AMBER GUIDANCE FOR MANAGING HEADACHE DISORDERS

Background

Headache is a common neurological condition that accounts for 4.4% of primary care consultations and 30% of neurology appointments. Primary headache disorders include migraine, tension-type and cluster headache. Twice as many women as men are affected by headache disorder. This is thought to be due to changes in hormone levels during the menstrual cycle, which can be more pronounced at puberty and menopause.

General guidance

Recommendations within this guideline are based on best evidence and national/international guidelines. They are followed by consultants and specialist nurses working within the neurology department. Some recommendations may be for medicines prescribed outside their product license i.e. off label. It is noted in the guideline when the medicine is off label and relevant guidelines should be followed when prescribing medicines off label. A number of British Association for the Study of Headache (BASH) leaflets have been linked in this guidance; these can be given to patients and cover the off license use of medicines and information about duration of prophylactic treatments.

Migraine

Migraine is often underdiagnosed, misdiagnosed and undertreated. It is estimated in UK that around £3 billion/annum is lost in direct and indirect costs due to migraine

Acute treatment

Offer combination therapy for acute treatment of attacks e.g. triptan plus NSAID. 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.

NSAIDs

Use ibuprofen 400mg or naproxen 500mg as a first line treatment option.

Both ibuprofen and naproxen are effective for 2 hours pain relief as well as relieving migraine associated symptoms of nausea and photophobia. Ibuprofen is licensed for acute migraine treatment and the dose can be increased to 600mg if ineffective. Naproxen is not licensed for acute treatment of migraine.

Ibuprofen can be used in pregnancy until 28 weeks and is the NSAID of choice in pregnancy. Repeated use should be avoided after 28 weeks gestation.

Aspirin

Aspirin 900mg is effective for 2 hour pain relief and is recommended as a first line treatment option. High dose aspirin is a potential gastric irritant, however single doses usually only have mild transient adverse effects. It is contraindicated in under 16s due to risk of Reyes syndrome and in the third trimester of pregnancy.

Triptans

Sumatriptan 50mg-100mg is the first line triptan. In patients with severe acute migraine or early vomiting non-oral triptans may be considered. An alternative triptan should be tried after two treatment failures with the first line triptan. Second line triptans are eletriptan and rizatriptan. Both eletriptan and rizatriptan are superior for pain free at 2 hours and eletriptan is associated with a reduced need for rescue medicines.

For menstrual migraine frovatriptan is the triptan of choice.

Antiemetics

If a prokinetic effect required either metoclopramide or domperidone are recommended. If nausea/vomiting are an issue buccal prochlorperazine should be considered. Consider risks and benefits of prokinetic antiemetic therapy as per summary of product characteristics cautions and contraindications and discuss with patients prior to prescribing.

Rimegepant (Amber 1)

This is an oral agent calcitonin gene-related peptide (CGRP) antagonist that is commissioned in line with its NICE TA (TA919) for treating acute migraine. That is:

- at least 2 triptans were tried and they did not work well enough or
- triptans were contraindicated or not tolerated, and nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol were tried but did not work well enough.

Rimegepant is a substrate of CYP3A4, P-glycoprotein and breast cancer resistance protein efflux transporters. It is not recommended to administer rimegepant to patients on strong inhibitors of CYP3A4 such as clarithromycin, itraconazole, ritonavir. Concomitant administration with moderate inhibitors such a erythromycin, diltiazem increases levels of rimegepant and dosing more frequently than 48 hourly is not recommended.

Inducers of CYP3A4 decrease concentrations of rimegepant; concomitant administration with strong inducer (e.g. phenobarbital, rifampicin, St John's wort) or moderate CYP3A4 inducers (e.g. bosentan, efavirenz, modafanil) is not recommended.

Paracetamol

Paracetamol should only be used for migraine when other treatments unsuitable.

Opiates

Opiate based medicines for the acute treatment of migraine and are not recommended.

Prevention of Migraine

Migraine can have considerable impact on quality of life and daily function. The decision about when to start migraine prophylaxis is best guided by the impact of migraine on each patient (rather than focusing on the absolute number of migraines per month). Overusing acute medicines can limit the effectiveness of prophylaxis medicines and medication overuse should be assessed and addressed.

Prophylactic treatment should be used for at least 3 months at maximum tolerated dose prior to deciding if it is effective or not. In many patients it is possible to phase out their prophylactic medicine after 6-12 months. Patients should titrate to dose that relief from migraines is achieved or maximum tolerated dose. There are very few trials comparing different prophylactic drugs for migraine and those that are available are not powered sufficiently to assess effectiveness between treatments; hence the first line treatments listed below should be offered dependent on patient preference and concomitant medicines and medical conditions.

Beta blockers

Beta blockers are a first line treatment for prophylaxis of episodic and chronic migraine as per NICE guidelines. The beta blocker of choice is propranolol. It should be initiated at dose of 10 mg twice a day and gradually increased in 10-20mg twice a day increments every week to a dose of 80-160mg per day (MR preparation preferred). Atenolol can also be used at a dose of 50-100mg/day if sleep disturbances are an issue. Beta blockers should not be used in asthmatic patients.

This leaflet may be given to patients to provide further information.

Candesartan

There is evidence suggesting that candesartan is effective at reducing number of headache days in migraine. This is an unlicensed use of candesartan. Candesartan is well tolerated

and has a good side effect profile. Candesartan can be prescribed at a dose of 16mg daily (normally in two divided doses) for episodic or chronic migraine. It does not usually affect blood pressure in normotensive patients. [SIGN 2018]

The starting dose for the prevention of migraine is 2 mg in the morning. If tolerated the dose can be increased by 2mg every week until at maximum of 8mg twice a day. This leaflet may be given to patients to provide additional information.

Tricyclic antidepressants (TCAs)

TCAs are a first line treatment for migraine. Amitriptyline can be used at a dose of 25-150mg at night – this can be started at 10mg and titrated up according to response and tolerance. TCAs are unlicensed for treatment of migraine. The main side effects from TCA therapy are drowsiness and dry mouth. If drowsiness is an issue with amitriptyline a less sedating TCA can be use – e.g. nortriptyline.

This leaflet may be given to patients to provide additional information.

Topiramate

Topiramate is effective at reducing monthly migraine frequency and monthly migraine days in trials. It is associated with a number of side effects including nausea, paraesthesia, anorexia and weight loss. In particular cognitive side effects are common, vary in severity, are dose related and often define drug tolerability. Topiramate is associated with an increased risk or abnormal oral cleft development in infants during the first trimester of pregnancy. Hence women who may become pregnant should be advised of the risks of topiramate during pregnancy, the need for effective contraception and the need to seek further advice on migraine prophylaxis if pregnant or planning a pregnancy. It is recommended as a first line treatment by NICE guidelines at a dose of 50-100mg daily (titrated as per licence). There is no benefit to doses greater than 100mg daily (minimal further reduction in migraine and increased risk of side effects).

This leaflet may be provided to give additional information.

Flunarizine (red drug)

Flunarizine is a calcium channel blocker that is unlicensed in the UK. It has a similar efficacy to propranolol, topiramate and valproate. It is generally well tolterated. Depression is a potential adverse drug reaction; so is not recommended in patients with a history of depression. As it is a calcium channel blocker must check blood pressure 2 weeks after initiation. Flunarizine dose is 10mg daily.

Rimegepant (Amber 2)

This is an oral agent calcitonin gene-related peptide (CGRP) antagonist that is commissioned in line with its NICE TA (TA906) for preventing episodic migraine. That is in adults who have at least 4 and fewered than 15 migraine attacks per month, only if at least 3 preventative treatment have not worked. Rimegepant is stopped if after 12 weeks of treatment the frequency of migraine attacks does not reduce by at least 50%.

Rimegepant is a substrate of CYP3A4, P-glycoprotein and breast cancer resistance protein efflux transporters. It is not recommended to administer rimegepant to patients on strong inhibitors of CYP3A4 such as clarithromycin, itraconazole, ritonavir. Concomitant administration with moderate inhibitors such a erythromycin, diltiazem increases levels of rimegepant and dosing more frequently than 48 hourly is not recommended.

Inducers of CYP3A4 decrease concentrations of rimegepant; concomitant administration with strong inducer (e.g. phenobarbital, rifampicin, St John's wort) or moderate CYP3A4 inducers (e.g. bosentan, efavirenz, modafanil) is not recommended.

Botulinum toxin type A (red drug)

Is commissioned as per NICE TA for chronic migraine. Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine):

- that has not responded to at least three prior pharmacological prophylaxis therapies **and**
- whose condition is appropriately managed for medication overuse.

Fremanezumab, galcanezumab, erenumab and eptinezumab(red drugs)

Fremanezumab (TA764), galcanezumab (TA659), erenumab (TA682) and eptinezumab (TA871) are commissioned as per their individual NICE TAs for chronic and episodic migraine. Fremanezumab, galcanezumab and erenumab are prescribed by the headache specialist team via homecare for self-injection. Eptinezumab is an IV infusion and is prescribed by the headache specialist team and administered within the hospital. The NICE criteria for chronic migraine are the same as Botulinum toxin A listed above. Patients will be offered treatment with either medicine dependent on patient factors, past treatment, patient preference and cost effectiveness. For episodic migraine, the criteria are same as listed above in the rimegepant section.

For fremanezumab, erenumab and galcanezumab patients receive the initial trial of 3 months after which they are reviewed by the clinical team and if responders will receive a prescription for 9 months (delivered in 3 monthly intervals). After 12 months of therapy they can have a treatment break for a minimum of 3 months; if the treatment break fails they can restart on the previous therapy. For patients who fail or have adverse drug

reactions on fremanezumab, galcanezumab or eptinezumab they can be offered a trial of therapy with erenumab due to different mechanism of action.

There are currently no known drug interactions with any of the therapies. The main adverse drug reactions are injection site reactions such as pain, induration, erythema, rash and urticaria. Rash and urticaria can occur up to 48 hours post injection and all types' injection site reactions generally resolve within a few hours/days post injection. Erenumab and galcanezumab can also cause constipation. As with all monoclonal antibodies there is a risk of serious hypersensitivity reactions including angiodema and anaphylaxis.

Menstrual migraine

A drop in oestrogen prior to mensturation is a known trigger for migraine. Triptans reduce the occurrence of migraine both menstrually related and pure menstrual migraine from 2 days before the start of bleeding and 3 days after. Frovatriptan 2.5mg twice a day is the triptan of choice (low NNT/high patient numbers). It is also effective at reducing migraine severity and need for rescue medication.

Management of migraine in pregnancy

Acute treatment

Migraine generally improves in pregnancy however if drug treatment is required paracetamol is the first line acute treatment for migraine in pregnancy. If paracetamol is not effective oral sumatriptan can be used. Ibuprofen can be used in first and second trimester if both paracetamol and sumatriptan are ineffective however; there is less evidence of safety (NSAIDs contraindicated in 3rd trimester). Codeine could be used however not recommended near term and should only be used if above therapies have failed. If an anti-emetic is required can use metoclopramide. Aspirin should not be used in pregnancy. Patients can be provided BUMPs medicines leaflets to aid discussions about treatment.

Preventative treatment

Patients already on preventative treatment may be able to discontinue treatment in pregnancy. If on propranolol or amitriptyline these can be continued if needed. Candesartan is a known teratogen and must be stopped in pregnancy and patients need referring to the relevant specialist teams. There is an increased risk of cleft palate with topiramate and consideration should be given to stopping in pregnancy.

If new preventative treatment is required during pregnancy, it generally shouldn't be initiated in primary care. First line preventative treatment would be low dose amitriptyline or propranolol.

Cluster Headache and other trigeminal-autonomic cephalalgias

All these headache syndromes have two features in common: short-lasting, severe headaches and accompanying typical cranial autonomic symptoms. There are differences in duration of attack, frequency and rhythmicity of the attacks and in the intensity of pain and autonomic symptoms.

Episodic and chronic cluster headache

Cluster headache (CH) is defined as a paroxysmal, strictly unilateral, very severe headache, typically with a maximum of pain focused in the retro orbital area. Even though the attacks are short-lasting, CH is excruciatingly painful and patients suffer badly. During a cluster period frequent attacks can be disabling to patients. The goal of treatment is attack cessation or suppression until the next episode.

Attack treatment

Oxygen.

Inhalation of 90% oxygen via a non-rebreathing face mask with a flow rate of at least 7L/min (sometimes more than 15 L/min is required). The oxygen should be inhaled for 10-20 minutes. About 60% of all cluster headache patients respond to this treatment with significant pain reduction. Oxygen can be ordered via the standard home oxygen ordering form – cluster headache is listed as condition 18 in primary clinical code.

Non-oral triptans

Sumatriptan subcutaneous (6mg), sumatriptan 20mg intranasal and zolmitriptan 5mg intranasal are effective in the acute treatment of cluster headache. The quantity supplied needs to match usage. There is no evidence supporting the use of oral triptans for cluster headache.

Doses:

- zolmitriptan intranasal 3 doses/24 hours,
- sumatriptan s/c max 12mg/24 hours,
- sumatriptan intranasal 10-20mg/dose max 100mg/24 hours.

Cluster headache prophylaxis
Verapamil – AMBER SCF

Verapamil in a total daily dose of 240-960mg is the first line choice in the prophylaxis of episodic and chronic cluster headache. Initially it should be started at a dose of 80mg TDS and titrated upwards usually every 14 days. Modified release formulations can be used to reduce tablet burden and aid compliance. The full efficacy of verapamil can be expected within 2-3 weeks.

Lithium carbonate – AMBER SCF

Lithium carbonate in a total daily dosage between 600 and 1500mg has been studied in multiple open trials. It is used in both episodic and chronic cluster headache if verapamil is ineffective or contraindicated. Monitoring of the lithium level is required (should be between 0.3 and 1.2mmol/l). Monitoring requirements are in the SCF for lithium carbonate.

Corticosteroids

Corticosteroids may be recommended for short term treatment (2-3 weeks) high dose prednisolone 30mg or greater. Initial dose may be as high as 60-100mg prednisolone for 2-5 days. Prednisolone may be used while titrating other prophylactic drugs to therapeutic dose.

Melatonin – red for this indication

As cluster headache is thought to be related to circadian effects melatonin has been tried as prophylaxis with varying results. As it is well tolerated with limited side effects then it may be tried in combination with other therapies at a dose of 10mg at night. Modified release preparations can be used.

Other treatments:

Greater occipital nerve block – Lidocaine with or without corticosteroids can be used in an outpatient setting by specialist teams. It often used instead of oral steroids as a bridging treatment while awaiting preventative medicine such as verapamil to take effect.

gammaCore: this is an innovative medical device treatment for cluster headache. It is a non-invasive vagus nerve stimulator which enable the patient to ‘zap’ their vagus nerve to reduce pain from cluster attacks. It is NHS England funded and NICE approved. It is

prescribed by specialist teams following failure of first line prophylactic treatment i.e. verapamil. It can be used as a daily prophylaxis and an acute treatment.

References

NICE Clinical Guidance (CG140), Headaches in over 12s: diagnosis and management, First published 19/09/2012, last updated 17/12/2021.
https://www.nice.org.uk/guidance/cg150

SIGN guidance 115 (2018), Pharmacological management of migraine,
https://www.sign.ac.uk/sign-155-migraine

British Association for the Study of Headaches (BASH), (2019), National Headache Management System for Adults. (Accessed June 2022) NATIONAL Headache Management SYSTEM FOR Adults 2018 (bash.org.uk)

Document control	**This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC (data sheet) or BNF for further prescribing information.**		
	Version number:		1.3
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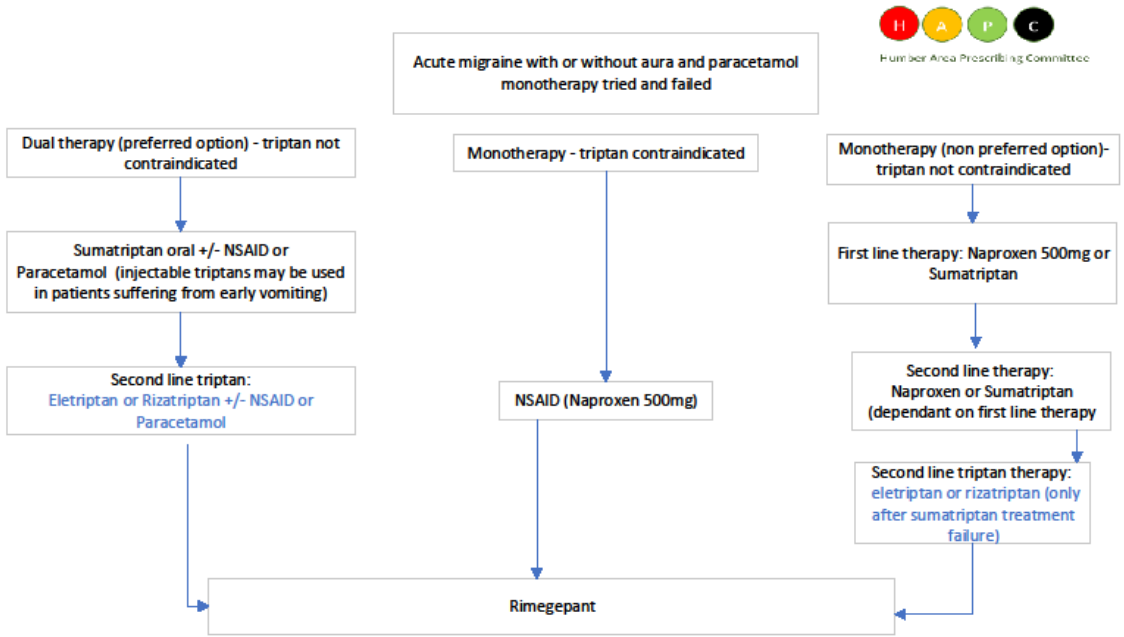
1.2	Jane Morgan	Principal Pharmacist – interface	Update with TA907 and pathways
1.3	Jane Morgan	Principal Pharmacist – interface	Update with TA919 and pathways

Appendix 1 – CGRP pathways

Acute CGRP pathway



Notes:
The Humber APC migraine guidance is available on the Humber APC website and includes details on doses and drug-drug interactions to consider when prescribing migraine therapies and when prophylactic treatment for migraine is indicated.

Prepared by Jane Morgan - Principal Pharmacist - Interface HUTH January 2024, review date January 2026

Episodic and chronic migraine CGRP pathway

Humber and North Yorkshire Health and Care Partnership

Migraine pathway

3 oral agents tried – propranolol, topiramate and amitriptyline, candesartan.

Episodic Migraine

4 or more migraine days a month

Choice of:-
Most cost effective Anti-Calcitonin Gene-Related Peptide. Stop if the migraine frequency does not reduce by at least 50% after 12 weeks
Or
Rimegepant 75mg Orally taken on alternate days. Stop if the migraine frequency does not reduce by at least 50% after 12 weeks.

Chronic Migraine

Headaches on more than 15 days per month or migraines on 8 days or more per month.

Choice of:-
Most cost effective Anti-Calcitonin Gene-Related Peptide. Stop if the migraine frequency does not reduce by at least 30% after 12 weeks
Or
Botulinum Toxin (Botox®)
155-195 units 12 weekly. Stop if the migraine frequency does not reduce by at least 30% after 2 treatment cycles or has changed to episodic migraine for 3 consecutive months.

Anti-Calcitonin Gene-Related peptides

- **Galcanezumab** S/C 240mg loading dose then 120mg 4 weekly
- **Fremanezumab** S/C 225mg 4 weekly
- **Erenumab** S/C 140mg 4 weekly.
- **Eptinezumab** I/V infusion 100 mg administered by intravenous infusion patient every 12 weeks. The dose can be increased if necessary to 300 mg every 12 weeks

For patients who fail treatment or have ADRs that require stopping consider changing to therapy with different mechanism of action

- Erenumab blocks the CGRP receptor
- Galcanezumab, fremanezumab and eptinezumab block the CGRP isoform from binding to the CGRP receptor

Rimegepant will be transferred to primary care prescribing if the meets the reduction in migraine frequency threshold at 12 weeks. Ongoing patient follow-up will be done by the Trust neurology teams.

References

NICE TA 659 (galcanezumab), NICE TA 764 (fremanezumab), NICE TA682 (erenumab)
NICE TA 871 (eptinezumab) NICE TA 906 (rimegepant)

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