

SIGN 155

Pharmacological management of migraine

A national clinical guideline

First published February 2018
Revised May 2026

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, for example, 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.



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

Scottish Intercollegiate Guidelines Network

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Scottish Intercollegiate Guidelines Network

Gyle Square, 1 South Gyle Crescent

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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.⁸ The Global Burden of Disease study ranks migraine as the fourth most common cause worldwide of years lived with disability in all ages and second in people under the age of 50.⁹ Prevalence is highest in women, but the prevalence of migraine in young men is increasing.¹⁵²

It is estimated that migraine costs the UK public economy around £12.2 billion a year.¹⁰

Higher prevalence of migraine in women is thought to be because of 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 (for example, 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

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 (for example, 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.

1.2.6 DIAGNOSTIC AND TREATMENT PATHWAY

The guideline informs the [National Headache Pathway](#), produced by the National Centre for Sustainable Delivery, which includes pathways on:¹⁵³

- acute treatment of migraine
- prophylaxis of episodic and chronic migraine
- migraine during pregnancy and following childbirth
- menstrual and perimenopause migraine.

1.2.7 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

3.3	Non-steroidal anti-inflammatory drugs	Minor update to advice on safety in pregnancy
3.6	Triptans	Minor update to safety advice
3.7	Oral calcitonin gene-related peptide receptor antagonists	New
3.8	Combined therapies	Good practice point added
4.5	Oral calcitonin gene-related peptide receptor antagonists	New
4.8	Topiramate	Minor update to safety advice
4.10	Sodium valproate	Minor update to safety advice

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 2 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.**
- R **Co-prescription of sumatriptan and naproxen 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 **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 person 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

Treatment response is defined as pain free at 2 hours and sustained pain free at 24 hours. A table of numbers needed to treat (NNTs) to achieve pain free at 2 hours for some acute therapies can be found in section 3.10. In addition, pain relief or headache relief (from severe or moderate to mild or no pain) is reported in some studies.

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

Rimegepant should be considered for those who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated and have inadequate pain relief with NSAIDs and paracetamol (*see section 3.7*).

✓ When starting acute treatment, healthcare professionals should warn patients about the risk of developing medication-overuse headache (*see section 5*).

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 2 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 2 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 2 hours was 9.7 for 200 mg and 7.2 for 400 mg.²³ 1++

Naproxen has also been found to be effective for 2-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 2 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++

It is uncertain whether ibuprofen taken in the early stages of pregnancy contributes to a higher rate of miscarriage. Ibuprofen may be considered for use up to week 20.^{17,154} 4

Ibuprofen is the only NSAID 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.

✓ During pregnancy, ibuprofen should be used with caution and only up to 20 weeks, if paracetamol or sumatriptan, or a combination of both, are ineffective in reducing pain.

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 2 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 2 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++

Paracetamol is commonly used in all trimesters of pregnancy, but should be used at the lowest dose and for the shortest duration.^{22,26,155} 1++

No serious adverse events were reported in the trials. Paracetamol is better tolerated than NSAIDs or triptans.²⁷

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.

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 2 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 2 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 2 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 2 hours and sustained pain relief at 24 hours.³¹⁻³⁵ 1⁺⁺
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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 2 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 2 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 2 hours for moderate to severe pain and 2.4 for mild pain. Intranasal sumatriptan is also effective for pain free at 2 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 2 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 2 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 2 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 2 hours.³³ 1⁺⁺

For patients with menstrually-related migraine (MRM), sumatriptan resulted in a therapeutic gain with 25% of patients pain free at 2 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⁺⁺

Adverse events reported in the trials were described as mild to moderate. Serious adverse events were rare.^{33 31} 1⁺⁺

Patients using rizatriptan with concurrent propranolol should be given a maximum dose of 5 mg rizatriptan due to the risk of interactions and rizatriptan should not be taken within 2 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, 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 and vascular risk factors should be taken into account before prescribing triptans in the over 65s.¹⁷ 1⁺⁺

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⁺

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 (in any trimester) fails, the use of triptans, in particular sumatriptan, can be considered in all stages of pregnancy. No triptans are classed as non-teratogenic.

R Triptans are recommended as first-line treatment for patients with acute migraine.

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.

- ✓ | Triptans should not be used in patients at high risk of ischaemic cardiovascular disease, including uncontrolled hypertension.

3.7 ORAL CALCITONIN GENE-RELATED PEPTIDE RECEPTOR ANTAGONISTS

Rimegepant is an oral calcitonin gene-related peptide (CGRP) receptor antagonist licensed for the acute treatment of patients with migraine. A meta-analysis identified two RCTs of rimegepant, which were appraised as high quality. Rimegepant outperformed placebo in achieving pain free at 2 hours (OR 2.0, 95% CI 1.45 to 2.75), freedom from most bothersome symptom at 2 hours (OR 1.61, 95% CI 1.35 to 1.91), and pain relief at 2 hours (OR 1.89, 95% CI 1.61 to 2.22). It was also better at enabling participants to remain pain free from 2 to 24 hours (OR 2.43, 95% CI 1.59 to 3.71) and sustaining pain relief for 2 to 24 hours (OR 2.24, 95% CI 1.89 to 2.65).¹⁵⁶ For the secondary outcome of sustained pain free 2-48 hours postdose, the individual studies reported a risk difference of 3.9% (95% CI 0.7 to 7.1) in one study and 8% (95% CI 4.9 to 11) in the other.¹⁵⁷ These results are confirmed in three further RCTs published since the meta-analysis.¹⁵⁸⁻¹⁶⁰

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All five RCTs were restricted to participants with 2–8 moderate to severe migraines per month (episodic migraine). Based on the premise that episodic migraine and chronic migraine are on a spectrum of the same condition, it is reasonable to consider rimegepant as an acute treatment in patients with chronic migraine. Rimegepant is given as a one-off fixed dose of 75 mg and should not be repeated on the same day.

Post-hoc analysis of the pooled results of three RCTs found that rimegepant was as effective in patients who have an insufficient response to two or more triptans as those that are triptan naïve and those with a current adequate response to triptans (pain free at 2 hours: triptan naïve 19.6% vs 14.7% placebo; current triptan users 20.4% vs 6.8% placebo; those with insufficient response to one triptan 20.7% vs 12.4%; insufficient response to ≥2 triptans 20.0% vs 10.2% placebo).¹⁶¹

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A phase 4 RCT assessed the effectiveness of rimegepant in patients with episodic migraine (4–14 days per month) for whom triptans were unsuitable.¹⁶² This group of patients included those with: documented insufficient response to ≥2 triptans with ≥1 reason due to prior intolerance (30.5%) and/or ≥1 reason due to lack of efficacy (84.9%). Triptan contraindications were present in 9.1%. Patients with cardiovascular risk factors were included, but those with current uncontrolled, unstable or recently diagnosed (during the 6 months prior to screening) cardiovascular disease and patients with systolic BP >150 mmHg or diastolic BP >100 mmHg were excluded. Rimegepant was better than placebo in achieving pain relief at 2 hours (55.9% vs 32.7% placebo) and all secondary end points, including 2-hour pain freedom (22.1% vs 7.4% placebo) and sustained migraine freedom at 24 hours (13.3% vs 4.9%) and 48 hours (11.7% vs 2.5%).

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Rimegepant is accepted by the SMC for restricted use within NHSScotland for the acute treatment of adults with migraine with or without aura. It is restricted to those who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated and have inadequate pain relief with NSAIDs and paracetamol.

In two RCTs, rimegepant was well tolerated and adverse events were similar between treatment and placebo groups.^{163,164} No significant adverse effects were identified in a one-year follow-up study.¹⁶⁵ Rimegepant was also well tolerated in the phase 4 trial (which included cardiovascular risk factors, but not active cardiovascular disease) and adverse events were similar between treatment and placebo groups.¹⁶² Mild hypertension was reported in one patient and moderate Raynaud's phenomenon in a further patient in the rimegepant group.¹⁶²

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Patients at high risk of ischaemic cardiovascular disease, including those with a blood pressure measurement of over 150/100 mmHg, were excluded from the trials. Since CGRP can mediate vasodilation, caution is advised with the use of monoclonal antibodies targeting the CGRP pathway in patients with vascular disease, vascular risk factors and Raynaud's phenomenon.¹⁶⁶ As oral CGRP receptor antagonists also target the CGRP pathway, it is suggested that similar cautions should be applied. Likewise, there may be a risk that medications blocking the effect of CGRP may predispose to hypertension in some people.

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R Rimegepant should be considered for patients with acute migraine who have had an inadequate response or poor tolerability to two or more triptans, and paracetamol or NSAIDs have been considered to be ineffective or unsuitable.

R Rimegepant can be considered for patients with acute migraine who have contraindications to triptans.

✓ Careful consideration should be given to the potential risks and benefits for patients at high risk of ischaemic cardiovascular disease, including uncontrolled hypertension, before prescribing oral CGRP receptor antagonists.

✓ Use of rimegepant should be avoided in pregnancy and breastfeeding due to insufficient safety data.

3.8 COMBINED THERAPIES

It can be helpful to try a combination of a triptan, non-steroidal agent, and an antiemetic if individual treatments are ineffective.¹⁵³

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

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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

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The [Scottish Medicines Consortium](#) has rejected the use of combination tablets of sumatriptan 85 mg and naproxen 457 mg for use within NHS Scotland. An alternative is to provide separate tablets of each treatment.

R Co-prescription of sumatriptan and naproxen should be considered for the treatment of patients with acute migraine.

✓ A combination of a triptan with a non-steroidal agent and/or an antiemetic can be considered for the treatment of patients with acute migraine.

3.9 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

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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.

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

3.10 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 (including eletriptan and rizatriptan) are effective (see section 3.6 for details) but NNTs were not included in the review. A treatment algorithm outlining good practice in acute treatment can be found in the [National Headache Pathway](#).

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

A good-quality systematic review and network meta-analysis of simple analgesics, triptans and the newer treatment options (including oral CGRP receptor antagonists) for patients with acute migraine found all treatments were more effective than placebo for pain freedom at 2 hours.¹⁶⁷ All except paracetamol and naratriptan were effective for sustained pain freedom from 2 to 24 hours post-dose compared to placebo. For 2-hour pain freedom, eletriptan was the most effective treatment (37% of participants), followed by rizatriptan (33%), oral sumatriptan (29%) and oral zolmitriptan (28%).

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4 Pharmacological prevention of migraine

4.1 INTRODUCTION

This section considers the preventative treatment options for patients with episodic and chronic migraine (for definitions, see section 1.2.3). For some treatments there is insufficient evidence 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 the prophylaxis of episodic migraine. Specific evidence for the effectiveness of preventative treatments for chronic migraine is available for atogepant, botulinum toxin A, the CGRP monoclonal antibodies and topiramate.

Migraine can have a 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 person, 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 Oral CGRP receptor antagonists, botulinum toxin A, CGRP monoclonal antibodies and topiramate are less likely to be affected by medication overuse. Prophylactic treatment should be used for eight weeks at the target dose or maximum tolerated dose (for those with a titration schedule) before deciding if it is effective or not. For treatments of fixed dose (for example, oral CGRP receptor antagonist), treatment effectiveness should be assessed at 3 months. In many patients, prophylactic medication can be successfully phased out and the need for ongoing prophylaxis considered after 12 months.

The decision regarding which medication to try first depends on evidence of effectiveness, comorbidities, other risk factors, drug interactions and patient preference. It is important to ensure adequate contraception while 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, the 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 for preventative treatments for women during pregnancy.

4.2 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 $\geq 50\%$ 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

Candesartan is a widely used and inexpensive drug with a good side-effect profile and no potential cognitive effects.

Candesartan is not licensed for migraine prophylaxis.

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

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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.

4.3 PROPRANOLOL

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 $\geq 50\%$ 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 the reduction of migraine frequency or use of acute analgesics were shown.⁴⁶ Atenolol 50–200 mg daily was reported to reduce the frequency of episodic migraine and use of acute therapies.⁴⁶

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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

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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 NHS Scotland. 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

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

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 (for example, 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

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A further meta-analysis found that amitriptyline (100 mg) was more effective than placebo in achieving a $\geq 50\%$ reduction in headache frequency, but more so in those with higher headache frequencies. This was based on low-quality evidence.⁴⁶

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In comparative trials, low-dose (for example, 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

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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*).

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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 ORAL CALCITONIN GENE-RELATED PEPTIDE RECEPTOR ANTAGONISTS

Two oral CGRP receptor antagonists, atogepant and rimegepant, are available for use in NHSScotland. They are started on a fixed dose and titration is not required.

Several meta-analyses of different combinations of RCTs with varying doses of atogepant, showed that atogepant reduced the number of monthly migraine days (MMDs), monthly headache days (MHDs) and acute medication days compared with placebo in patients with episodic or chronic migraine over 12 weeks.¹⁶⁸⁻¹⁷⁰ In one meta-analysis, atogepant statistically significantly reduced MMDs compared with placebo at all doses (standardised mean difference (SMD) -0.40, 95% CI -0.46 to -0.34, $p < 0.00001$).¹⁶⁹ Another meta-analysis reported a reduction in MMDs with a 60 mg dose of atogepant compared with placebo (weighted mean difference (WMD) -1.40, 95% CI -2.02 to -0.78, $p < 0.01$).¹⁷⁰ Likewise, another meta-analysis showed a reduction in MMDs with atogepant 60 mg (mean difference in MMD -1.35, 95% CI -1.85 to -0.85).¹⁶⁸ With respect to 50% responder rates, one analysis reported a risk ratio of 1.82 (95% CI 1.34 to 2.48) for $\geq 50\%$ reduction in MMDs with 60 mg atogepant in patients with episodic and chronic migraine.¹⁶⁹ In patients with episodic migraine, 60 mg atogepant compared with placebo, the OR for $\geq 50\%$ reduction in MMDs was 2.57 (95% CI 1.56 to 4.23).¹⁶⁸ Data from the individual trials reported 50% responder rates with atogepant 60 mg as follows:

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- Goadsby et al (episodic migraine), 52% (vs 40% placebo)
- ADVANCE (episodic migraine), 60.8% (vs 29% placebo)
- ELEVATE (episodic migraine where 2-4 conventional oral prophylactic agents had failed), 51% (vs 18% placebo)
- PROGRESS (chronic migraine), 41% (vs 26% placebo).¹⁷¹⁻¹⁷⁴

In an open-label trial the $\geq 50\%$ reduction in MMDs at 52 weeks was 84.2%. The dropout rate for the treatment group was 31%, but only 1% reported lack of efficacy as the reason.¹⁷⁵

A prespecified subgroup analysis of the PROGRESS RCT of atogepant in patients with chronic migraine and concomitant medication overuse, demonstrated similar efficacy (MMDs, MHDs and 50% responder rates) in those with and without medication overuse.¹⁷⁶

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Atogepant is accepted for restricted use by the SMC for use in NHSScotland for the prevention of migraine in adults who have at least four migraine days per month. Use is restricted to patients with chronic and episodic migraine who have had prior insufficient response on three or more migraine preventive treatments.

Systematic reviews identified one RCT, of moderate quality, on the use of rimegepant (75 mg on alternate days) in participants experiencing headache (migraine and non-migraine) 4 to 18 days per month (Croop et al 2021).^{168,177,178} The average number of moderate or severe attacks per month was 7.8 in both the rimegepant and placebo groups. It reported a reduction of -4.3 (95% CI -4.8 to -3.9) MMDs compared with -3.5 (95% CI -4.0 to -3.0) in the placebo group, equating to a modest difference of -0.8 ($p = 0.0099$) during weeks 9 to 12. The 50% responder rate was 49% (95% CI 44 to 54) for those taking rimegepant, compared with 41% (95% CI 36 to 47) for the placebo group. The RCT was continued in a 52-week open-label trial (30% dropout, mostly due to lost to follow-up). It reported a reduction in MMDs of -6.2, indicating a sustained and cumulative effect.¹⁷⁹ Patients who had two or more failed migraine preventatives were excluded from the RCT. Information on

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medication overuse headache was not reported. A Japanese RCT with the same specifications reported a reduction of -2.4 (95% CI -2.93 to -1.96) MMDs compared with -1.4 (95% CI -1.87 to -0.91) in the placebo group, equating to a modest difference of -1.11 (p=0.002) during weeks 9 to 12.¹⁸⁰ The 50% responder rate was 41.7% (95% CI 35.5 to 47.9) for those taking rimegepant, compared with 34.4% (95% CI 28.5 to 40.4) for the placebo group. Patients could remain on one migraine preventative medication (excluding CGRP antagonists and monoclonal antibodies) in addition to the study drug. Information on the prior number of migraine preventatives used and medication overuse headache was not reported.

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In a phase 4 RCT of patients with episodic migraine (4–14 days per month), who had experienced treatment failure with up to four previous therapies, the reduction in MMDs at 12 weeks was -2.1 (95% CI -2.5 to -1.7) compared with -0.5 (95% CI -0.8 to -0.1) in the placebo group.¹⁸¹ The 50% responder rate was 34.0% for those taking rimegepant, compared with 13.8% for the placebo group (difference 20.1%, 95% CI 13.7 to 26.5).

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An RCT designed to show the superiority of galcanezumab over rimegepant in patients with episodic migraine found that both therapies achieved a similar 50% responder rate (galcanezumab 62%; rimegepant 61%). The reductions in MMDs were also comparable (galcanezumab -4.8; rimegepant -4.4).¹⁸²

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Rimegepant is accepted for restricted use by the SMC for use in NHSScotland for the preventive treatment of adults with episodic migraine who have at least four migraine attacks per month but fewer than 15 headache days per month and who have had prior failure on three or more migraine preventive treatments.

None of the studies reported serious adverse effects from use of atogepant or rimegepant. Both were well tolerated.^{170,175,177-179} Nausea was the most common side effect associated with 75 mg (alternate days) rimegepant and the 60 mg dose of atogepant.^{170,177,178} Long-term use of atogepant was also associated with upper respiratory tract infection and constipation.¹⁷⁵

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People at a high risk of vascular events were excluded from the trials. Safety in this high-risk population, and for long-term vascular health, is yet to be determined. Since CGRP can mediate vasodilation, the European Headache Federation guidelines for the use of monoclonal antibodies targeting CGRP advise caution in people with vascular disease, vascular risk factors and Raynaud's phenomenon (*see section 4.14*).¹⁶⁶ As oral CGRP receptor antagonists also target the CGRP pathway, it is suggested that similar cautions should be applied until further evidence is available.

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Likewise, there may be a risk that medications blocking the effect of CGRP may predispose to hypertension in some people.

R Atogepant is recommended for the prophylactic treatment of patients with episodic or chronic migraine who have at least four migraine days per month, where medication overuse headache has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.

R Rimegepant is recommended for the prophylactic treatment of patients with episodic migraine (4 to 14 days per month), where medication overuse headache has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.

✓ Careful consideration should be given to the potential risks and benefits for patients at high risk of ischaemic cardiovascular disease, including uncontrolled hypertension, before prescribing oral CGRP receptor antagonists.

✓ Use of atogepant or rimegepant should be avoided during pregnancy and breastfeeding. A washout period of at least 1 week is advised before trying for a pregnancy.

✓ Medication overuse headache should be addressed before treatment with atogepant or rimegepant (*see section 5*), however, in patients where treatment of medication overuse headache has been unsuccessful, atogepant or rimegepant can still be considered.

4.6 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 vs -6.4; $p=0.006$) and migraine days (-7.6 vs -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 vs -6.7; $p<0.001$) and migraine days (-8.7 vs -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 vs -4.6; $p=0.003$).⁶⁹

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 vs -4.7; $p<0.001$) and migraine days (-7.1 vs -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

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

Adverse events were slightly more common in patients injected with botulinum toxin A compared to placebo (RR 1.25, 95% CI, 1.14 to 1.36), 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}

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.

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

4.7 CALCITONIN GENE-RELATED PEPTIDE MONOCLONAL ANTIBODIES

Three CGRP monoclonal antibodies are available for use in NHSScotland. Erenumab targets the CGRP receptor. Fremanezumab and galcanezumab target the CGRP ligand. All are provided by monthly subcutaneous injections. Fremanezumab can also be given quarterly. A further CGRP monoclonal antibody, eptinezimab, also targets the CGRP ligand. It is only available as a quarterly intravenous infusion and is not currently available for use in NHSScotland.

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).

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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)
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)

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)
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)
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 eptinezumab 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

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<p>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 $\geq 50\%$ 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 (<i>see section 5</i>).</p>	1++
<p>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 $\geq 50\%$ reduction was achieved in 71% of participants.¹³⁰</p>	2++
<p>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 $\geq 50\%$ 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}</p>	1++ 2++
<p>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 $\geq 50\%$ 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.</p>	1++ 2++
<p>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</p>	1++
<p>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 $\geq 50\%$ 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.</p>	1++
<p>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 $\geq 50\%$ 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</p>	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 $\geq 50\%$ 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 $\geq 50\%$ 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

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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

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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

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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.

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When compared to topiramate in an RCT, erenumab was more effective in reducing MMDs (-5.86 erenumab vs -4.02 topiramate). There was a $\geq 50\%$ 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.

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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 (for example,

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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.

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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.

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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

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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.

Initiation should be under the guidance of appropriately trained healthcare professionals. 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 prophylaxis of migraine in adults who have at least 4 migraine days per month. Use is restricted to the treatment of patients with chronic and episodic migraine 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, galcanezumab 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.

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

✓ When initiating CGRP monoclonal antibodies, it is reasonable to measure blood pressure before treatment initiation, and periodically thereafter. Treatment with these agents in patients with uncontrolled hypertension is cautioned.

- ✓ 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.

4.8 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 $\geq 50\%$ 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 MMDs, 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

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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 5 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

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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

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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

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Children exposed to topiramate in utero are at high risk of serious developmental disorders, congenital malformations and low birth weight.¹⁸³ The risk of congenital malformations is 4–9/100 babies compared with 1–3/100 in the general population and is dose dependent. The risk of intellectual disability, autistic spectrum disorder and attention deficit hyperactivity disorder (ADHD) may be around 2–3 times that of the general population. Topiramate is contraindicated in pregnancy and women who have a chance of becoming pregnant must be on highly-effective contraception in line with the MHRA Topiramate Pregnancy Prevention Programme.¹⁸³ Advice on contraception is available from the Royal College of Obstetricians and Gynaecologists Faculty of Sexual and Reproductive Healthcare, [Standards and Guidelines | CoSRH](#). A washout period of 4 weeks is advised before trying for a pregnancy.¹⁸³

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Topiramate should not be used by women who are breastfeeding as it can be present in breast milk.¹⁷

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R Topiramate (50–100 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine. It should not be prescribed in women of childbearing potential unless the conditions of a pregnancy prevention programme are fulfilled.

- R** Prescribers should be aware that topiramate is associated with an increased risk of serious developmental disorders, congenital malformations and low birth weight in children exposed to topiramate in utero. For women who may become pregnant, topiramate should only be considered as a prophylactic treatment when:
- other treatment options have been exhausted
 - patients are using highly-effective contraception in line with the MHRA [Topiramate Pregnancy Prevention Programme](#).
- 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 woman is aware she is pregnant
 - the need to use effective contraception
 - the need to seek urgent advice on migraine prophylaxis and stopping topiramate if planning a pregnancy
 - the need to stop taking topiramate (for migraine prevention) straight away if they do become pregnant and contact their GP.
- ✓ If prescribing topiramate, check the [MHRA website](#) for current advice.
 - ✓ A washout period of at least 4 weeks after the last dose of topiramate is advised before trying for a pregnancy.
 - ✓ Topiramate should not be used during breastfeeding.

4.9 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 nicaldipine over placebo in patients with episodic or chronic migraine.^{46,53}

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 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.

Comparative trial data was limited, but there is some evidence that flunarazine has similar efficacy to propranolol, topiramate and sodium valproate.^{53,58}

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 flunarazine should be avoided during pregnancy.¹⁴⁸

Flunarazine 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** **Flunarazine (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.

4.10 SODIUM VALPROATE

For patients with episodic migraine, sodium valproate is more effective than placebo providing a $\geq 50\%$ 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 congenital malformations and neurodevelopmental disorders. It should therefore not be used during pregnancy or prescribed to any woman of childbearing age.⁵⁷

4

There is a potential risk of neurodevelopmental disorders in children whose fathers were treated with valproate in the 3 months prior to conception, compared to those treated with other antiepileptic therapies (lamotrigine or levetiracetam).⁵⁷

4

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 no other effective or tolerated treatment is available.

As a precaution, it is also recommended that male patients (of any age) use effective contraception (condoms and contraception used by the female partner) while on valproate and for 3 months after stopping it.⁵⁷ Sources of further advice for prescribing sodium valproate for women who may become pregnant are available in section 7.2. 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, inform the patient of the risks to children exposed to valproate in utero and the need to use effective contraception while taking valproate and for 3 months after stopping (*see Valproate Pregnancy Prevention Programme and CoSRH Guidelines and Statements | CoSRH*).

✓ Male patients (of any age) on valproate should use effective contraception (condoms and female contraception) and continue to for 3 months after stopping valproate.

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

4.11 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

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⁻

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.

4.12 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.

4.13 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++

4.14 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++

4.15 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++

4.16 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 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+

4.17 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.

4.17.1 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 triptans³⁴

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+

- 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.

4.17.2 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+

4.17.3 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+

4.17.4 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+

4.17.5 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

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

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

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.

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.

1+
31+
2+
31++
1+
3

1++

- 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 <https://www.sign.ac.uk/patient-public-involvement/plain-language-versions-of-guidelines/migraine>. Patients may also find the following booklet helpful: Managing chronic pain: a booklet for patients and carers. <https://www.sign.ac.uk/patient-public-involvement/plain-language-versions-of-guidelines/managing-chronic-pain>.

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

Canopi, 82 Tanner Street, London, SE1 3GN

Tel: 0808 802 0066 (Mon-Fri, 10am-4pm)

www.migrainetrust.org

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

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.

<p>Initial consultation with GP</p>	<ul style="list-style-type: none"> • Exclude a serious cause for headache by appropriate history and examination. • If time allows: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> o all headaches and their severity o medication taken o menstruation o normal activities missed. <p>Possible additional information:</p> <ul style="list-style-type: none"> o food and drink o sleep times o exercise o stressful days o complementary therapies used. <p>Ask what medication and what doses the patient has tried so far. Consider acute and/or prophylactic treatment where appropriate.</p> <p>If appropriate, give the patient an explanation that they have a primary headache called migraine.</p>
<p>First follow up with GP (after 2–8 weeks)</p>	<ul style="list-style-type: none"> • 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.

<p>Follow-up review with GP (after 6–8 weeks)</p>	<ul style="list-style-type: none"> • 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.
<p>Further follow up reviews with GP</p>	<ul style="list-style-type: none"> • 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, for example, 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_

Sumatriptan 85 mg/naproxen 457mg (Suvexx[®]) combined tablet is not recommended for use within NHSScotland for the acute treatment of the headache phase of migraine attacks with or without aura. [sumatriptan \(Suvexx[®]\)](#)

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 (Vypti®) 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-vypti-abb-smc2547

Atogepant (Aquipta®) 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 and episodic migraine who have had prior failure on three or more migraine preventive treatments. (October 2023). [atogepant \(Aquipta\)](#)

Rimegepant (Vydura®) is accepted for restricted use within NHSScotland for the acute treatment of migraine with or without aura in adults. It is restricted to patients who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated, and have inadequate pain relief with non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol (May 2023). [rimegepant \(Vydura\)](#)

Rimegepant (Vydura®) is accepted for restricted use within NHSScotland for the preventive treatment of episodic migraine in adults who have at least four migraine attacks per month. It is restricted to patients with episodic migraine who have at least four migraine attacks per month, but fewer than 15 headache days per month and who have had prior failure on three or more migraine preventive treatments (September 2023). [rimegepant \(Vydura\)](#)

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 2022 and 2026 updates, searches of Medline, Embase and the Cochrane Library were carried out. The year ranges covered were 2016–2022 and 2019–2025, respectively.

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 nortriptyline 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 2026. It will be considered for update again in 3 years.

The review history and any updates to the guideline 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 2022 and 2026 updates adhered to the 2019 and 2025 editions, respectively.

10.2 THE GUIDELINE DEVELOPMENT GROUP

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

2026 update

Dr Callum Duncan (<i>Chair and main author</i>)	<i>Consultant Neurologist, Aberdeen Royal Infirmary</i>
Dr Krishna Dani (<i>Main author</i>)	<i>Consultant Neurologist, Queen Elizabeth University Hospital, Glasgow</i>
Dr Francisco Javier Carod Artal	<i>Consultant Neurologist, Raigmore Hospital, Inverness</i>
Mr Alan Bigham	<i>Programme Manager, SIGN</i>
Dr Graham Boniface	<i>Health Services Researcher, Healthcare Improvement Scotland</i>
Ms Arlene Coulson	<i>Neurology Specialist Clinical Pharmacist, NHS Tayside</i>
Dr Mireia Moragas Garrido	<i>Consultant Neurologist, Western General Hospital, Edinburgh</i>
Ms Anne Keane	<i>Lay representative, Edinburgh,</i>
Dr Iain Maltman	<i>Neurology Specialty Registrar, Royal Infirmary of Edinburgh</i>
Dr Carolyn Sleith	<i>Evidence and Information Scientist, Healthcare Improvement Scotland</i>
Ms Ailsa Stein	<i>Programme Manager, SIGN</i>
Dr David PB Watson	<i>GPwER (GP with an extended role) Headache, Aberdeen Royal Infirmary</i>

2022 update

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

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk. During the 2026 guideline update, three group members declared interests. Their full participation was agreed in light of their expertise and experience in managing patients with migraine in NHSScotland. To mitigate, prior to consultation, the draft recommendations were reviewed in the context of the evidence base and SMC advice, by the SIGN Chair.

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.

Dr Graham Boniface	<i>Health Services Researcher</i>
Ms Karen Graham	<i>Patient and Public Involvement Advisor</i>
Mr Domenico Romano	<i>Publications Designer</i>
Ms Gaynor Rattray	<i>Guideline Co-ordinator</i>
Dr Carolyn Sleith	<i>Information Scientist</i>
Dr Lorna Thompson	<i>Health Services Researcher</i>

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	<i>Headache Nurse Practitioner, Queen Elizabeth University Hospital, Glasgow</i>
Ms Jennifer Gray	<i>Specialist Clinical Pharmacist in Neurosurgery, Ninewells Hospital, Dundee</i>
Mr Conor McKay	<i>Patient Representative, Inverurie</i>

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	<i>Consultant Neurologist and Honorary Senior Lecturer, Hull York Medical School</i>
Dr Anish Bahra	<i>Consultant Neurologist, National Hospital for Neurology and Neurosurgery, London</i>
Dr Anne Coker	<i>General Practitioner with a Special Interest in Headache, Dundee</i>
Dr Richard Davenport	<i>Consultant Neurologist, Western General Hospital, Edinburgh</i>
Dr Kay Kennis	<i>General Practitioner with a Special Interest in Headache, Bradford</i>
Dr David Kernick	<i>General Practitioner with a Special Interest in Headache, Exeter</i>
Professor Anne MacGregor	<i>Consultant Gynaecologist, The Royal London Hospital</i>
Dr Mireia Moragas Garrido	<i>Consultant Neurologist, Western General Hospital, Edinburgh</i>
Ms Lesley Murray	<i>Advanced Pharmacist for Neurology, NHS Greater Glasgow and Clyde</i>
Dr Richard Peatfield	<i>Consultant Neurologist, Charing Cross Hospital, London</i>
Dr Alok Tyagi	<i>Consultant Neurologist, Queen Elizabeth University Hospital, Glasgow</i>
Ms Rebecca Wicks	<i>Clinical Support Pharmacist, Right Medicine Pharmacy, Stirling</i>
Dr Ann Wilkinson	<i>Patient representative, Burton-on-Trent</i>

2026 update

Dr Fayyaz Ahmed	<i>Consultant Neurologist and Honorary Senior Lecturer, Hull York Medical School</i>
Dr Sabine Dedner	<i>GP with special interest in Neurology, Kenilworth</i>
Dr Arina Tamborska	<i>Neurology Specialist Registrar, Royal Infirmary of Edinburgh</i>

2022 update

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

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

2026 update

Dr Jill Fowlie	<i>Royal College of General Practitioners</i>
Dr Roberta James	<i>SIGN Programme Lead; Co-Editor</i>
Dr Safia Qureshi	<i>Director of Evidence, Healthcare Improvement Scotland</i>
Professor Angela Timoney	<i>Chair of SIGN; Co-Editor</i>

2022 update

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

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

ADHD	attention deficit hyperactivity disorder
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
WMD	weighted mean difference

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	<p>1. What is the clinical and cost effectiveness of abortive treatments for adults with acute migraine?</p> <ul style="list-style-type: none"> 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 (acetaminophen) <p>Comparison: placebo, other pharmacological therapies, device therapies</p> <p>Outcomes: pain free, pain free within two hours, sustained pain relief at 24 hours, adverse effects, QALYs, ICER</p> <p>Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension stroke/cerebrovascular risk.</p>
6	<p>2. What is the clinical and cost effectiveness of treatment with devices for adults with acute migraine?</p> <ul style="list-style-type: none"> a. Gamma core (vagal nerve stimulation) b. Cefaly (transcutaneous supraorbital nerve stimulation) c. Transcutaneous/transcranial magnetic stimulation <p>Comparison: placebo, other devices, pharmacological treatment</p> <p>Outcomes: pain free within two hours, adverse effects, QALYs, ICER</p> <p>Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension stroke/cerebrovascular risk.</p>

4	<p>3. What is the clinical and cost effectiveness of preventative treatment for adults with episodic or chronic migraine?</p> <ul style="list-style-type: none"> 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, levetiracetam, 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) <p>Comparison: placebo, other pharmacological therapies, device therapies</p> <p>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</p> <p>Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension stroke/cerebrovascular risk.</p>
6	<p>4. What is the clinical and cost effectiveness of preventative treatment with devices for adults with episodic or chronic migraine?</p> <ul style="list-style-type: none"> a. Gamma core (vagal nerve stimulation) b. Cefaly (transcutaneous supraorbital nerve stimulation) c. Transcutaneous magnetic stimulation <p>Comparison: placebo or usual care, other devices, pharmacological treatment</p> <p>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</p> <p>Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension, stroke/cerebrovascular risk.</p>

5	<p>5. What strategies are effective in the management of adults with medication overuse headache?</p> <ul style="list-style-type: none"> 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 <p>Comparison: other strategies</p> <p>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</p> <p>Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension, stroke/cerebrovascular risk.</p>
2026 update	
	<p>1. What is the effectiveness of abortive treatments for adults with acute migraine?</p> <p>Intervention: calcitonin gene-peptide receptor antagonists</p> <p>Comparison: placebo, other pharmacological therapies, device therapies</p> <p>Outcomes: pain free, pain free within two hours, sustained pain relief at 24 hours, adverse effects, QALYs, ICER</p> <p>Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension, stroke, cerebrovascular risk.</p>
	<p>2. What is the effectiveness of preventative treatment for adults with episodic or chronic migraine?</p> <p>Intervention: calcitonin gene-peptide receptor antagonists</p> <p>Comparison: placebo, other pharmacological therapies, device therapies</p> <p>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</p> <p>Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension, stroke, cerebrovascular risk.</p>

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 (for example, 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, opioids, 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.

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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