NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Pharmacological Prophylaxis Management of Migraine in Adults

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

NHSGGC Pharmacological Prophylaxis of Migraine in Adults

Introduction

This guideline focuses on local pathways for the preventative treatment of migraine in adults. Further information on diagnosis and management of headache can be found in the Scottish Headache Pathways . Local neurology referral guidelines can be found here.

Acute Management of Migraine

For information and guidance on the acute management of migraine in primary care please see:

National Headache Pathways: link

Prophylaxis of Migraine

The decision if or when to start oral prophylaxis should be tailored to the individual patient. As per SIGN 155, there is no specific number of migraine days or migraine attacks per month that indicates the need for prophylaxis. For example, patients with a few disabling migraine days per month may elect to start treatment, but patients with a larger number of mild headache days per month may not.

General Points

- Migraine prophylactics may take many weeks to work. Judgment of efficacy should be made once on the target dose or highest tolerated dose at 8-12 weeks.
- If the migraine prophylactic is ineffective at 8-12 weeks, it should be weaned over at least 2 weeks and an alternative considered.
- If it is effective (i.e. reduced monthly headache or migraine days by at least 30-50%) consider weaning the drug after 6 to 12 months (it should be weaned at the approximate rate it was increased).
- If side effects are experienced after a dosage increase, decrease to the previous dose and then attempt a dosage increase after 2 weeks. Patients should be warned to refrain from driving if they become drowsy.

The flowchart on the following page outlines the treatment pathway, further information on each drug class can be found in the accompanying prescribing notes.

Who to refer:

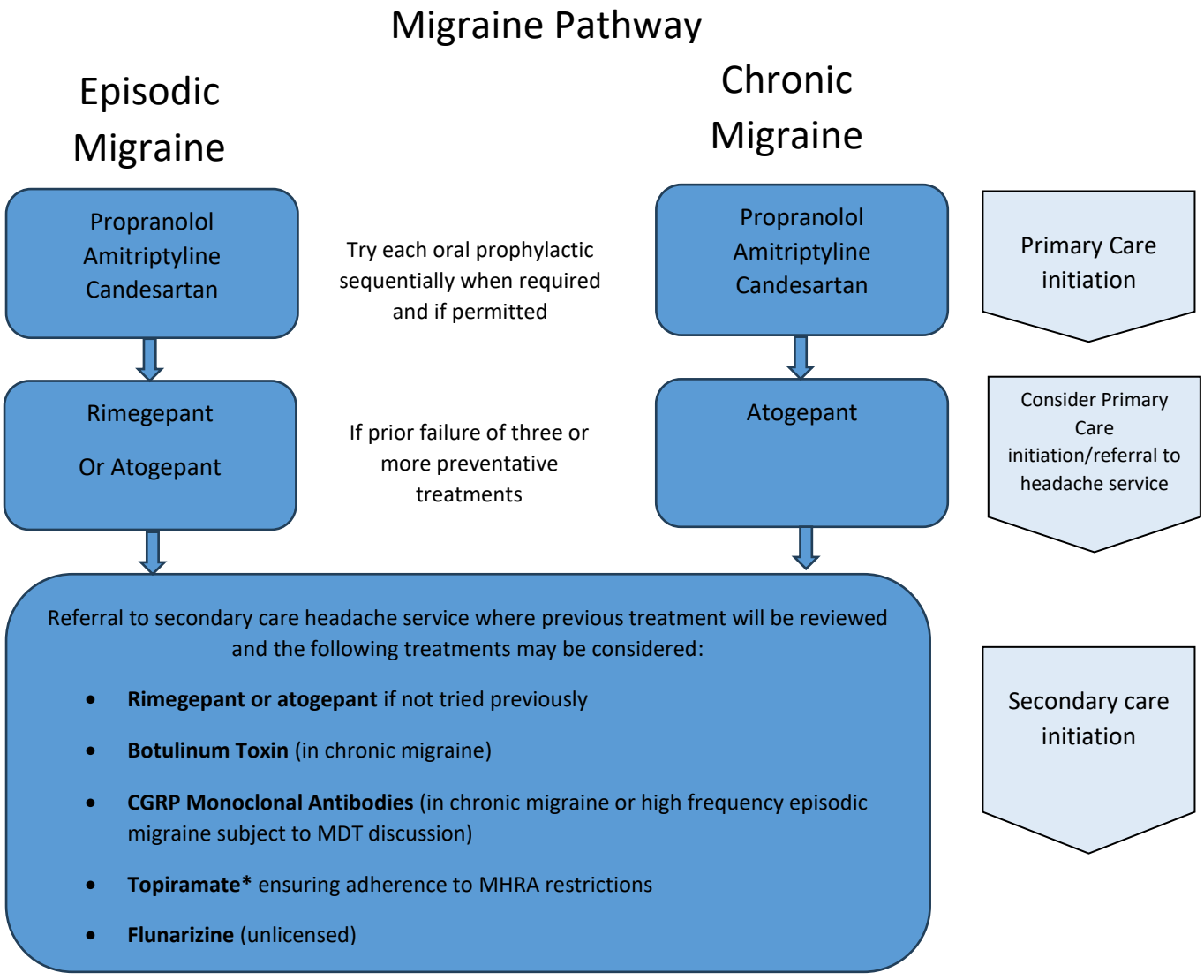
Examples of people who may benefit from being referred to the headache clinic

- People with a headache where there is **significant diagnostic uncertainty** OR
- People with disabling migraine for whom at least **3 preventative medications** have been tried (if not contra-indicated) and have either been ineffective after 2 months at target dose, or have not been tolerated.
- GPs may also consider optional prescription of a ‘gepant’ e.g. Rimegepant for episodic migraine (4 or more migraine attacks per month but fewer than 15 headache days per month), or atogepant for either episodic migraine or chronic migraine (i.e. 4 or more migraine days per month) in those who have had prior failure of three preventative treatments.

- In some patients with co-morbidities and medication contra-indications, we acknowledge that it may not be possible to try as many as 3 medications prior to referral. Trials of at least 3 preventative medications from the following list (see prescribing notes for further details) should have been attempted or considered, if safe to prescribe:
  - propranolol
  - amitriptyline
  - candesartan
  - rimegepant (episodic migraine only) or atogepant (episodic or chronic migraine) could be considered as an additional option if 3 previous migraine prophylactics have failed

Preventative Treatment of Migraine

The flowchart below outlines the overall treatment pathway, further details on the medicines included can be found in the prescribing notes later in the guideline.



* We do not recommend starting topiramate in women of child bearing potential. See MHRA advice for full details of safety issues surrounding pregnancy and requirements of the pregnancy prevention programme.

Chronic migraine = 15 or more headache days per month for three months, at least 8 of which have migraine features
Episodic migraine = Less than 15 headache days per month (high frequency episodic migraine 8-14 days per month)

Migraine Prophylaxis Prescribing Notes

1. First line/standard oral prophylactic medicines

Drug & Dose	**Prescribing notes**
Propranolol	
Start propranolol 10-20mg twice a day. Increase by 10-20mg twice a day every 1-2 weeks, to a target dose of 80mg twice a day. Some patients benefit from lower doses if they experience side effects at higher doses	For a full list of contraindications and cautions we recommend review of the Summary of Product Characteristics (SPC). Propranolol is contraindicated in a number of conditions including asthma, severe peripheral vascular disease, second or third degree AV block and should not be used in patients taking verapamil. Side effects include bradycardia, hypotension, fatigue, sexual dysfunction, sleep disorders and wheezing. Note potential interaction with rizatriptan: rizatriptan dose should be limited to 5mg in patients prescribed propranolol and administration should be separated by at least 2 hours
Amitriptyline	
Start at 10mg at night Increase by 10mg every 1-2 weeks. The typical first target dose is 50mg per day. If well tolerated many patients benefit from a higher dose with further up titration up to 1mg/kg, typically a maximum of 100mg per day.	For a full list of contraindications and cautions, we recommend review of the Summary of Product Characteristics (SPC). Contraindications include concomitant use of monoamine oxidase inhibitors, recent myocardial infarction, heart block, disorders of cardiac rhythm, and coronary artery insufficiency, and severe liver disease. We also recommend avoiding use in those patients at risk of glaucoma, and QT prolongation. Caution in those patients taking serotonergic drugs. Side effects include constipation, difficulty with micturition, arrhythmias, syncope, confusion, nausea, dry mouth, drowsiness and weight gain. Patients should seek immediate medical attention if they are unable to micturate or experience visual blurring or symptoms of acute glaucoma.
Candesartan (off-label use)	
Start at 2-4mg per day Increase by 2-4mg every 1-2 weeks to a maximum of 16mg per day.	For a full list of contraindications and cautions we recommend review of the Summary of Product Characteristics (SPC). Caution in patients with renal artery stenosis, hypotension and renal impairment. Candesartan is cautioned in those patients receiving lithium therapy, and in those who are taking medications which increase serum potassium such as spironolactone. Consider monitoring of U+Es at baseline and during titration as per BNF/SPC recommendations.

	Candesartan should not be used in pregnancy, and should be discontinued before planning a pregnancy. Women of child bearing age should ensure appropriate contraception is in place. Candesartan is not recommended during breast feeding. Alternative agents should be considered in those with renal impairment and those patients taking regular NSAIDS, since in such populations close monitoring of kidney function and potassium would be required. If using candesartan in older patients, monitoring of kidney function and potassium should be considered. Candesartan should be withheld if patients become acutely dehydrated (e.g. during a diarrhoea and vomiting illness). Side effects include hypotension, renal impairment and cough

2. Additional prophylactic medicines that can be considered in primary care

Calcitonin Gene Related Peptide (CGRP) Small Molecule Antagonists (gepants)

Atogepant and rimegepant were approved for use and added to the GGC formulary for migraine prophylaxis in 2023. They are a small molecule antagonists to calcitonin gene related peptide (CGRP), which is a key neuropeptide in the pathogenesis of migraine.

Patients must have had prior failure of **three or more** migraine preventative treatments before atogepant or rimegepant can be considered. These medicines can be initiated and prescribed in primary care.

It is important to note that licensed indications differ for these medicines; atogepant is licensed for treatment of episodic and chronic migraine in adults (at least 4 migraine days per month); rimegepant is licensed for episodic migraine in adults only (more than four migraines per month but less than 15 headache days per month).

Actions Prior to Prescribing Atogepant or Rimegepant

- Check patient has had prior failure of three preventative migraine treatments
- Assess whether patient has episodic or chronic migraine and select appropriate licensed treatment for indication
- Ensure blood pressure is normal
- Screen for Raynaud's phenomenon
- Screen for and treat constipation
- Advise against use in pregnancy, avoid in breast feeding as limited information available
- Recommend the use of headache diaries, with headache pain scores recorded daily
- Prescribe for three months and arrange a three month review
- Advise to avoid driving if drowsy

Prescribing Considerations

- See table overleaf for detailed prescribing notes for each drug
- Atogepant and rimegepant are new medications and therefore the long term side effects are unknown.
- It is uncertain whether adverse events associated with monoclonal antibodies to CGRP apply to the small molecule 'gepants' but until further data are available, we advise similar cautions.
- Trials of atogepant and rimegepant were not enriched with patients with significant cardiovascular or cerebrovascular disease therefore we suggest caution in these patients. We recommend particular caution in those who have suffered an acute cardiovascular or stroke event within the last 6 months.
- We recommend measuring blood pressure prior to starting atogepant or rimegepant. We do not recommend in patients with uncontrolled hypertension. Blood pressure should be monitored during treatment with atogepant and rimegepant, including measurements at 3 months and 12 months.
- Monoclonal antibodies to CGRP have been associated with de novo Raynaud's phenomenon or worsening Raynaud's phenomenon and therefore caution is advised with significant or uncontrolled Raynaud's phenomenon.

Review of efficacy and tolerance at 3 months

- If medication is ineffective at 3 months, it should be discontinued.
- Treatment efficacy may be defined as a reduced of total monthly headache days by at least 30%, or reduction in monthly migraine days by at least 50%. Quality of life reports may also be considered.
- Check BP and if uncontrolled hypertension is identified, discontinue atogepant or rimegepant permanently or until BP is treated.
- Screen for side effects including nausea and constipation
- If it is effective then we suggest continue for a period to complete a total of 6-12 months therapy followed by a treatment holiday. If headache worsens during the treatment holiday consider restarting with a further planned treatment holiday after 12 months therapy.
- The optimal duration of therapy is unknown.

Atogepant Prescribing Notes	
Eligible Patient population	Patients with episodic or chronic migraine who have at least four migraine days per month and who have had prior failure of at least three previous migraine preventative treatments. We recommend targeting populations with either high frequency episodic migraine (8-14 headache days per month) or chronic migraine (15 or more headache days per month)
Starting atogepant	• Recommended dose for episodic and chronic migraine = 60mg daily *10mg daily in certain patients – see below Acute treatments • If abortive therapy is required, simple analgesia such as non steroidal anti-inflammatory medications (as per SIGN 155) and prochlorperazine may be used. • If triptans are not contra-indicated, a triptan may be used for abortive therapy. The frequency of use should be less than 10 days per month • In clinical trials combinations of different gepants e.g. atogepant plus abortive rimegepant were not permitted
Cautions/ Contraindications	Please see the BNF and summary of product characteristics for full information and see above for general considerations. We do not recommend Atogepant in pregnancy. Avoid in breast feeding as limited data available. The license advises to avoid use in patients with severe hepatic impairment. In patients with severe renal impairment (creatinine clearance 15-29ml/min) and end stage renal failure (creatinine clearance <15ml/min) the recommended dose is 10mg daily. Baseline U+Es and LFTs should be considered if clinical concern but routine monitoring is not required.
Interactions Please note lists of interacting drugs are not exhaustive, please check recognised sources such as BNF and discuss with pharmacy if further information required particularly for specialist medicines	The dose of atogepant should be reduced to 10mg daily in patients taking - strong inhibitors of CYP3A4 (*e.g. clarithromycin, ketoconazole, itraconazole, voriconazole, telithromycin, indinavir, nelfinavir, ritonavir, saquinavir*) - strong OATP inhibitors (*e.g. rifampicin, atazanavir, ritonavir, tipranavir, ciclosporin, erythromycin, telmisartan*) For short courses of a strong CYP3A4 or OATP inhibitor, if an alternative non-interacting drug is not an option, temporary discontinuation of atogepant is permitted. No specific advice is given regarding co-prescription of atogepant with CYP3A4 inducers but be alert to the possibility of reduced efficacy as atogepant levels may be reduced.
Side effects	Decreased appetite, constipation, drowsiness, fatigue, nausea, weight decrease. Patients should be counselled on risk of somnolence and potential effects on driving and performance of skilled tasks.

Rimegepant Prescribing Notes	
Eligible Patient Population	Patients who have at least 4 migraine days per month but less than 15 headache days per month who have had prior failure of three previous migraine preventive treatments. We recommend targeting the population with high frequency episodic migraine (8-14 headache days per month)
Starting Rimegepant	The recommended dose for prophylaxis of episodic migraine is 75mg taken on alternate days. Abortive therapy: • If abortive therapy is required, simple analgesia such as non steroidal anti -inflammatory medications (as per SIGN 155) and prochlorperazine may be used. • If triptans are not contra-indicated, a triptan may be used for abortive therapy. The frequency of use should be less than 10 days per month. • Alternatively, or if triptans are contra-indicated, they may however take a Rimegepant tablet for abortive therapy on a day when Rimegepant has not been taken provided there are no interactions. The maximum dose is 75mg daily and this dose should not be exceeded.
Cautions/ Contraindications	Please see the BNF and summary of product characteristics for full information and see above for additional considerations. We do not recommend Rimegepant in pregnancy. Avoid in breast feeding as limited data available. Rimegepant should not be used in patients with patients with severe hepatic impairment or in patients with end-stage renal disease (CrCl < 15 ml/min).
Interactions Please note lists of interacting drugs are not exhaustive, please check recognised sources such as BNF and discuss with pharmacy if further information required, particularly for specialist medicines	Rimegepant is not recommended in combination with - Strong inhibitors of CYP3A4 (e.g. *clarithromycin, ketoconazole, itraconazole, voriconazole, telithromycin, indinavir, nelfinavir, ritonavir, saquinavir*) - Strong or moderate inducers of CYP3A4 (*e.g. carbamazepine, phenytoin, rifampicin, phenobarbital, bosentan, efavirenz, St. John's wort*) Another dose of rimegepant should be avoided within 48 hours (e.g. an additional dose could not be taken for abortive therapy) if concomitantly administered with - Moderate inhibitors of CYP3A4 or strong inhibitors of p-glycoprotein (*e.g. diltiazem, erythromycin, azithromycin, fluconazole, ciclosporin, amiodarone, verapamil, quinidine*) If prescription of an interacting drug is short term e.g. clarithromycin, if an alternative non-interacting drug is not an option, rimegepant could be withheld for the duration of the treatment course.
Side effects	Nausea, hypersensitivity reactions.

3. Prophylactic Medicines Initiated by Secondary Care Headache Team

3.1 Topiramate

The MHRA issued new safety measures for topiramate including a pregnancy prevention programme in June 2024 {link}. Following this, the NHSGGC headache team have agreed that topiramate for migraine should only be initiated in secondary care for appropriate patients and ensuring adherence to the safety advice. This recommendation will be communicated to primary care by letter for initiation in the community, the prescribing notes below may be useful in these cases.

Topiramate	
Start topiramate at 25mg daily Increase by 25mg every 1-2 weeks, to a target dose of 50mg twice a day. If partially effective and well tolerated further up titration to a maximum of 100mg twice a day could be considered in selected patients	**We do not recommend this medication to be started in women of child bearing potential. See MHRA advice for full details of safety issues surrounding pregnancy and requirements of the pregnancy prevention programme, and also the Faculty of Sexual and Reproductive Health Guidelines for advice on contraception interactions.** For a full list of contraindications and cautions we recommend review of the Summary of Product Characteristics (SPC). We do not recommend topiramate for use in patients who have a history of glaucoma or renal stones or who have anorexia nervosa. Caution should also be exercised in patients with a history of depression. There may be interactions with digoxin, metformin, carbonic anhydrase inhibitors, and thiazide derivatives. There is a potential for serious interaction with sodium valproate. Side effects are common and include acute glaucoma, peripheral paraesthesias, fatigue, nausea, diarrhoea or weight loss, taste change, concentration difficulties, word finding difficulties, insomnia, anxiety, and depression

3.2 Prophylactic treatments prescribed in secondary care

Patients who are under the care of the headache team may be considered for the following prophylactic treatments which will be prescribed and supplied in secondary care:

- Botulinum toxin. See here for further information.
- Monoclonal antibodies to CGRP (erenumab, eptinezumab, fremanezumab, galcanezumab). See here for further information.
- Flunarizine (unlicensed)

For patients prescribed the above treatments, this will be communicated to primary care via letter. Please add to GP prescribing system as an outside medication for interaction checking and awareness, and also so that it is visible on ECS.