Healthcare Improvement Scotland | SIGN Evidence-based clinical guidelines

Pharmacological management of migraine

A national clinical guideline

Consultation draft, October 2025

NHS SCOTLAND

Key to evidence statements and recommendations

Levels of evidence

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

Recommendations

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

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

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

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

R For '**conditiona**l' 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.

Contents

1. Introduction

1.1 The need for a guideline

Headache is common, with a lifetime prevalence of over 90% of the general population in the United Kingdom (UK).[1] It accounts for 4.4% of consultations in primary care and 30% of neurology outpatient consultations.[1-4] Headache disorders are classified as either primary or secondary.[5] Primary headache disorders are not associated with an underlying pathology and include migraine, tension-type, and cluster headache. Secondary headache disorders are attributed to an underlying pathological condition. Medication-overuse headache (MOH) is increasingly recognised as a problem and affects around 1% of the population worldwide, but can vary significantly between countries (0.5% to 2.6%).6,7 In patients with MOH, migraine is the most common underlying headache disorder (approximately 80%).

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

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

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

In recent years there have been advances in the diagnosis and treatment of migraine. There are new therapies available for both acute and preventative treatment of patients with migraine, such as oral calcitonin gene-related peptide receptor (CGRP) antagonists and CGRP monoclonal antibodies. The revised guideline considers the evidence for these new treatments and their use alongside established therapies.

1.2.6 Diagnostic and treatment pathway

The guideline informs the National Headache Pathway, produced by the National Centre for Sustainable Delivery.[152] It includes pathways on:

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

3 Treatment for patients with acute migraine

3.1 Introduction

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

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

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.

Rimegepant can 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).

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. 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]

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

3.2 Aspirin

A Cochrane review of 13 studies (4,222 participants) reported that aspirin 900 mg and aspirin 1,000 mg were effective in achieving pain free at two hours compared to placebo (NNT=8.1). For sustained pain relief at 24 hours aspirin 1,000 mg had an NNT of 6.6 compared to placebo.[21]	1++
Aspirin alone had similar efficacy to sumatriptan 50 mg, and sumatriptan 100 mg was superior to aspirin and metoclopramide combined.[21]	1++
Associated symptoms of nausea, vomiting, photophobia (NNT=7.7) and phonophobia	1++

(NNT=6.6) were reduced by aspirin when compared to placebo. The addition of metoclopramide further reduced nausea (NNT=2.6) and vomiting.[21]	
Aspirin is a potential gastrointestinal irritant and may cause ulcers or gastrointestinal bleeding, however adverse effects from short-term use are mostly mild and transient.[21] Aspirin should not be used in patients under 16 years of age due to the risk of Reye's syndrome.[17] The use of aspirin during pregnancy, especially of intermittent high doses, should be avoided.[22] Aspirin is contraindicated during the third trimester of pregnancy.[17]	1++

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

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

3.3 Non-steroidal anti-inflammatory drugs

A Cochrane review found ibuprofen to be superior to placebo in all doses between 200 mg and 600 mg for pain free at two hours and sustained pain relief at 24 hours for patients with acute migraine with moderate to severe baseline pain. The NNT for achieving the outcome of pain free at two hours was 9.7 for 200 mg and 7.2 for 400 mg.[23]	1++
Naproxen has also been found to be effective for two hour pain relief compared to placebo for patients with acute migraine. The NNT for pain free at two hours was 11. Results did not vary for doses of 500 mg and 825 mg.[24]	1++
Diclofenac potassium 50 mg is reported to have a relative benefit over placebo, relative risk (RR) 2.0 (95% confidence interval (CI) 1.6 to 2.6), NNT=8.9, for pain free at two hours in patients with acute migraine.[25]	1++
Naproxen and ibuprofen were also effective in relieving migraine-associated symptoms of nausea, photophobia, phonophobia and functional disability compared to placebo.[23,24]	1++
No serious adverse events were reported in the trials.[23-25] NSAIDs can cause gastrointestinal problems with long-term use.[17] They should also be used with caution in patients with asthma as NSAIDs may worsen the condition.[17]	1++
It is uncertain whether ibuprofen taken in the early stages of pregnancy contributes to a higher rate of miscarriage. Ibuprofen may be considered under specialist recommendation up to week 20. [17,153]	4

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

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

✓ 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 two hours as 1.8 (95% CI, 1.2 to 2.6), NNT=12, compared to placebo in patients with moderate or severe acute migraine.[27]	1++
In two studies including 1,140 patients with acute migraine, a combination of paracetamol 1,000 mg plus metoclopramide 10 mg had similar efficacy to sumatriptan 100 mg for headache relief at two hours (39% of participants reported relief using paracetamol and metoclopramide versus 42% for sumatriptan).[27]	1++
For pain free and sustained headache relief at 24 hours, paracetamol was more effective than placebo, but not compared to rizatriptan.[27]	1++
Paracetamol is commonly used in all trimesters of pregnancy, but should be used at the lowest dose and for the shortest duration.[22,26,154]	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 the first choice for the short-term relief of mild-to-moderate headache during any trimester of pregnancy.[22,26]

3.5 Antiemetics

Metoclopramide 10 mg (oral) in combination with aspirin 900 mg had similar efficacy to 100 mg sumatriptan in achieving the outcome of pain free at two hours.[21] Similar results were found for paracetamol 1,000 mg combined with metoclopramide 10 mg versus sumatriptan.[27] However, aspirin and metoclopramide provided significantly better relief of associated symptoms, with an NNT of 2.6 (95% CI 2.1 to 3.1). It was particularly beneficial in reducing vomiting, NNT=2.1 (95% CI 1.5 to 3.7).[21]	1++
A randomised controlled trial (RCT) comparing different doses of metoclopramide found that all doses provided an improvement in pain response, measured using an 11-point numerical rating score for pain (NRS). Most patients improved by more than 50%. Individual improvement with metoclopramide was 4.7 NRS units for 10 mg, 4.9 for 20 mg and 5.3 for 40 mg.[28]	1+
A meta-analysis found that phenothiazines are superior to placebo for complete headache relief up to one hour after treatment (odds ratio (OR) 15.02, 95% CI 7.57 to 29.82). There was no significant difference in efficacy for complete headache relief when compared to metoclopramide.[29]	1+
Both prochlorperazine 10 mg and metoclopramide 20 mg (both co-administered with diphenhydramine and given intravenously) were found to be effective for pain relief at one hour for patients with acute migraine, as recorded on the NRS scale. At two hours the NRS for pain after treatment with prochlorperazine was 6.4 from a baseline NRS of 8.4, and for metoclopramide 5.9 from a baseline NRS of 8.8. The overall difference was 0.6 (95% CI -0.6 to 1.8), with an NNT of 17 for pain free at two hours.[30]	1+
Reporting of side effects was inconsistent amongst trials.[21,29] Most side effects were minor.21 Akathisia was reported in trials of metoclopramide and prochlorperazine in 5–9% of participants.[28,30] Drowsiness and dizziness was also noted. More dropouts were noted as the dose of metoclopramide increased.[28]	1+

R	Metoclopramide (10 mg) or prochlorperazine (10 mg) can be considered in the treatment of headache in patients with acute migraine. They can be used either as an oral or parenteral formulation depending on presentation and setting.	
R	Metoclopramide (10 mg) or prochlorperazine (10 mg) should be considered for patients presenting with migraine-associated symptoms of nausea or vomiting. They can be used either as an oral or parenteral formulation depending on presentation and setting.	
✓	Metoclopramide should not be used regularly due to the risk of extrapyramidal side effects.	

3.6 Triptans

	For patients experiencing acute migraine, triptans are superior to placebo, for pain relief, pain free within two hours and sustained pain relief at 24 hours.[31-35]	1++ 1+ 2++
	An overview of Cochrane reviews reported that sumatriptan is an effective abortive treatment for acute migraine episodes.[33] The subcutaneous route is the most effective in terms of pain relief at two hours from moderate to severe baseline pain, with an NNT of 2.5 for 4 mg and 2.3 for a 6 mg dose. Efficacy was significantly improved if treatment was taken early, while pain was mild. For oral sumatriptan 50 mg the NNT for pain free at two hours was 6.1 for moderate to severe baseline pain and 4.4 for mild baseline pain. For 100 mg sumatriptan the NNT was 4.7 for pain free at two hours for moderate to severe pain and 2.4 for mild pain. Intranasal sumatriptan is also effective for pain free at two hours (NNT=3.1).[33]	1++
	In studies comparing sumatriptan to other triptans, zolmitriptan and almotriptan showed similar efficacy.[33] Rizatriptan 10 mg was superior to all doses of sumatriptan for achieving pain free at two hours. Rizatriptan 5 mg had similar efficacy to sumatriptan 50 mg. Eletriptan 40 mg and 80 mg was superior to both doses of sumatriptan for the outcome of pain free at two hours and was associated with reduced need for rescue medication.[33]	1++
	Compared to other therapies, sumatriptan 100 mg was superior for achieving pain free at two hours than aspirin 900 mg with metoclopramide 10 mg, or paracetamol 1,000 mg and metoclopramide 10 mg.[33] Sumatriptan was superior to effervescent aspirin 1,000 mg for headache relief at two hours.[33]	1++
	For patients with menstrually-related migraine (MRM), sumatriptan resulted in a therapeutic gain with 25% of patients pain free at two hours with 50 mg and 34% with 100 mg compared to placebo.[35] Rizatriptan, frovatriptan and zolmitriptan were also reported to provide benefit for acute treatment of patients with MRM.[34,35]	1++ 1+
	Adverse events reported in the trials were described as mild to moderate. Serious adverse events were rare.[33 31]	1++
	Patients using rizatriptan and propranolol should be given a maximum dose of 5 mg rizatriptan due to the risk of interactions and rizatriptan should not be taken within two hours of taking propranolol.[17]	
	One study of cardiovascular outcomes with triptan use reported an OR of 0.86 (95% CI 0.52 to 1.43), for a serious cardiovascular event.[36] Triptans are contraindicated in patients with uncontrolled hypertension and in symptomatic cardiovascular and cerebrovascular disease.[17] Trials of triptans have focused on a population aged 18–65 years. There is therefore no information on triptan use in the over 65s. Hypertension, cardiovascular disease and cerebrovascular disease are all more common in older people. Age is not a contraindication to use of triptans but age and vascular risk factors should be taken into	1++

account before prescribing triptans in the over 65s.[17]	
The United States Food and Drug Administration (FDA) issued a warning following a small number of case reports of possible 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 have 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 (all trimesters)) fails, the use of triptans, in particular sumatriptan, in all stages of pregnancy can be considered. 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.

3.7 Oral calcitonin gene-related peptide receptor antagonists

Rimegepant is an oral CGRP receptor antagonist licensed for the acute treatment of patients with migraine. A meta-analysis identified two RCTs in rimegepant 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 superior for remaining pain free from 2 to 24 hours (OR 2.43, 95% CI 1.59 to 3.71) and pain relief for 2 to 24 hours (OR 2.24, 95% CI 1.89 to2.65).[155] For the secondary outcome of sustained pain free 2-48 hours post dose, 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.[156] 1+

The 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 the two RCTs and an unpublished RCT 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).[157] See section 3.10 for comparison of effectiveness with triptans. 3

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 the two published RCTs, rimegepant was well tolerated and adverse events were similar between treatment and placebo groups.[158,159] No significant adverse effects were identified in a one year follow-up study.[160] 1++

Patients at high risk of ischaemic cardiovascular disease were excluded from the trials. Since CGRP can mediate vasodilation, caution is advised with the use of monoclonal antibodies targeted to the CGRP pathway in patients with vascular disease, vascular risk factors and Raynaud's phenomenon.[161] As oral CGRP receptor antagonists also target the CGRP pathway, it is suggested that similar cautions should be applied. 3 4

Likewise, there may be a risk that medications blocking the effect of CGRP may predispose to hypertension in some people. It is suggested that oral CGRP receptor antagonists should not be used in patients with uncontrolled hypertension.

R Rimegepant should be considered as second-line treatment for patients with acute migraine who have had an inadequate response to two or more triptans.

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

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

✓ Treatment with rimegepant in patients with uncontrolled hypertension is cautioned. Therefore it is recommended that blood pressure is measured before treatment initiation, and periodically thereafter.

✓ 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.[152]

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

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

The Scottish Medicines Consortium has rejected the use of combination tablets of sumatriptan 85 mg and naproxen 475 mg for use within NHSScotland. An alternative is to provide separate tablets of each treatment.

R Coprescription of sumatriptan and naproxen can be considered for the treatment of patients with acute migraine.

✓ A combination of a triptans with a non-steroidal therapy 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] 1+

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

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

3.10 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 were not measured against placebo so NNTs could not be calculated for comparison. A treatment algorithm outlining good practice in acute treatment can be found in 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. 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%), followed by rizatriptan (33%), oral sumatriptan (29%) and oral zolmitriptan (28%). Rimegepant was comparatively less effective than the triptans (18%) and was similar to ibuprofen (20%). The most efficacious treatments for sustained pain freedom (2–24 hours) were eletriptan (26%) and ibuprofen (38%).[162] 1+

4 Pharmacological prevention of migraine

4.1 Introduction

This section considers the preventative treatment options for patients with episodic and chronic migraine. Most of the available evidence is based on studies of a patient population with episodic migraine rather than chronic migraine *(for definitions, see section 1.2.3*). For some treatments there is insufficient data to make specific treatment recommendations for patients with chronic migraine. Recommendations are therefore based on the premise that chronic migraine and episodic migraine are on a spectrum of the same condition and patients with chronic migraine may benefit from the therapies found to be effective for prophylaxis of episodic migraine. Specific evidence for the effectiveness of preventative treatments in chronic migraine is available for atogepant, botulinum toxin A, the CGRP monoclonal antibodies and topiramate.

Migraine can have considerable impact on quality of life and daily function. Modest improvements in the frequency or severity of migraine headaches may provide considerable benefits to an individual. Within trials, a reduction in migraine headache severity and/or frequency of 30–50% is regarded as a successful outcome. The decision about when to start migraine prophylaxis is best guided by establishing the impact of migraine on each patient, rather than just focusing on the absolute number of headaches or migraines per month. For example, a few severe incapacitating migraines per month may warrant prophylactic treatment whereas more frequent but milder migraines that have little impact on daily function may not warrant treatment. Overusing acute medication can limit the effectiveness of preventative medication and medication overuse should also be assessed and addressed.[44] 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 where there is a titration schedule) before deciding if it is effective or not. For treatments on a fixed dose (eg oral CGRP receptor antagonist) treatment effectiveness should be assessed at 3 months. In many patients, prophylactic medication can be successfully phased out again and the need for ongoing prophylaxis should be considered after 12 months.

The decision regarding which medication to try first is dependent on evidence of effectiveness, patient comorbidities, other risk factors, drug interactions and patient preference. It is important to ensure adequate contraception 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, potential harmful effects of therapies need to be discussed with women who are, or may become, pregnant. No evidence was identified on which to base recommendations on preventative treatments for women during pregnancy.

4.2 Candesartan

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

The evidence base for candesartan is small. However, candesartan is a widely used and inexpensive drug with a good side-effect profile, and no potential cognitive effects.

R	Candesartan (16 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine.
R	Use of candesartan should be avoided during pregnancy and breastfeeding. Women using candesartan who are planning to become pregnant, or who are pregnant, should seek advice from their healthcare professional on switching to another therapy.

4.3 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 ≥50% compared to placebo (NNT=4, 95% CI 3 to 7).[46] Metoprolol (200 mg daily, slow release) reduced migraine severity, but no consistent benefits in reduction of migraine frequency or use of acute analgesics was shown.[46] Atenolol 50–200 mg daily was reported to reduce frequency of episodic migraine and use of acute therapies.[46]	1++
Direct comparative trials of the effectiveness of propranolol with other medications used for migraine prevention in patients with episodic and chronic migraine were of low quality due to risk of bias and failure to analyse data according to intention-to-treat principles. Within these constraints the likelihood of a 50% reduction in headache frequency did not differ between propranolol and topiramate. Propranolol was better than nifedipine but there was no clear evidence to suggest it was better than other beta blockers such as metoprolol and timolol. Similarly there was no difference when compared to amitriptyline or nortriptyline. The use of combined tricyclic antidepressant and propranolol was no better than propranolol monotherapy.[46]	1++
Propranolol use led to treatment side effects more commonly than placebo and specific adverse events leading to discontinuation included nausea (43 per 1,000 treated) and diarrhoea (89 per 1,000 treated).[46] However, it is a well-established therapy and is widely used in NHSScotland. Beta blockers should be used with caution if the patient has a history of asthma.[17] Patients using rizatriptan and propranolol should be given a maximum dose of 5 mg rizatriptan as propranolol increases the plasma concentration of rizatriptan. Rizatriptan should not be taken within two hours of taking propranolol.[17]	1++

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

4.4 Tricyclic antidepressants

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

A further meta-analysis found that amitriptyline (100 mg) was more effective than placebo in achieving a ≥50% reduction in headache frequency but more so in those with higher headache frequencies. This was based on low-quality evidence.[46]	1++
In comparative trials, low-dose (eg an average amitriptyline dose of 50 mg) TCAs were more likely to produce at least a 50% improvement in episodic migraine headache frequency than SSRIs. Studies comparing beta blockers and TCAs, amitriptyline and topiramate, and amitriptyline and flunarizine found no difference in the likelihood of gaining a 50% reduction in headache attacks. However there are relatively few trials and most were underpowered to assess clinical equivalence.[46]	1++
Across 37 studies of various TCAs, only dry mouth and drowsiness were reported as more frequent in the TCA group than the placebo group. Some TCAs are less sedating than others.[17] Withdrawal from treatment due to an adverse event was similar between patients taking placebo or TCA.[52] TCAs are unlicensed for the treatment of patients with migraine (*see section 1.3.2).*	1+

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

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

4.5 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, using 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 to placebo in patients with episodic or chronic migraine over 12 weeks.[163-165] In one meta-analysis atogepant reduced MMDs compared to placebo with statistically significant differences at all doses (standardised mean difference (SMD) -0.40, 95% CI -0.46 to -0.34, p<0.00001).[164] Another meta-analysis reported a reduction in MMDs for the 60 mg dose of atogepant compared to placebo (weighted mean difference (WMD) -1.40, 95% CI -2.02 to -0.78, p<0.01).[165] Likewise, another meta-analysis showed a reduction in MMDs for atogepant 60 mg (mean difference in MMD -1.35, 95% CI -1.85 to -0.85).[163] With respect to 50% responder rates, for 60 mg atogepant, one analysis reported a risk ratio of 1.82 (95% CI 1.34 to 2.48) for ≥50% reduction in MMDs in patients with episodic and chronic migraine.[164] In patients with episodic migraine, 60 mg atogepant compared to placebo, the OR for ≥50% reduction in MMDs was 2.57 (95% CI 1.56 to 4.23).[163] Data from the individual trials reported 50% responder rates for atogepant 60 mg as follows: Goadsby et al (episodic migraine) 52% (vs 40% placebo); ADVANCE (episodic migraine) 60.8% (vs 29% placebo); PROGRESS (chronic migraine) 41% (vs 26% placebo); ELEVATE (episodic migraine where 2-4 conventional oral prophylactic agents had failed) 51% (vs 18% placebo).[166-169]In an open-label trial the ≥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.[170]	1++ 1+
A prespecified subgroup analysis of the PROGRESS RCT in the use 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.[171]	3

Atogepant is accepted by the SMC for use in NHSScotland for the prevention of migraine in adults who have at least 4 migraine days per month and who have had prior failure 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).[163,172,173] 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 (-4.8 to -3.9) MMDs compared to -3.5 (-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% (44 to 54) for those taking rimegepant, compared with 41% (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 accumulating effect.[174] Patients who had two or more failed migraine preventatives were excluded from the RCT. Information on medication overuse headache was not reported.

1+
1++
3

An RCT designed to show superiority of galcenezumab over rimegepant in patients with episodic migraine found that both therapies had a similar 50% responder rate (galcenezumab 62%; rimegepant 61%). The reduction in MMDs was equally similar (galcenezumab -4.8; rimegepant -4.4).[175]

1++

Rimegepant is accepted 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, who have had three or more unsuccessful migraine preventive treatments.

None of the studies reported serious adverse effects from use of atogepant or rimegepant. Both were well tolerated.[165,170,172-174] Nausea was the most common side effect associated with 75 mg (alternate days) rimegepant and the 60 mg dose of atogepant.[165,172,173] Long-term use of atogepant was also associated with upper respiratory tract infection and constipation.[170]

1+
1++
3

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 to CGRP advise caution in people with vascular disease, vascular risk factors and Raynaud's phenomenon (see section 4.14).[161] As oral CGRP receptor antagonists also target the CGRP pathway, it is suggested that similar cautions should be applied until further evidence is available.

4

Likewise, there may be a risk that medications blocking the effect of CGRP may predispose to hypertension in some people. It is suggested that neither atogepant nor rimegepant should be used in patients with uncontrolled hypertension.

R **Atogepant is recommended for the prophylactic treatment of patients with episodic or chronic migraine who have at least 4 migraine days per month, where medication overuse headache has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments.**

R **Rimegepant should be considered 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 been appropriately treated with 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 before prescribing oral CGRP receptor antagonists.

✓ When initiating oral CGRP receptor antagonists 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 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 *v* -6.4; p=0.006) and migraine days (-7.6 *v* -6.1; p=0.002).[68]	1++
In PREEMPT 2 the primary endpoint was changed (prior to completion of the trial and before analysis) to reduction in headache days. It was stated that this was a better measure than headache episodes in patients with chronic migraine due to the prolonged, continuous nature of their headaches. There was a significant reduction in both headache days for botulinum toxin A versus placebo (-9.0 *v* -6.7; p<0.001) and migraine days (-8.7 *v* -6.3; p<0.001) compared with baseline. There was also a significant reduction in headache episodes in PREEMPT 2 for botulinum toxin A versus placebo (-5.3 *v* -4.6; p=0.003).[69]	1+
Post-hoc analysis of pooled data from both trials of those patients who had previously used three or more migraine preventatives reported a bigger difference, compared to placebo, in headache days and migraine days for botulinum toxin A (-7.4 *v* -4.7; p<0.001) and migraine days (-7.1 *v* -4.3; p<0.001) compared with baseline.[70]	
In both PREEMPT trials about two thirds of the patients overused abortive treatments. In such patients MOH should be addressed first (*see section 5*). However, in patients where treatment of MOH has been unsuccessful, botulinum toxin A should still be considered.	
A meta-analysis of trials of patients with episodic migraine or tension-type headache found no difference in efficacy compared to placebo.[66]	1+
Five individual RCTs provided low-strength evidence about the comparative effectiveness of botulinum toxin A versus other drugs for chronic migraine prevention in 350 adults ages 18–65 with 12–24 migraine days per month. No significant differences in likelihood of migraine prevention or improvement in migraine disability assessment were found for botulinum toxin A compared to topiramate. Absolute scores of the Headache Impact Test were significantly better with topiramate than botulinum toxin A, however, the need for acute drugs did not differ between the two. A single RCT examined the comparative effectiveness of botulinum toxin A versus divalproex sodium and found no differences between the two drugs for migraine prevention, migraine-related disability, or quality of life.[46]	1++
Adverse events were slightly more common in patients injected with botulinum toxin A compared to placebo (RR 1.25, 95% CI, 1.14 to1.36), although they were not more likely to withdraw from the study as a result. Adverse events included ptosis, muscle weakness, neck pain and stiffness, paraesthesia and skin tightness.[46,66]	1++ 1+
Botulinum toxin A (Botox®) has been accepted with restricted use in NHSScotland for adults with chronic migraine (headaches on at least 15 days per month of which at least eight days are with migraine) whose condition has failed to respond to ≥3 prior oral prophylactic treatments, where medication overuse has been appropriately managed.[70]	

This was based on clinical effectiveness and a cost-utility analysis (Markov model) which compared botulinum toxin A to best supportive care, over a three-year time horizon. The analysis reported that botulinum toxin A resulted in an incremental cost-effectiveness ratio (ICER) of £10,816 and quality-adjusted life year (QALY) gain of 0.12.[70] Botulinum toxin A is required to be administered by appropriately trained personnel in hospital specialist centres, which may have implications for service delivery.

R	**Botulinum toxin A is not recommended for the prophylactic treatment of patients with episodic migraine.**
R	**Botulinum toxin A is recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments.**
✓	Botulinum toxin A should only be administered by appropriately trained individuals under the supervision of a headache clinic or the local neurology service.

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

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

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

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

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

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

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

1++

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

1++

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

2++

The HALO episodic migraine trial compared monthly doses of fremanezumab (225 mg) to quarterly doses (675 mg) or placebo. The baseline number of migraine days was 8.9±2.6 for the cohort receiving a monthly dose and 9.3±2.7 for the quarterly cohort, indicating

that the majority of participants had a higher frequency of episodic migraine. There was a significant reduction in MMDs (-3.7 in the group who received monthly fremanezumab (225 mg) vs -3.4 with quarterly fremanezumab (675 mg), vs -2.2 with placebo (p<0.001)).[123] In the open-label extension study, which included episodic migraine, chronic migraine and new enrollees, this increased to -5.1 MMDs with the monthly dose and -5.2 with the quarterly dose at 12 months in the episodic migraine cohort.[132] There was a ≥50% reduction in MMDs in 41% of participants with the monthly dose and in 44.4% with the quarterly dose, which increased to 68% and 66% respectively at 12 months.[123,132]	1++ 2++
In the chronic migraine cohort of the HALO trial there was a significant reduction in MMDs compared to placebo at 12 weeks (-5.0 in the group who received monthly fremanezumab (675 mg loading and 225 mg monthly thereafter) vs -4.9 with quarterly fremanezumab (675 mg) vs -3.2 with placebo p<0.001).[124] This increased to -8.0 for the monthly dose and -7.2 with the quarterly dose in the open-label extension study.[132] There was a ≥50% reduction in MMDs in 47.7% with the monthly dose and 38% with the quarterly dose, which increased to 57% and 53% respectively at 12 months.[124,132] The dose of 675 mg then a monthly dose of 225 mg used in the trial differs from the licensed monthly dose of 225 mg monthly or 675 mg quarterly.	1++ 2++
In a study, FOCUS, of patients who had had treatment failure with up to four previous therapies, in which 60% of the patients had chronic migraine and 40% had episodic, the reduction in MMDs at 12 weeks was -4.1 with monthly fremanezumab (225 mg), and -3.7 with quarterly fremanezumab (675 mg). The 50% responder rate was 34% for both regimens.[125]	1++
In the EVOLVE 1 and EVOLVE 2 RCTs of galcanezumab in patients with episodic migraine, there was a significant reduction in monthly migraine headache days (MHD) compared to placebo at 12 weeks (EVOLVE 1: -4.7 with 120 mg vs -4.6 with 240 mg vs -2.8 with placebo p<0.001, and EVOLVE 2: -4.3 with 120 mg vs -4.2 with 240 mg vs -2.3 with placebo p<0.001).[126,127] There was a ≥50% reduction in monthly MHDs in 62.3% of participants with 120 mg and in 60.9% with 240 mg in EVOLVE 1, and in 59.3% with 120 mg and in 56.5% with 240 mg in EVOLVE 2. The baseline number of migraine days in EVOLVE 1 was 9.2±3.1 with 120 mg and 9.1±2.9 with 240 mg, and in EVOLVE 2 it was 9.07±2.9 with 120 mg and 9.06±2.9 with 240 mg, indicating that the trial cohort had higher frequency episodic migraine.	1++
An RCT, REGAIN, of galcanezumab in patients with chronic migraine (64% of whom overused abortive treatments) reported a significant reduction in monthly MHDs compared to placebo at 12 weeks (-4.8 with 120 mg vs -4.6 with 240 mg vs -2.7 with placebo, p<0.001, from a baseline of 19.4 monthly MHDs).[128] There was a ≥50% reduction in monthly MHDs in 27.6% of participants with 120 mg and in 27.5% with 240 mg. Ninety- nine percent of patients entered the open-label extension with 81% completing 12 months of treatment. Patients remained blinded as per their original allocation. At month three all patients were given a 240 mg loading dose and then maintained on 120 mg monthly (with the option of a 120 mg top up at the discretion of the treating clinician). At 12 months the reduction in monthly MHDs improved to -9.0 in the previous 120 mg group, -8.0 in the previous 240 mg group and -8.5 in the previous placebo group.[133]	1++
In the CONQUER RCT in patients with harder-to-treat migraine, participants received galcanezumab 120 mg or placebo.129 This included a loading dose of either 2 x 120 mg galcanezumab or 2 x placebo injections. At 12 weeks the reduction in monthly MHDs was -2.9 with 120 mg vs -0.3 with placebo in patients with episodic migraine (p<0.0001), 48.1% had a ≥50% reduction in monthly MHDs. For patients with chronic migraine the reduction was -6.0 with 120 mg galcanezumab vs -2.2 with placebo (p<0.0001), and 32% had a ≥50% reduction in monthly MHDs.129 All except two patients who completed the double-blind phase entered the open-label phase and 96% of these completed the study.[134] All patients previously in the placebo group had a 240 mg loading dose at month three (2 x 120mg in the placebo group and 1 x 120mg and 1 x placebo in the 120 mg group). At 6 months the reduction in monthly MHDs was -3.8 for the previous 120 mg group versus -4.5 for the previous placebo group in patients with episodic migraine and -8.2 for the previous 120 mg group vs -6.5 for the previous placebo group in patients with	1++ 2++

chronic migraine.[134]	
In the PROMISE 1 RCT of eptinezumab in patients with episodic migraine there was a significant reduction of MMDs compared to placebo at 12 weeks with 100 mg and 300 mg (-4.0 with 30 mg (p=0.0046) versus -3.9 with 100 mg (p=0.0182) versus -4.3 with 300 mg (p=0.0001) versus -3.2 with placebo).[149] There was a >50% reduction in MMDs in 48.9% of participants with 100 mg and 56.3% with 300 mg, and a >75% reduction in MMDs in 22.2% of participants with 100 mg and 29.7% with 300 mg. There was an observed preventative effect on the first day after dosing (percentage of patients with migraine on day 1 was 14.8% with 100 mg versus 13.9% with 300 mg versus 22.5% with placebo). The baseline number of migraine days was 8.7 with 100 mg and 8.6 with 300 mg and 8.4 with placebo.[149]	1++
In the PROMISE 2 RCT of eptinezumab in patients with chronic migraine there was a significant reduction of MMDs compared to placebo at 12 weeks with 100 mg and 300 mg (-7.6 with 100 mg versus -8.2 with 300 mg versus -5.7 with placebo p<0.0001).[150] There was a >50% reduction in MMDs in 57.6% of participants with 100 mg and 61.4% with 300 mg, and a >75% reduction in MMDs in 26.7% of participants with 100 mg and 33.1% with 300 mg. There was an observed preventative effect on the first day after dosing (percentage of patients with migraine on day 1 was 28.6% with 100 mg versus 27.8% with 300 mg versus 42.3% with placebo). The baseline number of migraine days was 16.1 with 100 mg and 300 mg and 16.2 with placebo.[150]	1+
The number of prior preventative treatments used is not reported in either PROMISE 1 or PROMISE 2. The study, DELIVER, of patients who had treatment failure with up to four previous preventative treatments, enrolled participants with both episodic and chronic migraine.[151] In the 100 mg group 13% had low- frequency episodic migraine (≤14 monthly headache days including 4–7 MMDs), 41% had high-frequency episodic migraine (≤14 monthly headache days including 8–14 MMDs), 46% had chronic migraine and 13% met criteria for MOH. The percentages were comparable in the 300 mg and placebo groups. Results for episodic and chronic migraine were not analysed separately. The mean MMDs was 13.8 with 100 mg, 13.7 with 300 mg and 13.9 with placebo. There was a significant reduction in mean MMDs compared to placebo at 12 weeks with 100 mg and 300 mg (-4.8 with 100 mg versus -5.3 with 300 mg versus -2.1 with placebo p<0.0001). This was sustained at 24 weeks (-5.4 with 100 mg versus -6.1 with 300 mg versus -2.4 with placebo p<0.0001). There was a >50% reduction in mean MMDs in 42% of participants with 100 mg and 49% with 300 mg, and a >75% reduction in mean MMDs in 16% of participants with 100 mg and 17% with 300 mg at 12 weeks.	1++
When compared to topiramate in an RCT, erenumab was more effective in reducing MMDs (-5.86 erenumab vs -4.02 topiramate). There was a ≥50% reduction in MMDs in 55.4% of participants in the erenumab group compared with 31.2% in the topiramate group. Erenumab was significantly better tolerated than topiramate (used at standard doses); 10.6% of the erenumab cohort discontinued treatment compared to 38.9% on topiramate.[135] Results from a network meta-analysis comparing CGRP monoclonal antibodies to topiramate or botulinum toxin A are limited.[136] More head-to-head trials are needed before a recommendation can be made. The primary endpoint for CGRP trials is MMDs, whereas trials of botulinum toxin A used MHD therefore they are not directly comparable.	1+
Subgroup analyses of patients with migraine and concomitant medication overuse in trials of erenumab, fremanezumab and galcanezumab demonstrated similar efficacy to those without medication overuse.[137-139] These subgroup analyses also demonstrated that the CGRP monoclonal antibodies reduced the use of acute medications. In the parent studies, medication overuse was defined as simple analgesia (eg paracetamol or NSAIDs) taken on 15 days per month, triptans on 10 days per month, and combination analgesics (including those with simple analgesia and opioids) taken on 10 days per month. Although inclusion criteria varied between studies, all of the parent studies had some restriction on the intake of opioid and/or barbiturate containing medications.	2++
There are very limited data, in two small case series, describing outcomes of switching to a second CGRP monoclonal antibody if the first is ineffective.[140,141] Further evidence is needed before a recommendation can be made.	3

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

1++

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

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

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

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

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

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

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

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

✓ When initiating oral 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 ≥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]	1++
	Topiramate at doses of 50–200 mg daily is effective in reducing monthly migraine frequency and MMDS 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]	1++
	In seven trials of topiramate versus active comparators (amitriptyline, flunarizine, propranolol, sodium valproate and relaxation) topiramate was found to be no better than any comparator except for a small, but significant, benefit over sodium valproate. However, these trials were underpowered and further evidence is needed to confirm these findings.[48]	1++
	Topiramate 100 mg daily was associated with a higher rate of adverse events than placebo, although these were mild to moderate.[47,48] Adverse effects include nausea, paraesthesia, anorexia and weight loss.[47-49] Cognitive adverse effects are common, vary in severity, tend to be dose related and often define drug tolerability.[50] As depression is also a common side effect, topiramate should be used with caution in patients with depression.[17]	1++ 1+ 2++
	Children exposed to topiramate in utero are at high risk of serious developmental disorders, congenital malformations and low birth weight.[176] The risk of intellectual disability, autistic spectrum disorder and attention deficit hyperactivity disorder (ADHD) is 2–3 times that of the general population. The risk of congenital malformations is 4–9/100 babies compared with 1--3/100 in the general population and is dose dependent. Cardiac malformations are the most frequent abnormality followed by hypospadias and multiple major congenital malformations. Topiramate is contraindicated in pregnancy and women who are at risk of pregnancy must be on highly effective contraception in line with the MHRA Topiramate Pregnancy Prevention Programme.[176] Advice on contraception is available from the Royal College of the Obstetricians and Gynaecologists Faculty of Sexual and Reproductive Healthcare, Standards and Guidelines | CoSRH	4
	Topiramate should not be used by women who are breast feeding as it can be present in breast milk.[17]	4
R	Topiramate (50–100 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine. It should not be considered 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.**

Before commencing treatment women should be informed of:

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

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

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 nicardipine over placebo in patients with episodic or chronic migraine.[46,53]	1++ 1+
Meta-analysis of seven trials of flunarazine at a dose of 10 mg daily reported a moderate benefit in patients with episodic migraine compared to placebo. The SMD for reduction in headache frequency was -0.60 (95% CI -1.2 to 0.005) at eight weeks and -0.84 (95% CI -1.3 to 0.34) at 12 weeks. No significant benefit was found at four weeks.[53] The trials included in the meta-analysis were small.	1+
Comparative trial data was limited, but there is some evidence that flunarazine has similar efficacy to propranolol, topiramate and sodium valproate.[53,58]	1+
Flunarazine is often well tolerated.[58] Depression is a possible side effect, so it should be used with caution in patients with depression.[58,59] Expert opinion recommends flunarizine should be avoided during pregnancy.[148] Flunarizine is not licensed for use in the UK. Provision is normally via hospital prescription by a specialist headache service. Clinicians should be familiar with the side-effect profile.[59]	
R Flunarizine (10 mg daily) should be considered as a prophylactic treatment for patients with episodic or chronic migraine.	
✓ Use of flunarazine should be avoided during pregnancy and breastfeeding. Women using flunarazine who are planning to become pregnant, or who are pregnant, should seek advice from their healthcare professional on switching to another therapy.	

4.10 Sodium valproate

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

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

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

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

✓ Although valproate is not recommended for those under the age of 55 for those who remain on it and who fulfil MHRA requirements, the safety advice is to inform the patient of the risks to children exposed to valproate in utero and the need to use effective contraception (see CoSRH Guidelines and Statements | CoSRH).

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

✓ 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.

4.16.1 Triptans

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

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

Triptan	*NNT*	Number of patients
Frovatriptan 2.5 mg daily	7.22	633
Frovatriptan 2.5 mg twice daily	3.90	584
Naratriptan 1 mg twice daily*	7.99	392
Zolmitriptan 2.5 mg twice daily	4.98	80
Zolmitriptan 2.5 mg 3 times daily	2.52	83

*1 mg twice daily naratriptan is not available in the UK. NNT for 2.5 mg daily was not available

Frovatriptan once daily and twice daily was also effective in reducing the secondary outcomes of migraine severity and rescue medication needed. Drug-related adverse events were low and similar to placebo for both doses. Zolmitriptan 2.5 mg twice and three-times daily also reduced the need for rescue medication and drug-related adverse events were similar for treatment and placebo in two small trials.[34]	1+

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

R	Zolmitriptan (2.5 mg three times daily) or naratriptan (2.5 mg twice daily) can be considered as alternatives to frovatriptan as prophylactic treatment in women with perimenstrual migraine from two days before until three days after bleeding starts.	
✓	Women with menstrual-related migraine who are using triptans at other times of the month should be advised that additional perimenstrual prophylaxis increases the risk of developing medication overuse headache.	

4.16.2	Prostaglandin inhibitors	
	While there is a small amount of evidence that mefenamic acid is effective for acute treatment of patients with menstrual migraine no trials on its use in perimenstrual prophylaxis were identified.[82]	1+
4.16.3	Non-steroidal anti-inflammatory drugs	
	One RCT reported significant headache improvement with naproxen, reaching over 50% after three months, however there was little difference when compared to placebo.[82]	1+
4.16.4	Oestrogens	
	One small crossover RCT (n=37) assessing perimenstrual oestradiol supplement, applied from the tenth day after the first day of peak fertility until the second full day of menstruation, reported a 22% reduction in migraine days but was followed by a rebound 40% increase in the five days following oestradiol.[82]	1+
4.16.5	Hormonal prophylaxis	
	Three studies were identified on the use of combined oral contraception. All reported benefit in menstrual migraine prophylaxis, but were of insufficient quality to be conclusive.[82]	1+

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 85mg/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 (Vyepti®) is accepted for restricted use within NHSScotland for the prophylaxis of migraine in adults who have at least four migraine days per month. It is restricted to the treatment of patients with chronic and episodic migraine who have had prior failure on three or more migraine preventive treatments (February 2023). www.scottishmedicines.org.uk/medicines-advice/eptinezumab-vyepti-abb-smc2547

Atogepant (Aquipta®) is accepted for restricted use within NHSScotland. for the prophylaxis of migraine in adults who have at least 4 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. 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 for 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. rimegepant (Vydura)

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 updates adhered to the 2019 and 2025 editions.

10.2 The guideline development group

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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. For the 2025 update, three group members declared interests. Their full participation was agreed due to 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 consistency with the advice from SMC, by the SIGN Chair.

Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest.

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Ms Karen King	Distribution and Office Co-ordinator
Mr Stuart Neville	Publications Designer
Mr Domenico Romano	Publications Designer
Ms Gaynor Rattray	Guideline Co-ordinator

10.4 Consultation and peer review

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.

Update 2025:

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Abbreviations (new)

ADHD	attention deficit hyperactivity disorder
WMD	weighted mean difference

Annex 1
Key questions addressed in this 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
	1. What is the clinical and cost effectiveness of abortive treatments for adults with acute migraine? Intervention: calcitonin gene-peptide receptor antagonists Comparison: placebo, other pharmacological therapies, device therapies Outcomes: pain free, pain free within two hours, sustained pain relief at 24 hours, adverse effects, QALYs, ICER Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension stroke/cerebrovascular risk.
	2. What is the clinical and cost effectiveness of preventative treatment for adults with episodic or chronic migraine? Intervention: calcitonin gene-peptide receptor antagonists Comparison: placebo, other pharmacological therapies, device therapies Outcomes: 30% or 50% reduction in number of headache days per cycle, reduction in number of migraine episodes, days or headache days, reduction in migraine disability assessment questionnaire (MIDAS, HIT6) scores, adverse effects, QALYs, ICER Consider comorbidities: chronic pain, fibromyalgia, depression, prepregnancy, pregnancy, menopause, contraception, cardiovascular risk, hypertension stroke/cerebrovascular risk.

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