens or naproxen found that the incidence of menstrual migraine was significantly lower when using frovatriptan than the other therapies.[82]

1+

R **Frovatriptan** (2.5 mg twice daily) **should be considered as a prophylactic treatment in women with perimenstrual migraine from two days before until three days after bleeding starts.**

R **Zolmitriptan** (2.5 mg three times daily) **or naratriptan** (2.5 mg twice daily) **can be considered as alternatives to frovatriptan as prophylactic treatment in women with perimenstrual migraine from two days before until three days after bleeding starts.**

✓ Women with menstrual-related migraine who are using triptans at other times of the month should be advised that additional perimenstrual prophylaxis increases the risk of developing medication overuse headache.

4.16.2 PROSTAGLANDIN INHIBITORS

While there is a small amount of evidence that mefenamic acid is effective for acute treatment of patients with menstrual migraine no trials on its use in perimenstrual prophylaxis were identified.[82] **1+**

4.16.3 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

One RCT reported significant headache improvement with naproxen, reaching over 50% after three months, however there was little difference when compared to placebo.[82] **1+**

4.16.4 OESTROGENS

One small crossover RCT (n=37) assessing perimenstrual oestradiol supplement, applied from the tenth day after the first day of peak fertility until the second full day of menstruation, reported a 22% reduction in migraine days but was followed by a rebound 40% increase in the five days following oestradiol.[82] **1+**

4.16.5 HORMONAL PROPHYLAXIS

Three studies were identified on the use of combined oral contraception. All reported benefit in menstrual migraine prophylaxis, but were of insufficient quality to be conclusive.[82] **1+**

5 Medication-overuse headache

Most medication-overuse headache is a complication of migraine.[6] Frequent use of acute medications for the treatment of migraine increases the frequency and intensity of headache. The treatment becomes the cause rather than the cure and a vicious cycle of increased medication use and increasing headache ensues. In this group of patients withdrawing the overused medication can reduce the headache frequency and intensity again. Withdrawing overused medication is often associated with transient worsening of headache frequency and intensity and patients should be warned to expect this.

Risk factors for the development of MOH include frequent headache, frequent acute medication use, another painful condition and psychiatric comorbidity.[6] Use of triptans, ergots, combination analgesics and/or opioids 10 or more days per month and simple analgesics 15 or more days per month is accepted to cause MOH (*see Annex 2*).[5] Importantly, not all patients overusing acute treatments have MOH and some just have poorly-treated migraine.[6]

The best treatment for MOH is not clear. A range of small RCTs, non-comparative observational, and retrospective studies report that various strategies are effective in reducing MOH:

- abrupt withdrawal alone (either by simple advice or by a structured detoxification programme)[83-86]
- abrupt withdrawal with prophylaxis[84,86-92]
- prophylaxis without withdrawal.[93-96]

1+
3

There is a lack of comparative studies to determine whether all patients should undergo acute medication withdrawal (either with simple advice or a detoxification programme) before starting preventative medication and whether preventative therapy should be started early or delayed until after the effect of completing withdrawal/detoxification is determined. The length of withdrawal period before starting preventative medication has not been clearly defined.

There is a lack of evidence regarding whether detoxication is best achieved in primary care, specialised (neurology) outpatient care or in-hospital care. A small open study did not find any differences in rates of complete drug withdrawal or headache frequency in patients attending as in- or outpatients, and recommended outpatient withdrawal in the first instance for patients with uncomplicated MOH.[97] Patients with complex MOH may benefit from multidisciplinary treatment programmes.[84] Results from an RCT of 137 patients with complicated MOH showed that inpatient withdrawal may be more effective than advice alone or an outpatient strategy.[86] Comorbidities may reduce the chance of successful withdrawal.[98]

1+
2+
3

For prophylactic therapy, there is evidence to support the use of botulinum toxin A without the need for abrupt withdrawal of overused medication.[99-101] Botulinum toxin A is not, however, accepted for use by the SMC for this indication (*see section 8.4*). Small RCTs have also reported a reduction in headache days using topiramate or valproate.[93,102] In a non-comparative observational study, patients who had previously not responded to prophylactic treatment responded to the previously ineffective treatment if reintroduced once medication overuse had been addressed.[44]

1++
1+
3

Two well-conducted, small RCTs comparing prednisolone with placebo and one comparing prednisolone with celecoxib found no difference in headache severity during the withdrawal period.[103-105] Given that steroids are associated with side effects and there is no evidence of benefit, prednisolone should not be used routinely for the management of patients with MOH.

1++

Naproxen is often used in clinical practice as a transitional treatment. No evidence was identified for this use in patients with MOH.

No studies were identified on the use of greater occipital nerve blocks, or combinations of triptans, analgesics, NSAIDs or opioids for the management of patients with MOH.

R **In patients overusing acute treatment, medication overuse should be addressed.**

R **The choice of strategy to address medication overuse should be tailored to the individual patient and may be influenced by comorbidities. Strategies include:**

- **abrupt withdrawal alone and preventative treatment may then be considered after a delay**
- **abrupt withdrawal and immediately starting preventative treatment**
- **starting a preventative treatment without withdrawal.**

✓ Consider withdrawing regular opioids gradually.

R **Prednisolone should not be used routinely in the management of patients with medication-overuse headache.**

6 Devices for migraine therapy

Devices may offer an alternative, or an addition, to pharmacological therapies, but few trials have been conducted on their efficacy and safety.[106,107] A small number of trials are ongoing.

6.1 VAGUS NERVE STIMULATION

One small RCT on the safety and tolerability of non-invasive vagus nerve stimulation (VNS) for the prevention of migraine reported no safety issues and tolerability was comparable to sham treatment. The study was not sufficiently powered to determine efficacy.[108] No further RCTs were identified. **1+**

6.2 TRANSCUTANEOUS SUPRAORBITAL NERVE STIMULATION

No RCTs were identified on the use of transcutaneous supraorbital nerve stimulation (TSNS) for patients with either acute or chronic migraine.

6.3 TRANSCRANIAL MAGNETIC STIMULATION

Only one RCT was identified in the use of transcranial magnetic stimulation (TMS) for the acute treatment of patients with migraine. Following treatment for one migraine, 39% of patients had a pain-free response at two hours compared to 22% of patients given sham treatment. There was a therapeutic gain of 17%.[109] **1++**

Two small RCTs reported conflicting results on the efficacy of TMS for migraine prevention. One trial reported benefit at one month, while another showed the sham treatment was superior after eight weeks.[110,111] Further, larger trials are required. **1+**

7 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing migraine with patients and carers and in guiding the production of locally-produced information materials.

7.1 PUBLICATIONS FROM SIGN

SIGN patient versions of guidelines are documents that 'translate' guideline recommendations and their rationales, originally developed for healthcare professionals, into a form that is more easily understood and used by patients and the public. They are intended to:

- help patients and carers understand what the latest evidence supports around diagnosis, treatment and self care
- empower patients to participate fully in decisions around management of their condition in discussion with healthcare professionals
- highlight for patients where there are areas of uncertainty.

A copy of the patient version of this guideline is available from www.sign.ac.uk/assets/pat155.pdf. Patients may also find the following booklet helpful: Managing chronic pain: a booklet for patients and carers. SIGN (2013) www.sign.ac.uk/assets/pat136.pdf

7.2 SOURCES OF FURTHER INFORMATION

Association of British Neurologists
www.theabn.org

The Association of British Neurologists aims to promote excellent standards of care and champion high-quality education and world-class research in neurology.

The British Association for the Study of Headache
www.bash.org.uk

The British Association for the Study of Headache (BASH) is the United Kingdom national society member of the International Headache Society (IHS) and the European Headache Federation (EHF). It is open to all healthcare professionals with an interest in headache.

The Migraine Trust
52–53 Russell Square, London, WC1B 4HP
Tel: 0808 802 0066 (Mon-Fri, 10am-4pm)
www.migrainetrust.org • Email: www.migrainetrust.org/about-us/contact-us

The Migraine Trust charity aims to improve the lives of people with migraine through research and education.

Migraine Action
www.migraine.org.uk

Migraine Action is a national advisory and support charity for people affected by migraine.

Toolkit on the risks of valproate medicines in female patients
www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients

This website provides guidance for healthcare professionals and patients on prescribing and dispensing valproate.

7.3 CHECKLIST FOR PROVISION OF INFORMATION TO PATIENTS

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Initial consultation with GP	• Exclude a serious cause for headache by appropriate history and examination. • If time allows: o Make a diagnosis if possible (remember the majority of patients with disabling headache will have migraine). o Consider if the headache/migraine is episodic (<15 days a month) or chronic (>15 days a month). o If a migraine diagnosis has been made, consider providing appropriate information leaflets or web addresses on migraine and its treatment, potential side effects and medication overuse headache (see section 7.1). o Ask the patient to complete a migraine diary. The diary may include: o all headaches and their severity o medication taken o menstruation o normal activities missed. Possible additional information: o food and drink o sleep times o exercise o stressful days o complementary therapies used. Ask what medication and what doses the patient has tried so far. Consider acute and/or prophylactic treatment where appropriate. If appropriate, give the patient an explanation that they have a primary headache called migraine.
First follow up with GP (after 2–8 weeks)	• Consolidate the first consultation which may involve repeating some of the initial consultation. • Find out what medication and what doses the patient has tried so far. • Consider the possibility of medication overuse and discuss the withdrawal of drugs where necessary. • Consider the impact the headaches have on the patient's work, education, family and social life. • Consider acute and/or prophylactic treatment where appropriate. • Give clear advice on timing of acute treatment. • Check that the patient has been given appropriate information leaflets or web addresses on migraine. • Look at any migraine diary they have completed and, if appropriate, ask them to continue it until the next review with any changes, if needed.

Follow-up review with GP (after 6–8 weeks)	• Review the migraine diary for frequency and severity of headaches, medication and triggers for migraine. • Discuss lifestyle improvements. • If appropriate discuss the impact headaches have on education, job, family, social life and holidays. • If appropriate discuss other factors, such as pre- and postpregnancy planning. • Review current medication and any changes needed. • Tell the patient that other treatments are available should they be needed but several drugs may need to be tried to find the best medication and other health problems need to be taken into account.
Further follow up reviews with GP	• As above. • Review of current medication should include dose, side effects and headache recurrence if it occurs after initial acute treatment. • Consider whether referral to a hospital specialist is required, eg because of treatment failure or uncertain diagnosis.

8 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.

8.1 IMPLEMENTATION STRATEGY

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.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

8.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full cost-impact analysis.

Botulinum toxin A injections require to be administered by appropriately trained personnel in hospital specialist centres. This may have implications for service delivery as well as for the patient. The decision to treat with botulinum toxin A may require additional consultation time and additional time and resource to administer the treatment.[70]

8.3 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 possible areas to audit to assist with the implementation of this guideline:

- GPs to review patients with migraine ordering on average 10 or more doses of triptan per month in their practice to identify patients who are not controlled or at risk of MOH
- An audit of the percentage of patients who have used three or more preventers prior to referral to a secondary headache unit.

8.4 ADVICE FOR NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM

Sumatriptan succinate (Imigran Radis®) film-coated tablets are accepted for use within NHSScotland for acute relief of migraine attacks, with or without aura, provided there is a clear diagnosis of migraine (October 2004).

www.scottishmedicines.org.uk/SMC_Advice/Advice/Sumatriptan_succinate__Imigran_Radis__174__/Sumatriptan_succinate__Imigran_Radis__

Frovatriptan (Migard) is accepted for use within NHSScotland for treatment of the headache phase of migraine attacks with or without aura (February 2004).

www.scottishmedicines.org.uk/SMC_Advice/Advice/Frovatriptan__Migard_/Frovatriptan__Migard_

Topiramate (Topamax) is accepted for restricted use within NHSScotland for the prophylaxis of migraine headache in adults. It should be restricted to patients who have not responded to prophylactic treatment with at least one other agent (August 2006).

www.scottishmedicines.org.uk/SMC_Advice/Advice/topiramate_25__50mg_tablets__25__50mg_sprinkle_capsules__Topamax_/topiramate_25__50mg_tablets__25__50mg_sprinkle_capsules__Topamax_

Advice regarding specialist prescribing has been superseded by the prescribing advice in the summary of product characteristics which no longer includes this requirement. www.medicines.org.uk/emc/medicine/6768

Botulinum toxin A (Botox®) is accepted for restricted use for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine) whose condition has failed to respond to ≥3 prior oral prophylactic treatments, where medication overuse has been appropriately managed (February 2017).

www.scottishmedicines.org.uk/SMC_Advice/Advice/692_11_botulinum_toxin_type_a_BOTOX/botulinum_toxin_A_Botox_2nd_Resub

Erenumab (Aimovig®) is accepted for restricted use within NHSScotland for the prophylaxis of migraine in adults who have at least four migraine days per month. It is restricted to patients with chronic migraine and in whom at least three prior prophylactic treatments have failed (April 2019).

www.scottishmedicines.org.uk/medicines-advice/erenumab-aimovig-full-submission-smc2134/

Fremanezumab (Ajovy®) is accepted for restricted use within NHSScotland for the prophylaxis of migraine in adults who have at least four migraine days per month. It is restricted to the treatment of patients with chronic and episodic migraine who have had prior failure on three or more migraine preventive treatments (December 2019).

www.scottishmedicines.org.uk/medicines-advice/fremanezumab-ajovy-full-smc2226/

Galcanezumab (Emgality®) is accepted for restricted use within NHSScotland for the prophylaxis of migraine in adults who have at least four migraine days per month. It is restricted to the treatment of patients with chronic and episodic migraine who have had prior failure on three or more migraine preventive treatments (March 2021).

www.scottishmedicines.org.uk/medicines-advice/galcanezumab-emgality-full-smc2313/

Eptinezumab (Vyepti®) is accepted for restricted use within NHSScotland for the prophylaxis of migraine in adults who have at least four migraine days per month. It is restricted to the treatment of patients with chronic and episodic migraine who have had prior failure on three or more migraine preventive treatments (February 2023).

www.scottishmedicines.org.uk/medicines-advice/eptinezumab-vyepti-abb-smc2547

9 The evidence base

9.1 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 an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2011–2016. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two Evidence and Information Scientists using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

For the update a search was conducted using Medline, Embase and the Cochrane Library, year range 2016–2022.

The search strategies are available on the SIGN website, www.sign.ac.uk

9.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to patients with migraine. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.

9.1.2 LITERATURE SEARCH FOR COST-EFFECTIVENESS EVIDENCE

The guideline development group identified key questions with potential cost-effectiveness implications, based on the following criteria, where it was judged particularly important to gain an understanding of the additional costs and benefits of different treatment strategies:

- treatments which may have a significant resource impact
- opportunities for significant disinvestment or resource release
- the potential need for significant service redesign
- cost-effectiveness evidence could aid implementation of a recommendation.

A systematic literature search for economic evidence for these questions was carried out by a SIGN Evidence and Information Scientist covering the years 2011–2016. Databases searched include Medline, Embase and NHS Economic Evaluation Database (NHS EED). Each of the selected papers was evaluated by a Health Economist, and considered for clinical relevance by guideline group members.

Interventions are considered to be cost effective if they fall below the commonly-accepted UK threshold of £20,000 per Quality-Adjusted Life Year (QALY).

9.2 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 (*see Annex 1)*. The following areas for further research have been identified:

- RCTs to determine the efficacy of TCAs in patients with chronic and frequent episodic migraine. There is a need for longer duration trials with head-to-head comparisons with other preventative treatments. The optimum dose needs to be established. Comparisons of the side-effect profile and effectiveness of amitriptyline and nortrityline are also needed.
- RCTs to determine the efficacy of lamotrigine in the prophylactic treatment of aura symptoms in migraine.
- Well-designed RCTs of pregabalin in patients with episodic and chronic migraine.

- RCTs to determine the role of levetiracetam in migraine prophylaxis, particularly because of its relative lack of adverse effects and lack of interactions with other drug therapies.
- RCTs comparing flunarazine with placebo, between drugs in this class, and with other pharmacological therapies for the prophylactic treatment of patients with migraine.
- RCTs comparing candesartan with placebo, between drugs in this class, and with other pharmacological therapies for the prophylactic treatment of patients with migraine.
- Studies into the optimum treatment regime and a clear GON protocol (ie inclusion of steroid, volume and site of injection).
- RCTs to determine the efficacy and safety of combination therapies for the prophylactic treatment of patients with chronic migraine.
- RCTs to determine the efficacy of continuous combined oral contraceptives for the prophylactic treatment of patients with perimenstrual migraine.
- RCTs directly comparing the three different strategies for treating patients with MOH; abrupt withdrawal alone, withdrawal with immediate prophylaxis, prophylaxis without withdrawal.
- RCTs on the use of NSAIDs as a transitional treatment for patients with MOH.
- RCTs to determine the efficacy of devices (VNS, TSNS, TMS) for acute therapy or the prophylactic treatment of patients with migraine.
- RCTs on the efficacy and safety of switching from one CGRP monoclonal antibody to another if the first agent is ineffective.
- Direct comparison RCTs between different CGRPs and botulinum toxin A.
- Studies of CGRP monoclonal antibodies in different populations and age groups, for example patients with cardiovascular risk factors.

9.3 REVIEW AND UPDATING

This guideline was issued in 2018 and was updated in 2022 and 2023. The review history, and any updates to the guideline in the interim period, are noted in the update report, which is available in the supporting material section for this guideline on the SIGN website: www.sign.ac.uk

Comments on new evidence that would update this guideline are welcome and should be sent to the SIGN Executive, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB (email: sign@sign.ac.uk).

10 Development of the guideline

10.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. 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

This guideline was developed according to the 2015 edition of SIGN 50 and the update adhered to the 2019 edition.

10.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Callum Duncan *(Chair)*	*Consultant Neurologist, Aberdeen Royal Infirmary*
Dr Francisco Javier Carod Artal	*Consultant Neurologist, Raigmore Hospital, Inverness*
Ms Arlene Coulson	*Neurology Specialist Clinical Pharmacist, NHS Tayside*
Mr Brian O'Toole	*Health Economist, Healthcare Improvement Scotland*
Dr Shona Scott	*Neurology Registrar, Western General Hospital, Edinburgh*
Dr Johann Selvarajah	*Consultant Neurologist, Queen Elizabeth University Hospital, Glasgow*
Dr Sandeep Sharma	*General Practitioner, Bonnybank Medical Practice, Bonnybridge*
Dr Carolyn Sleith	*Evidence and Information Scientist, Healthcare Improvement Scotland*
Ms Ailsa Stein	*Programme Manager, SIGN*
Dr David PB Watson	*General Practitioner, Hamilton Medical Group, Aberdeen*
Ms Katrine West	Patient Representative, Edinburgh

Updates:

Dr Callum Duncan *(Chair and main author)*	*Consultant Neurologist, Aberdeen Royal Infirmary*
Dr Krishna Dani *(Main author)*	*Consultant Neurologist, Queen Elizabeth University Hospital, Glasgow*
Dr Francisco Javier Carod Artal	*Consultant Neurologist, Raigmore Hospital, Inverness*
Ms Arlene Coulson	*Neurology Specialist Clinical Pharmacist, NHS Tayside*
Dr Shona Scott	*Neurology Registrar, Western General Hospital, Edinburgh*
Dr Sandeep Sharma	*General Practitioner, Bonnybank Medical Practice, Bonnybridge*
Ms Ailsa Stein	*Programme Manager, SIGN*
Ms Katrine West	*Patient Representative, Edinburgh*
Dr David PB Watson	*General Practitioner, Hamilton Medical Group, Aberdeen*

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. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website www.sign.ac.uk

Mr Euan Bremner	*Project Officer*
Ms Juliet Brown	*Evidence and Information Scientist, Healthcare Improvement Scotland*
Ms Karen Graham	*Patient and Public Involvement Adviser*
Ms Karen King	*Distribution and Office Co-ordinator*
Mr Stuart Neville	*Publications Designer*
Ms Gaynor Rattray	*Guideline Co-ordinator*

10.3 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Ms Catherine Gillies	*Headache Nurse Practitioner, Queen Elizabeth University Hospital, Glasgow*
Ms Jennifer Gray	*Specialist Clinical Pharmacist in Neurosurgery, Ninewells Hospital, Dundee*
Mr Conor McKay	*Patient Representative, Inverurie*

10.4 CONSULTATION AND PEER REVIEW

10.4.1 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 15 June 2017 and was attended by 45 representatives of 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.

10.4.2 SPECIALIST REVIEWERS

This guideline was 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. A report of the peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Fayyaz Ahmed	*Consultant Neurologist and Honorary Senior Lecturer, Hull York Medical School*
Dr Anish Bahra	*Consultant Neurologist, National Hospital for Neurology and Neurosurgery, London*
Dr Anne Coker	*General Practitioner with a Special Interest in Headache, Dundee*
Dr Richard Davenport	*Consultant Neurologist, Western General Hospital, Edinburgh*
Dr Kay Kennis	*General Practitioner with a Special Interest in Headache, Bradford*
Dr David Kernick	*General Practitioner with a Special Interest in Headache, Exeter*
Professor Anne MacGregor	*Consultant Gynaecologist, The Royal London Hospital*
Dr Mireia Moragas Garrido	*Consultant Neurologist, Western General Hospital, Edinburgh*
Ms Lesley Murray	*Advanced Pharmacist for Neurology, NHS Greater Glasgow and Clyde*

Dr Richard Peatfield	*Consultant Neurologist, Charing Cross Hospital, London*
Dr Alok Tyagi	*Consultant Neurologist, Queen Elizabeth University Hospital, Glasgow*
Ms Rebecca Wicks	*Clinical Support Pharmacist, Right Medicine Pharmacy, Stirling*
Dr Ann Wilkinson	*Patient representative, Burton-on-Trent*

Update, September 2022:

Dr Richard Davenport	*Consultant Neurologist, Royal Infirmary of Edinburgh*
Ms Christine Hepburn	*Principal Pharmaceutical Analyst, Scottish Medicines Consortium*
Dr Anne-Marie Logan	*Consultant Physiotherapist in Headache, St George's University Hospitals NHS Foundation Trust, London*
Ms Fiona Milligan	*Public Partner, Healthcare Improvement Scotland*
Dr Alok Tyagi	*Consultant Neurologist, Queen Elizabeth University Hospital, Glasgow*
Dr David Watson	*General Practitioner, Hamilton Medical Group, Aberdeen*

10.4.3 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 Jenny Bennison	*Royal College of General Practitioners*
Mr Gary Cook	*Royal Pharmaceutical Society*
Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Professor John Kinsella	*Chair of SIGN; Co-Editor*
Ms Karen Macpherson	*Lead Health Services Researcher, Healthcare Improvement Scotland*
Dr David Stephens	*Royal College of General Practitioners*

Update, September 2022:

Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Dr Safia Qureshi	*Director of Evidence, Healthcare Improvement Scotland*
Professor Angela Timoney	*Chair of SIGN; Co-Editor*

All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website www.sign.ac.uk

Abbreviations

CGRP	calcitonin gene-related peptide
CI	confidence interval
COC	combined oral contraception
FDA	Food and Drug Administration
GMC	General Medical Council
GON	greater occipital nerve
GP	general practitioner
ICER	incremental cost-effectiveness ratio
ICHD	International Classification of Headache Disorders
MA	marketing authorisation
MHD	monthly migraine headache days
MHRA	Medicines and Healthcare products Regulatory Agency
MMD	monthly migraine days
MOH	medication-overuse headache
MRM	menstrually-related migraine
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
NRS	numerical rating score
NSAID	Non-steroidal anti-inflammatory drug
OR	odds ratio
PREEMPT	Phase III REsearch Evaluating Migraine Prophylaxis Therapy
QALY	quality-adjusted life year
RCT	randomised controlled trial
RR	relative risk
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMD	standardised mean difference
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TMS	transcranial magnetic stimulation
TSNS	transcutaneous supraorbital nerve stimulation
UK	United Kingdom
VNS	vagus nerve stimulation

Annex 1

Key questions used to develop the guideline

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Guideline section	Key question	
3	1.	What is the clinical and cost effectiveness of abortive treatments for adults with acute migraine? a. Triptans b. Aspirin c. Non-steroidal anti-inflammatory drugs (NSAIDs) (high dose aspirin, ibuprofen, naproxen) d. Combinations of triptans and NSAIDS or aspirin and paracetamol e. Antiemetics (prochlorperazine, domperidone, metoclopramide) f. Steroids (prednisolone, methylprednisolone, dexamethasone) g. Paracetamol (acetominophen) Comparison: placebo, other pharmacological therapies, device therapies Outcomes: pain free, pain free within two hours, sustained pain relief at 24 hours, adverse effects, QALYs, ICER Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension stroke/cerebrovascular risk.
6	2.	What is the clinical and cost effectiveness of treatment with devices for adults with acute migraine? a. Gamma core (vagal nerve stimulation) b. Cefaly (transcutaneous supraorbital nerve stimulation) c. Transcutaneous/transcranial magnetic stimulation Comparison: placebo, other devices, pharmacological treatment Outcomes: pain free within two hours, adverse effects, QALYs, ICER Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension stroke/cerebrovascular risk.

4	3.	What is the clinical and cost effectiveness of preventative treatment for adults with episodic or chronic migraine? a. Beta blockers (atenolol, metoprolol, propranolol, bisoprolol, timolol, nadolol) b. Tricyclic antidepressants (amitriptyline, nortriptyline, dosulepin) c. Serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine) d. Antiepileptics (topiramate, valproate, zonisamide, pregabalin, levitiracetam, gabapentin) e. Pizotifen f. Calcium channel blockers (flunarizine, verapamil) g. Angiotensin-II receptor blockers (candesartan) h. Angiotensin-converting enzyme inhibitors (lisinopril, ramipril) i. Calcitonin gene related peptide antagonists j. Occipital nerve block k. Botulinum toxin A l. Perimenstrual prophylaxis (oestrogen gel, prostaglandin inhibitors: naproxen, mefenamic acid, frovatriptan, naratriptan, zolmitriptan) Comparison: placebo, other pharmacological therapies, device therapies Outcomes: 30% or 50% reduction in number of headache days per cycle, reduction in number of migraine episodes, days or headache days, reduction in migraine disability assessment questionnaire (MIDAS, HIT6) scores, adverse effects, QALYs, ICER Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension stroke/cerebrovascular risk.
6	4.	What is the clinical and cost effectiveness of preventative treatment with devices for adults with episodic or chronic migraine? a. Gamma core (vagal nerve stimulation) b. Cefaly (transcutaneous supraorbital nerve stimulation) c. Transcutaneous magnetic stimulation Comparison: placebo or usual care, other devices, pharmacological treatment Outcomes: 30% or 50% reduction in number of headache days per cycle, reduction in number of migraine episodes, days or headache days, reduction in migraine disability assessment questionnaire (MIDAS, HIT6) scores, adverse effects, QALYs, ICER Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension, stroke/cerebrovascular risk.
5	5.	What strategies are effective in the management of adults with medication overuse headache? a. Stopping b. Stopping and prevention c. Prevention d. Adjunctive therapy: steroids, naproxen e. Greater occipital nerve (GON) blocks f. Combinations of triptans, analgesics, NSAIDS, opioids Comparison: other strategies Outcomes: 30% or 50% reduction in number of headache days per cycle, reduction in number of migraine episodes, days or headache days, reduction in migraine disability assessment questionnaire (MIDAS, HIT6) scores, adverse effects, QALYs, ICER Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension, stroke/cerebrovascular risk.

Annex 2

Diagnostic criteria

International Classification of Headache Disorders, 3rd edition (beta version)[5]

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 five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hr (untreated or unsuccessfully treated)
C. Headache has at least two of the following four 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 better accounted for by another ICHD-3 diagnosis.

1.2 Migraine with aura

Description:
Recurrent attacks, lasting minutes, of unilateral fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least two of the following four characteristics:

1. at least one aura symptom spreads gradually over ≥5 min, and/or two or more symptoms occur in succession
2. each individual aura symptom lasts 5–60 min
3. at least one aura symptom is unilateral
4. the aura is accompanied, or followed within 60 min, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

1.3 Chronic migraine

Description: Headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.

Diagnostic criteria:

A. Headache (tension-type-like and/or migraine-like) on 15 days per month for >3 months and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura

C. On 8 days per month for >3 months, fulfilling any of the following:

1. criteria C and D for 1.1 Migraine without aura

2. criteria B and C for 1.2 Migraine with aura

3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.

1.4.1 Status migrainosus

Description: A debilitating migraine attack lasting for more than 72 hours.

Diagnostic criteria:

A. A headache attack fulfilling criteria B and C

B. Occurring in a patient with 1.1 Migraine without aura and/or 1.2 Migraine with aura, and typical of previous attacks except for its duration and severity

C. Both of the following characteristics: 1. unremitting for >72 hours, 2. pain and/or associated symptoms are debilitating

D. Not better accounted for by another ICHD-3 diagnosis.

8.2 Medication-overuse headache

Description: Headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more, or 15 or more days per month, depending on the medication) for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped.

General comment: In the criteria set out below for the various subtypes, the specified numbers of days of medication use considered to constitute overuse are based on expert opinion rather than on formal evidence.

Diagnostic criteria:

A. Headache occurring on 15 days per month in a patient with a pre-existing headache disorder

B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache:

1. Triptans, ergots, opiods, combination analgesics or multiple drug classes - regular intake of one or more triptans, in any formulation, on 10 days per month for >3 months

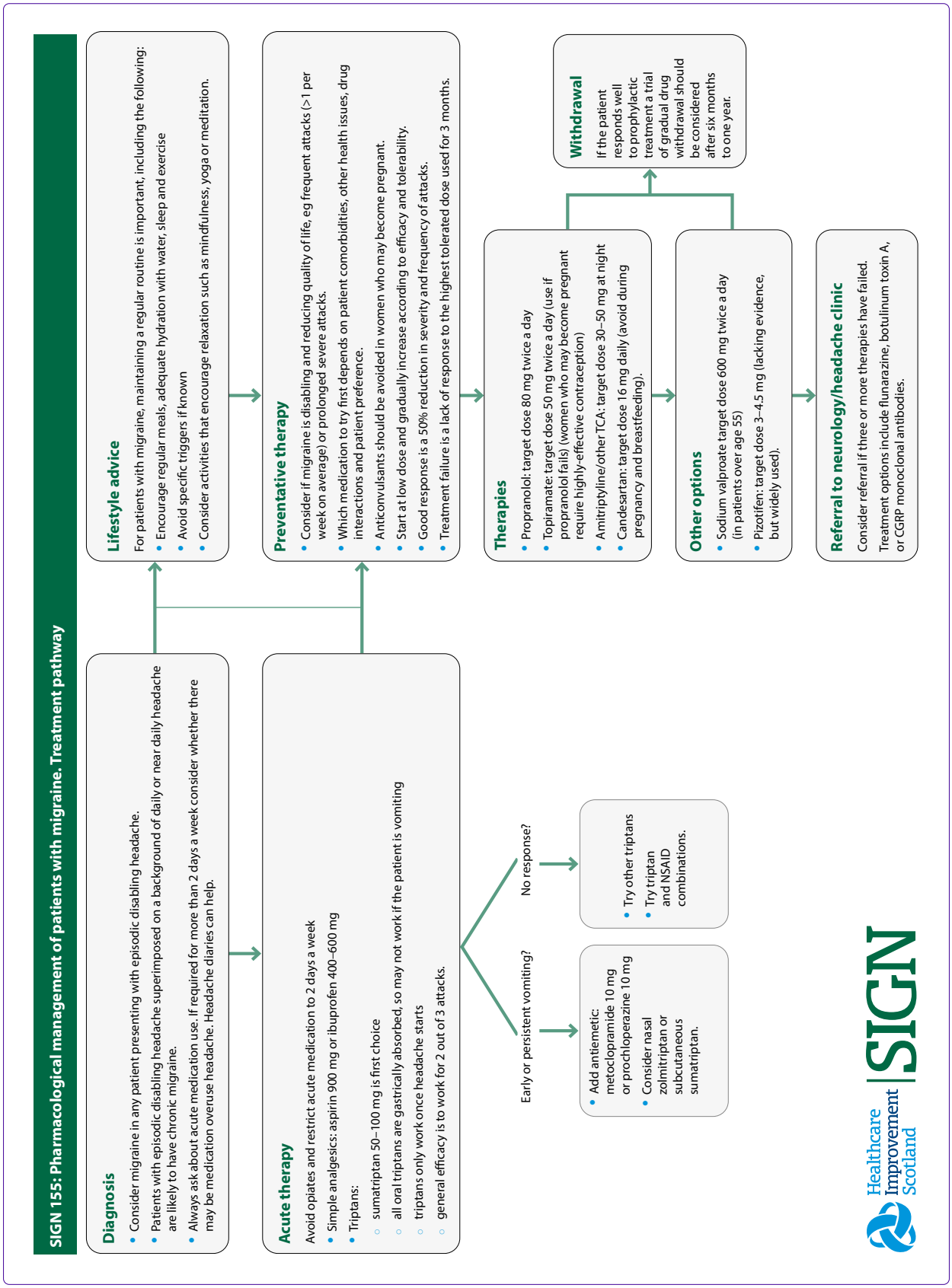
2. Simple analgesics - regular intake of one or more triptans, in any formulation, on 15 days per month for >3 months

C. Not better accounted for by another ICHD-3 diagnosis.

Annex 3

Treatment pathway

This pathway is drawn from evidence identified in the guideline, the British National Formulary[17] and the clinical experience of the guideline development group.



References

1 Boardman HF, Thomas E, Croft PR, Millson DS. Epidemiology of headache in an English district. Cephalalgia 2003;23(2):129-37.

2 Larner AJ. Guidelines for primary headache disorders in primary care: an "intervention" study. Headache Care 2006;3(1):1-2.

3 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.

4 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.

5 Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):629-808.

6 Diener HC, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. Nat Rev Neurol 2016;12(10):575-83.

7 Westergaard ML, Hansen EH, Glumer C, Olesen J, Jensen RH. Definitions of medication-overuse headache in population-based studies and their implications on prevalence estimates: a systematic review. Cephalalgia 2014;34(6):409-25.

8 Steiner TJ, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. J Headache Pain 2013;14:1.

9 Steiner TJ, Stovner LJ, Vos T. GBD 2015: migraine is the third cause of disability in under 50s. J Headache Pain 2016;17(1):104.

10 All-Party Parliamentary Group on Primary Headache Disorders (APPGPHD). Headache Disorders - not respected, not resourced: A Report of the All-Party Parliamentary Group on Primary Headache Disorders (APPGPHD). 2010. [cited 22 Nov 2017]. Available from url: http://www.migrainetrust.org/wp-content/uploads/2015/12/2010Mar-APPGPHD_REPORT_Headache_Disorders-NotRespNotReso.pdf

11 Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol 2017;16(1):76-87.

12 MacGregor EA. Migraine, the menopause and hormone replacement therapy: a clinical review. J Fam Plann Reprod Health Care 2007;33(4):245-9.

13 Schreiber CP, Hutchinson S, Webster CJ, Ames M, Richardson MS, Powers C. Prevalence of migraine in patients with a history of self-reported or physician-diagnosed "sinus" headache. Arch Intern Med 2004;164(16):1769-72.

14 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.

15 Faculty of Sexual and Reproductive Health. UK medical eligibility criteria for contraceptive use (UKMEC). Faculty of Sexual and Reproductive Health; 2016. [cited 22 Nov 2017]. Available from url: https://www.fsrh.org/documents/ukmec-2016/final-book-july-2017.pdf

16 Headache Classification Committee, Olesen J, Bousser MG, Diener HC, Dodick D, First M, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 2006;26(6):742-6.

17 Joint Formulary Committee. Guidance on prescribing. In: British National Formulary (online) London: BMJ Group and Pharmaceutical Press. [cited 22 Nov 2017]. Available from url: https://www.medicinescomplete.com/mc/bnf/current/PHP97234-guidance-on-prescribing.htm

18 General Medical Council (GMC). Good practice in prescribing and managing medicines and devices. London: General Medical Council; 2013. [cited 22 Nov 2017]. Available from url: http://www.gmc-uk.org/Prescribing_guidance.pdf_59055247.pdf

19 Medicines and Healthcare products Regulatory Agency. Off-label or unlicensed use of medicines: prescribers' responsibilities. Drug safety update 2009;2(9):6-7.

20 British Association for the Study of Headache (BASH). Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. Hull; 2010. [cited 22 Nov 2017]. Available from url: http://www.bash.org.uk/wp-content/uploads/2012/07/10102-BASH-Guidelines-update-2_v5-1-indd.pdf

21 Kirthi V, Derry S, Moore RA. Aspirin with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2013, Issue 4.

22 Briggs G, Freeman R, Towers C, Forinash A. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 11th edition. Philadelphia, Pa: Lippincott Williams & Wilkins; 2017.

23 Rabbie R, Derry S, Moore RA. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2013, Issue 4.

24 Law S, Derry S, Moore RA. Naproxen with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2013, Issue 10.

25 Derry S, Rabbie R, Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2013, Issue 4.

26 Schaefer C, Peters PWJ, RK. M. Drugs During Pregnancy and Lactation. 3rd edition. London: Academic Press; 2014.

27 Derry S, Moore RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2013, Issue 4.

28 Friedman BW, Mulvey L, Esses D, Solorzano C, Paternoster J, Lipton RB, et al. Metoclopramide for acute migraine: A dose-finding randomized clinical trial. Ann Emerg Med 2011;57(5):475-82.

29 Kelly AM, Walcynski T, Gunn B. The relative efficacy of phenothiazines for the treatment of acute migraine: a meta-analysis. Headache 2009;49(9):1324-32.

30 Friedman BW, Esses D, Solorzano C, Dua N, Greenwald P, Radulescu R, et al. A Randomized Controlled Trial of Prochlorperazine Versus Metoclopramide for Treatment of Acute Migraine. Ann Emerg Med 2008;52(4):399-406.

31 Bird S, Derry S, Moore RA. Zolmitriptan for acute migraine attacks in adults. Cochrane Database of Systematic Reviews 2014, Issue 5.

32 Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. Headache 2015;55(Suppl 4):221-35.

33 Derry CJ, Derry S, Moore RA. Sumatriptan (all routes of administration) for acute migraine attacks in adults - overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2014, Issue 5.

34 Hu Y, Guan X, Fan L, Jin L. Triptans in prevention of menstrual migraine: a systematic review with meta-analysis. J Headache Pain 2013;14:7.

35 Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headache: evidence-based review. Neurology 2008;70(17):1555-63.

36 Roberto G, Raschi E, Piccinni C, Conti V, Vignatelli L, D'Alessandro R, et al. Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: systematic review of observational studies. Cephalalgia 2015;35(2):118-31.

37 Evans RW, Tepper SJ, Shapiro RE, Sun-Edelstein C, Tietjen GE. The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. Headache 2010;50(6):1089-99.

38 Marchenko A, Etwel F, Olutunfese O, Nickel C, Koren G, Nulman I. Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis. Headache 2015;55(4):490-501.

39 Spielmann K, Kayser A, Beck E, Meister R, Schaefer C. Pregnancy outcome after anti-migraine triptan use: A prospective observational cohort study. Cephalalgia 2017;Epub ahead of print.

40 Wood ME, Lapane K, Frazier JA, Ystrom E, Mick EO, Nordeng H. Prenatal Triptan Exposure and Internalising and Externalising Behaviour Problems in 3-Year-Old Children: Results from the Norwegian Mother and Child Cohort Study. Paediatr Perinat Epidemiol 2016;30(2):190-200.

41 Law S, Derry S, Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. Cochrane Database of Systematic Reviews 2016, Issue 4.

42 Huang Y, Cai X, Song X, Tang H, Huang Y, Xie S, et al. Steroids for preventing recurrence of acute severe migraine headaches: a meta-analysis. Eur J Neurol 2013;20(8):1184-90.

43 Singh A, Alter HJ, Zaia B. Does the addition of dexamethasone to standard therapy for acute migraine headache decrease the incidence of recurrent headache for patients treated in the emergency department? A meta-analysis and systematic review of the literature. Acad Emerg Med 2008;15(12):1223-33.

44 Zeeberg P, Olesen J, Jensen R. Discontinuation of medication overuse in headache patients: recovery of therapeutic responsiveness. Cephalalgia 2006;26(10):1192-8.

45 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.

46 Shamliyan TA, Kane RL, Taylor FR. Migraine in adults: preventive pharmacologic treatments. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2013. [cited 22 Nov 2017]. Available from url: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/migraine-prevention_research-2013.pdf

47 Guo Y, Han X, Yu T, Yao G. Meta-analysis of efficacy of topiramate in migraine prophylaxis. Neural Regen Res 2012;7(23):1806-11.

48 Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6.

49 Donegan S, Dixon P, Hemming K, Tudur-Smith C, Marson A. A systematic review of placebo-controlled trials of topiramate: How useful is a multiple-indications review for evaluating the adverse events of an antiepileptic drug? Epilepsia 2015;56(12):1910-20.

50 Shank RP, Maryanoff BE. Molecular pharmacodynamics, clinical therapeutics, and pharmacokinetics of topiramate. CNS Neurosci Ther 2008;14(2):120-42.

51 Alsaad AMS, Chaudhry SA, Koren G. First trimester exposure to topiramate and the risk of oral clefts in the offspring: A systematic review and meta-analysis. Reprod Toxicol 2015;53:45-50.

52 Jackson JL, Shimeall W, Sessums L, Dezee KJ, Becher D, Diemer M, et al. Tricyclic antidepressants and headaches: systematic review and meta-analysis. BMJ 2010;341:c5222.

53 Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. PLoS ONE 2015;10(7):e0130733.

54 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.

55 Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia 2014;34(7):523-32.

56 Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6.

57 Medicines and Healthcare products Regulatory Agency (MHRA). Update on MHRA review into safe use of valproate (cited 6 March 23). Available from: www.gov.uk/government/news/update-on-mhra-review-into-safe-use-of-valproate

58 National Institute for Health and Care Excellence (NICE). Migraine prophylaxis: flunarizine. NICE; 2014. [cited 23 Nov 2017]. Available from url: https://www.nice.org.uk/advice/esuom33/chapter/Key-points-from-the-evidence

59 Irish Pharmaceutical Healthcare Association (IPHA). Summary of Product Characteristics. Sibelium 5mg tablets (flunarizine). [cited 23 Nov 2017]. Available from url: http://www.medicines.ie/medicine/14498/SPC/Sibelium+5+mg+tablets/

60 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.

61 Linde M, Mulleners WM, Chronicle EP, McCrory DC. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6.

62 Scottish Intercollegiate Guideline Network (SIGN). Management of chronic pain. Edinburgh: SIGN; 2013. (SIGN publication no. 136). [cited 23 Nov 2017]. Available from url: http://www.sign.ac.uk/guidelines/fulltext/136/index.html

63 Health and Social Care Board. Advice for prescribers on the risk of the misuse of pregabalin and gabapentin. [cited 23 Nov 2017]. Available from url: http://niformulary.hscni.net/Formulary/Adult/PDF/PregabalinAndGabapentinRiskOfMisuseAdviceHSCBWebVersion.pdf

64 Banzi R, Cusi C, Randazzo C, Sterzi R, Tedesco D, Moja L. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of tension-type headache in adults. Cochrane Database of Systematic Reviews 2015, Issue 5.

65 Linde M, Mulleners WM, Chronicle EP, McCrory DC. Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6.

66 Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA 2012;307(16):1736-45.

67 Kim M, Danielsson A, Ekelund AC, Kemppainen E, Sjögren P, Svanberg T, et al. Botulinum toxin type A for prophylactic treatment of chronic migraine. Gothenburg: The Regional Health Technology Assessment Centre (HTA-centrum), Region Vastra Gotaland; 2014. (HTA Report 2014:70). [cited 23 Nov 2017]. Available from url: https://www2.sahlgrenska.se/upload/SU/HTA-centrum/HTA-rapporter/HTA-report%20Botulinum%20toxin%20type%20A%20for%20Prophylactic%20Treatment%20till%20publicering%202014-05-23.pdf

68 Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 2010;30(7):793-803.

69 Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 2010;30(7):804-14.

70 Scottish Medicines Consortium. Advice note for Botulinum Toxin A for the prophylaxis of of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine). [cited 23 Nov 2017]. Available from url: https://www.scottishmedicines.org.uk/files/advice/botulinum_toxin_A_BOTOX_2nd_Resub_FINAL_Jan_2017_for_website.pdf

71 Ashkenazi A, Matro R, Shaw JW, Abbas MA, Silberstein SD. Greater occipital nerve block using local anaesthetics alone or with triamcinolone for transformed migraine: a randomised comparative study. J Neurol Neurosurg Psychiatry 2008;79(4):415-7.

72 Cuadrado ML, Aledo-Serrano A, Navarro P, Lopez-Ruiz P, Fernandez-de-las-Penas C, Gonzalez-Suarez I, et al. Short-term effects of greater occipital nerve blockades in chronic migraine: A double-blind, randomised, placebo-controlled clinical trial. Cephalalgia 2017;37(9):864-72.

73 Inan LE, Inan N, Karadas O, Gul HL, Erdemoglu AK, Turkel Y, et al. Greater occipital nerve blockade for the treatment of chronic migraine: A randomized, multicenter, double-blind, and placebo-controlled study. Acta Neurol Scand 2015;132(4):270-7.

74 Dilli E, Halker R, Vargas B, Hentz J, Radam T, Rogers R, et al. Occipital nerve block for the short-term preventive treatment of migraine: A randomized, double-blinded, placebo-controlled study. Cephalalgia 2015;35(11):959-68.

75 Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol 2015;14(11):1081-90.

76 Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: A randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 2014;13(11):1100-7.

77 Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol 2014;13(9):885-92.

78 Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol 2016;15(4):382-90.

79 Goadsby PJ, Reuter U, Hallstrom Y, Broessner G, Bonner JH, Zhang F, et al. A Controlled Trial of Erenumab for Episodic Migraine. The New England journal of medicine 2017;377(22):2123-32.

80 Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. The New England journal of medicine 2017;377(22):2113-22.

81 Ho TW, Connor KM, Zhang Y, Pearlman E, Koppenhaver J, Fan X, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology 2014;83(11):958-66.

82 Nierenburg HdelC, Ailani J, Malloy M, Siavoshi S, Hu NN, Yusuf N. Systematic Review of Preventive and Acute Treatment of Menstrual Migraine. Headache 2015;55(8):1052-71.

83 Boe MG, Salvesen R, Mygland A. Chronic daily headache with medication overuse: a randomized follow-up by neurologist or PCP. Cephalalgia 2009;29(8):855-63.

84 Munksgaard SB, Bendtsen L, Jensen RH. Detoxification of medication-overuse headache by a multidisciplinary treatment programme is highly effective: a comparison of two consecutive treatment methods in an open-label design. Cephalalgia 2012;32(11):834-44.

85 Pijpers JA, Louter MA, de Bruin ME, van Zwet EW, Zitman FG, Ferrari MD, et al. Detoxification in medication-overuse headache, a retrospective controlled follow-up study: Does care by a headache nurse lead to cure? Cephalalgia 2016;36(2):122-30.

86 Rossi P, Faroni JV, Tassorelli C, Nappi G. Advice alone versus structured detoxification programmes for complicated medication overuse headache (MOH): a prospective, randomized, open-label trial. J Headache Pain 2013;14:10.

87 Andrasik F, Grazzi 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.

88 Ghiotto N, Sances G, Galli F, Tassorelli C, Guaschino E, Sandrini G, et al. Medication overuse headache and applicability of the ICHD-II diagnostic criteria: 1-year follow-up study (CARE I protocol). Cephalalgia 2009;29(2):233-43.

89 Grazzi L, Andrasik F, Usai S, Bussone G. Day-hospital withdrawal for chronic migraine with medication overuse: results at 3 years follow-up. Neurol Sci 2013;34(Suppl 1):S167-9.

90 Krymchantowski AV, Tepper SJ, Jevoux C, Valenca MM. Medication-Overuse Headache: Differences between Daily and Near-Daily Headache Patients. Brain Sci 2016;6(3):30.

91 Trucco M, Meineri P, Ruiz L, Gionco M, Neurolgical Hospital Interregional Group for the Study of Headaches. Medication overuse headache: withdrawal and prophylactic therapeutic regimen. Headache 2010;50(6):989-97.

92 Zidverc-Trajkovic J, Pekmezovic T, Jovanovic Z, Pavlovic A, Mijajlovic M, Radojicic A, et al. Medication overuse headache: clinical features predicting treatment outcome at 1-year follow-up. Cephalalgia 2007;27(11):1219-25.

93 Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ, et al. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia 2007;27(7):814-23.

94 Hagen K, Albretsen C, Vilming ST, Salvesen R, Gronning M, Helde G, et al. Management of medication overuse headache: 1-year randomized multicentre open-label trial. Cephalalgia 2009;29(2):221-32.

95 Hagen K, Albretsen C, Vilming ST, Salvesen R, Gronning M, Helde G, et al. A 4-year follow-up of patients with medication-overuse headache previously included in a randomized multicentre study. J Headache Pain 2011;12(3):315-22.

96 Hagen K, Stovner LJ. A randomized controlled trial on medication-overuse headache: outcome after 1 and 4 years. Acta Neurol Scand Suppl 2011(191):38-43.

97 Creac'h C, Frappe P, Cancade M, Laurent B, Peyron R, Demarquay G, et al. In-patient versus out-patient withdrawal programmes for medication overuse headache: a 2-year randomized trial. Cephalalgia 2011;31(11):1189-98.

98 Rossi P, Faroni JV, Nappi G. Short-term effectiveness of simple advice as a withdrawal strategy in simple and complicated medication overuse headache. Eur J Neurol 2011;18(3):396-401.

99 Negro A, Curto M, Lionetto L, Crialesi D, Martelletti P. OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. Springerplus 2015;4:826.

100 Sandrini G, Perrotta A, Tassorelli C, Torelli P, Brighina F, Sances G, et al. Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. J Headache Pain 2011;12(4):427-33.

101 Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC, et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci 2013;331(1-2):48-56.

102 Sarchielli P, Messina P, Cupini LM, Tedeschi G, Di Piero V, Livrea P, et al. Sodium valproate in migraine without aura and medication overuse headache: a randomized controlled trial. Eur Neuropsychopharmacol 2014;24(8):1289-97.

103 Boe MG, Mygland A, Salvesen R. Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. Neurology 2007;69(1):26-31.

104 Rabe K, Pageler L, Gaul C, Lampl C, Kraya T, Foerderreuther S, et al. Prednisone for the treatment of withdrawal headache in patients with medication overuse headache: a randomized, double-blind, placebo-controlled study. Cephalalgia 2013;33(3):202-7.

105 Taghdiri F, Togha M, Razeghi Jahromi S, Paknejad SM. Celecoxib vs prednisone for the treatment of withdrawal headache in patients with medication overuse headache: a randomized, double-blind clinical trial. Headache 2015;55(1):128-35.

106 National Institute for Health and Care Excellence (NICE). Transcranial magnetic stimulation for treating and preventing migraine. London: NICE; 2014. (Interventional procedure guidance no.477). [cited 23 Nov 2017]. Available from url: https://www.nice.org.uk/guidance/ipg477

107 National Institute for Health and Care Excellence (NICE). Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine. London: NICE; 2016. (Interventional Procedures Guidance no.552). [cited 23 Nov 2017]. Available from url: https://www.nice.org.uk/guidance/ipg552/resources/transcutaneous-stimulation-of-the-cervical-branch-of-the-vagus-nerve-for-cluster-headache-and-migraine-1899871983899845

108 Silberstein SD, Calhoun AH, Lipton RB, Grosberg BM, Cady RK, Dorlas S, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. Neurology 2016;87(5):529-38.

109 Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 2010;9(4):373-80.

110 Conforto AB, Amaro E, Jr., Goncalves AL, Mercante JP, Guendler VZ, Ferreira JR, et al. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. Cephalalgia 2014;34(6):464-72.

111 Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study. J Neurol 2013;260(11):2793-801.

112 Medicines and Healthcare products Regulatory Agency (MHRA). Patient card - key facts - valproate and pregnancy. [cited 12 Sept 2022]. Available from url: 107995_Valproate_Patient_Card_v05_DS_07-01-2021.pdf (publishing.service.gov.uk)

113 Medicines and Healthcare products Regulatory Agency (MHRA). Treatment with valproate for female patients. Annual risk acknowledgement form: valproate has risks in pregnancy [cited 12 Sept 2022]. Available from url: Risk-acknowledgment.pdf (publishing.service.gov.uk)

114 Alasad YW, Asha MZ. Monoclonal antibodies as a preventive therapy for migraine: A meta-analysis. Clinical Neurology and Neurosurgery 2020;195 Epub.

115 Deng H, Li GG, Nie H, Feng YY, Guo GY, Guo WL, et al. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine - An updated systematic review and meta-analysis. BMC Neurology 2020;20(1):57.

116 Gao B, Sun N, Yang Y, Sun Y, Chen M, Chen Z, et al. Safety and efficacy of Fremanezumab for the prevention of migraine: A meta-analysis from randomized controlled trials. Frontiers in Neurology 2020;11:1-12.

117 Gklinos P, Mitsikostas DD. Galcanezumab in migraine prevention: a systematic review and meta-analysis of randomized controlled trials. Therapeutic Advances in Neurological Disorders 2020;13:1-11.

118 Lattanzi S, Brigo F, Trinka E, Vernieri F, Corradetti T, Dobran M, et al. Erenumab for Preventive Treatment of Migraine: A Systematic Review and Meta-Analysis of Efficacy and Safety. Drugs 2019;79(4):417-31.

119 Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med 2017;377(22):2123-32.

120 Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia 2018;38(6):1026-37.

121 Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. Lancet 2018;392(10161):2280-7.

122 Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017;16(6):425-34.

123 Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: a Randomized Clinical Trial. JAMA 2018;319(19):1999-2008.

124 Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med 2017;377(22):2113-22.

125 Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet 2019;394(10203):1030-40.

126 Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: the EVOLVE-1 Randomized Clinical Trial. JAMA neurology 2018;75(9):1080-8.

127 Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia 2018;38(8):1442-54.

128 Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91(24):e2211-e21.

129 Mulleners WM, Kim BK, Lainez MJA, Lanteri-Minet M, Pozo-Rosich P, Wang S, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurology 2020;19(10):814-25.

130 Ashina M, Goadsby PJ, Reuter U, Silberstein S, Dodick DW, Xue F, et al. Long-term efficacy and safety of erenumab in migraine prevention: results from a 5-year, open-label treatment phase of a randomized clinical trial. European journal of neurology 2021;28(5):1716-25.

131 Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol 2016;15(4):382-90.

132 Goadsby PJ, Silberstein SD, Yeung PP, Cohen JM, Ning X, Yang R, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: A randomized study. Neurology 2020;95(18):e2487-e99.

133 Pozo-Rosich P DH, Wang S, Doležil D, Li LQ, Aurora SK, et al. Long-term treatment with galcanezumab in patients with chronic migraine: results from the open-label extension of the REGAIN study. Curr Med Res Opin 2022;38(5):731-42.

134 Reuter U, Lucas C, Dolezil D, Hand AL, Port MD, Nichols RM, et al. Galcanezumab in Patients with Multiple Previous Migraine Preventive Medication Category Failures: Results from the Open-Label Period of the CONQUER Trial. Adv Ther 2021;38(11):5465-83.

135 Reuter U, Ehrlich M, Gendolla A, Heinze A, Klatt J, Wen S, et al. Erenumab versus topiramate for the prevention of migraine – a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia 2021;42(2):108-18.

136 Yang CP, Zeng BY, Chang CM, Shih PH, Yang CC, Tseng PT, et al. Comparative Effectiveness and Tolerability of the Pharmacology of Monoclonal Antibodies Targeting the Calcitonin Gene-Related Peptide and Its Receptor for the Prevention of Chronic Migraine: a Network Meta-analysis of Randomized Controlled Trials. Neurotherapeutics 2021;18(4):2639-50.

137 Dodick DW, Doty EG, Aurora SK, Ruff DD, Stauffer VL, Jedynak J, et al. Medication overuse in a subgroup analysis of phase 3 placebo-controlled studies of galcanezumab in the prevention of episodic and chronic migraine. Cephalalgia 2021;41(3):340-52.

138 Silberstein JD, Cohen JM, Seminerio MJ, Yang R, Ashina S, Katsarava Z. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. J Headache Pain 2020;21(1):114.

139 Tepper SJ, Diener HC, Ashina M, Brandes JL, Friedman DI, Reuter U, et al. Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. Neurology 2019;92(20):e2309-e20.

140 Overeem LH, Peikert A, Hofacker MD, Kamm K, Ruscheweyh R, Gendolla A, et al. Effect of antibody switch in non-responders to a CGRP receptor antibody treatment in migraine: A multi-center retrospective cohort study. Cephalalgia 2022;42(4-5):291-301.

141 Patier Ruiz I, Sanchez-Rubio Ferrandez J, Carcamo Fonfria A, Molina Garcia T. Early Experiences in Switching between Monoclonal Antibodies in Patients with Nonresponsive Migraine in Spain: A Case Series. European Neurology 2022;85(2):132-5.

142 Diener HC, McAllister P, Jürgens TP, Kessler Y, Ning X, Cohen JM, et al. Safety and tolerability of fremanezumab in patients with episodic and chronic migraine: a pooled analysis of phase 3 studies. Cephalalgia 2022;42(8):769-80.

143 Kudrow D, Pascual J, Winner PK, Dodick DW, Tepper SJ, Reuter U, et al. Vascular safety of erenumab for migraine prevention. Neurology 2020;94(5):e497-e510.

144 Oakes TM, Kovacs R, Rosen N, Doty E, Kemmer P, Aurora SK, et al. Evaluation of Cardiovascular Outcomes in Adult Patients With Episodic or Chronic Migraine Treated With Galcanezumab: Data From Three Phase 3, Randomized, Double-Blind, Placebo-Controlled EVOLVE-1, EVOLVE-2, and REGAIN Studies. Headache 2020;60(1):110-23.

145 Saely S, Croteau D, Jawidzik L, Brinker A, Kortepeter C. Hypertension: A new safety risk for patients treated with erenumab. Headache 2021;61(6):202-8.

146 BMJ Group and the Royal Pharmaceutical Society. British National Formulary (BNF): Guidance on Prescribing. [cited 04 Nov 2021]. Available from url: https://www.medicinescomplete.com/mc/bnf/current/PHP97234-guidance-on-prescribing.htm

147 Bjørk MH, Zoega H, Leinonen MK, Cohen JM, Dreier JW, Furu K, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. JAMA Neurol. 2022 Jul 1;79(7):672-681.

148 González-García N, Díaz de Terán J, López-Veloso AC, Mas-Sala N, Mínguez-Olaondo A, Ruiz-Piñero M, et al. Headache: pregnancy and breastfeeding. Recommendations of the Spanish Society of Neurology's Headache Study Group. Neurologia (Engl Ed). 2022 Jan-Feb;37(1):1-12.

149 Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1), Cephalalgia 2020;40(3): 241-254.

150 Lipton RB, Goadsby PJ, Smith J, Schaeffler BA, Biondi DM, Hirman J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Neurology 2020;94(13):e1365-e1377.

151 Ashina M, Lanteri-Minet M, Pozo-Rosich P, Ettrup A, Christoffersen CL, Josiassen MK, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventative treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol. 2022 Jul;21(7):597-607.

ISBN 978 1 909103 62 7

SIGN155

Healthcare Improvement Scotland

Edinburgh Office
Gyle Square
1 South Gyle Crescent
Edinburgh
EH12 9EB
0131 623 4300

Glasgow Office
Delta House
50 West Nile Street
Glasgow
G1 2NP
0141 225 6999