Acute Treatments for Migraine

Dr Louise Rusk

GPwER Headache Ulster Hospital

Disclosures last 5 years

- Speaker honoraria: Pfizer, Abbvie
- Educational grant to attend conferences: TEVA
- Non-financial: Trustee of The Migraine Trust. Past Council Member British Association for the Study of Headache

Overview of the session

- Focus on migraine specific treatments
  - What happens during a migraine attack
  - How to use the newer acute therapies
  - Explanation of anti-CGRP Mabs, gepants and how these are used
- Dr Louise Rusk – Acute
- Dr Martin Harley, consultant neurologist – Preventative
- Signposting now to previous GPNI webinars
  - Dr Raeburn Forbes, consultant neurologist, SHSCT 2020
  - Sonya Thomson, physiotherapist, BHSCT 2022

Understanding the Science of Migraine

How to explain to patients how the targeted treatments work

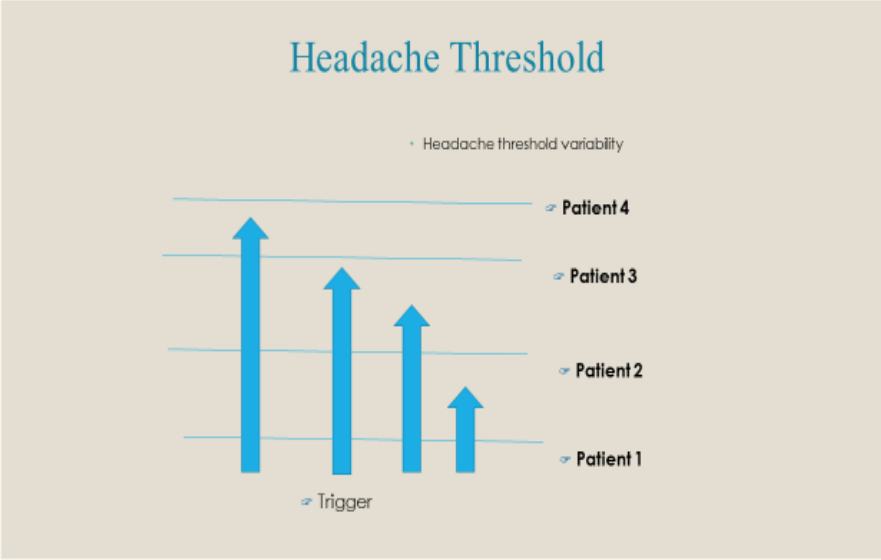
So, What is Migraine?

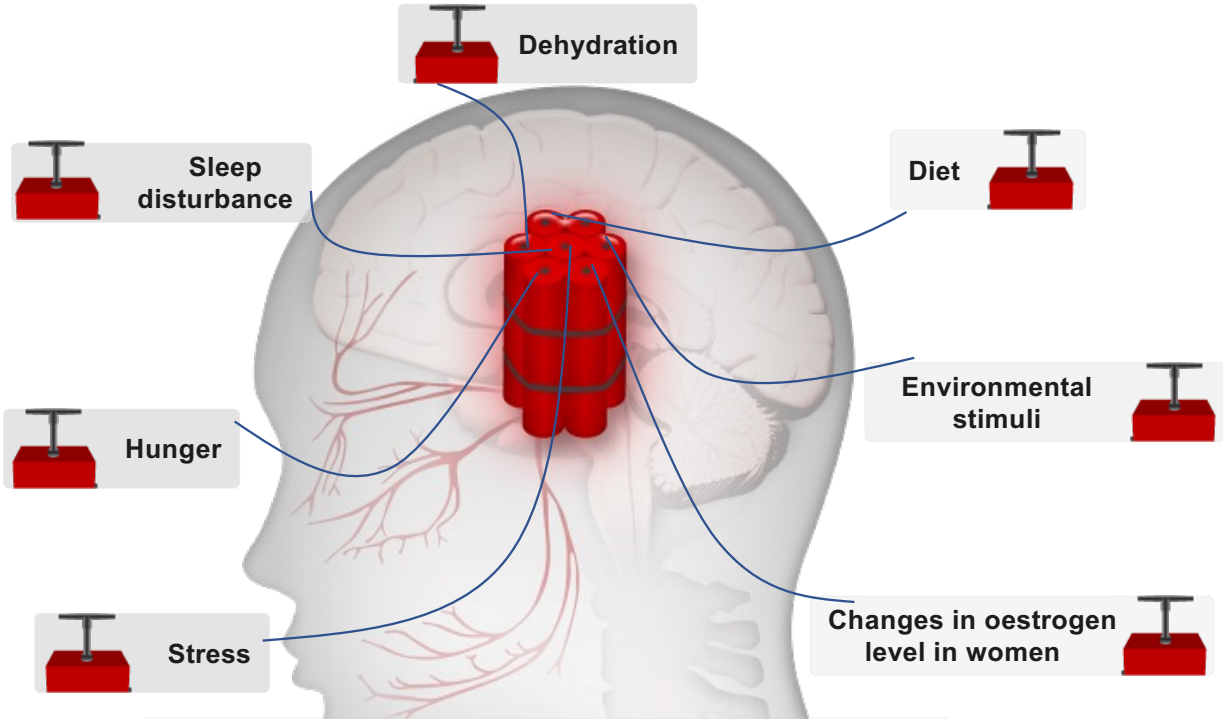
Migraine is a neurological condition which features amplification of a number of sensory pathways[1]. Some studies suggest that genetic components contribute to susceptibility to the condition[5]

- May be lifelong but varies in impact, severity and frequency throughout life (epigenetics)[2]
- Is a spectrum condition; attacks may be mild, moderate or severe[1]
- Can lead to attacks which may start at any age; usually in early adulthood[3]
- Has a natural history, often eventually improving with age[2]
- Migraine is NOT just a bad headache[4]

1. Brennan K., Pietrobon D. A systems neuroscience approach to migraine. *Neuron*. 2018;97(5):1004-1021. 2. Kelman L. Migraine Changes with Age: IMPACT on Migraine Classification. *Headache*. 2006;46(7):1161-71. 3. Migraine Trust. What is Migraine? Available at: https://migrainetrust.org/wp-content/uploads/2023/05/What-is-migraine-factsheet.pdf . Accessed October 2023. 4. Lai C. Flashing lights and poor funding: more than a headache. *Lancet*. 2017 (Radio). 5. Bron et al. Exploring the Hereditary Nature of Migraine. *Neuropsychiatric Disease and Treatment*. 2021;17. 1183-1194.

Consider the migraine brain to be sensitive to normal life events

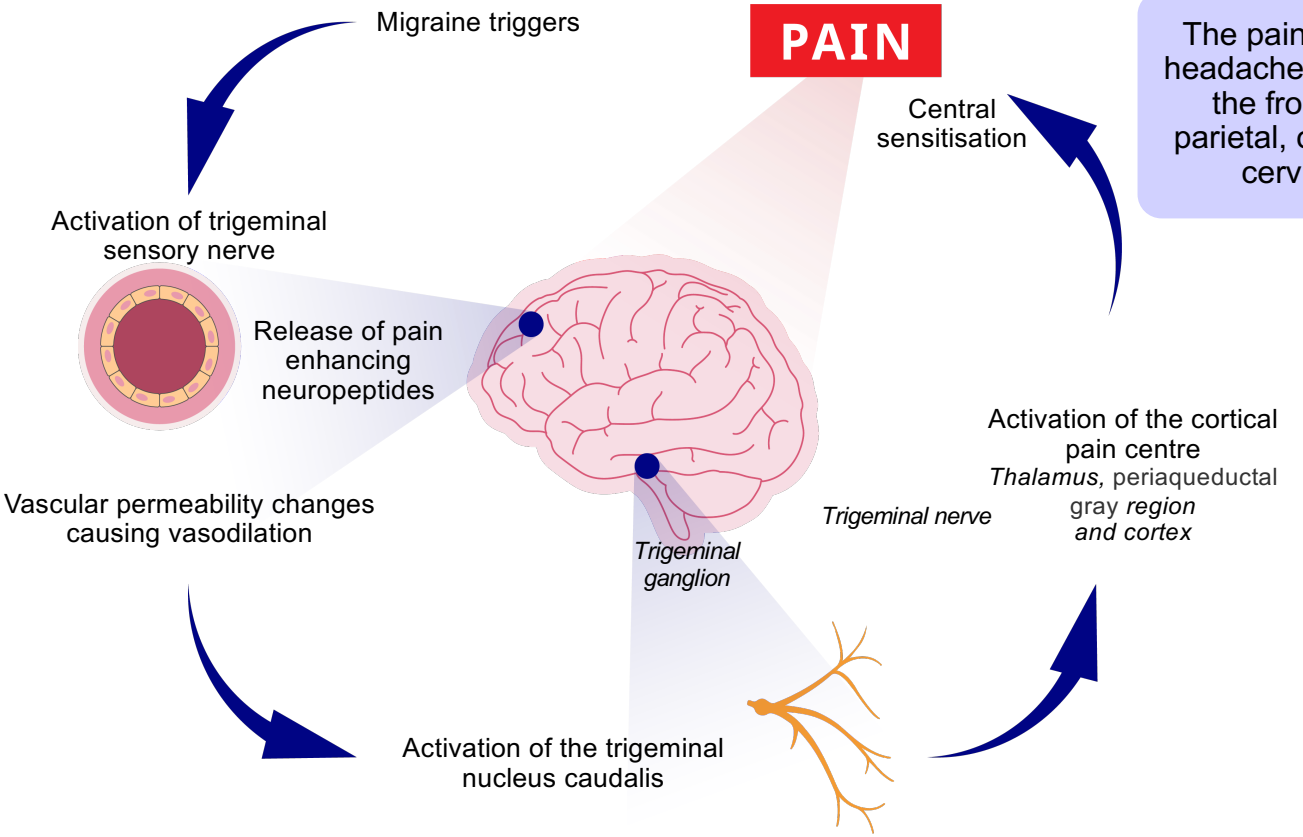




ola G et al. *Cephalalgia*. 2007;27:1429–1439; Kelman L. *Cephalalgia*. 2007; 27:394–402; Pietrobon D et al. *Nat Rev Neurosci*. 2003;4:386–398.

Migraine Pain Is Believed To Be Caused By The Activation Of The Trigeminal Sensory Pathways[1]

Migraine pain is believed to be caused by the hyperactivation of **trigeminal sensory pathways** that innervate pain sensitive structures (e.g., eye, dura, cerebral blood vessels), together termed the trigeminovascular system[1]



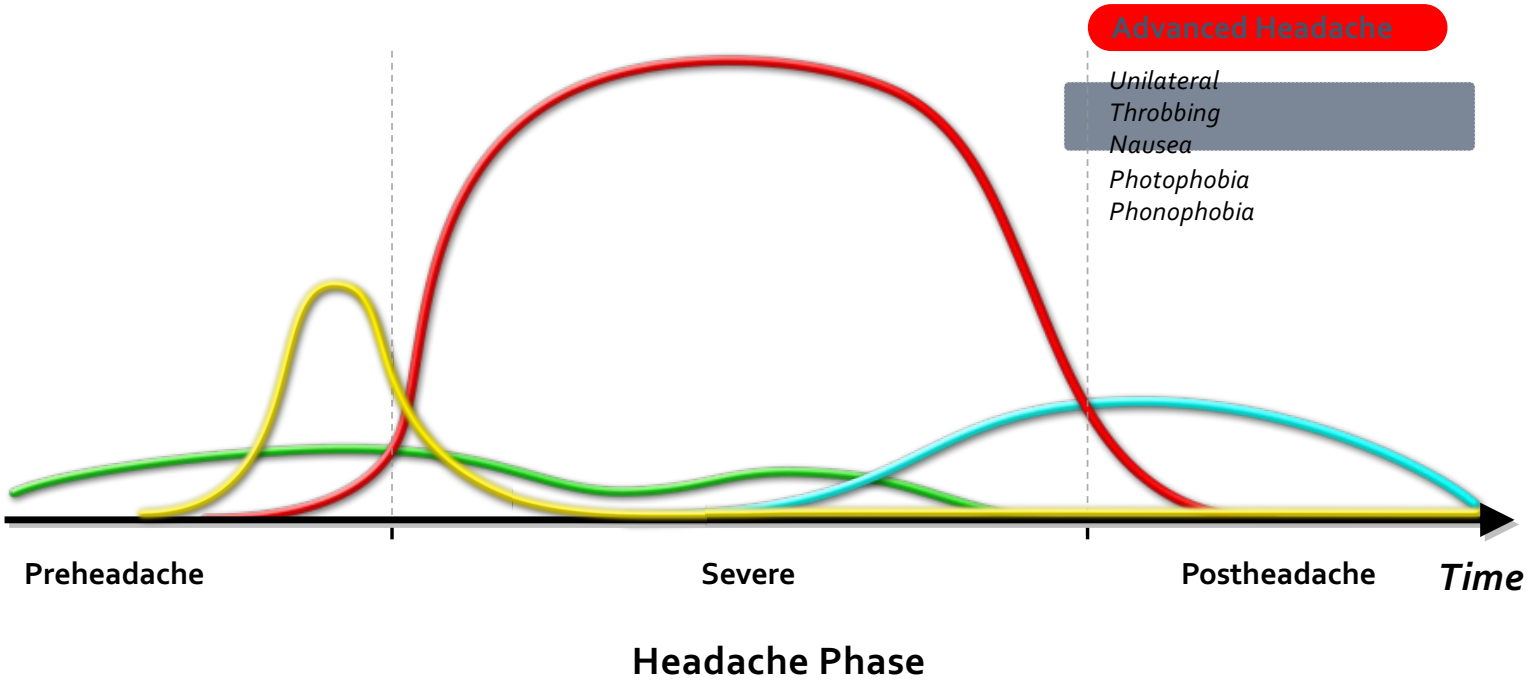
The pain associated with headache is experienced in the frontal, temporal, parietal, occipital and high cervical regions[1]

PAG, periaqueductal gray.

1. Goadsby P, *et al. Physiol Rev* 2017;97:553–622; 2. Durham P, Papapetropoulos S. *Headache* 2013;53:1262–1277.

Adapted from Durham P, Papapetropoulos S. *Headache* 2013.

Migraine:
Headache Not Always Gradual



Cady R et al. *Headache.* 2002;42:204–216.
Linde M. *Acta Neurol Scand*. 2006;114:71–83.
Linde M. *Cephalgia*. 2006; 26; 712–721.

Focus on Acute Treatments for Migraine

Triptans

Rimegepant

4.7.4 Antimigraine drugs

Also in this Section

4.7.4.1 Treatment of acute migraine attack

4.7.4.2 Migraine prophylaxis

4.7.4.3 Drug treatment of cluster headache

Overview of acutes

Step 1
- NSAID/paracetamol +/- antiemetic

Step 2
- Triptan +/- anti-emetic
- PO/melt/nasal spray/SC injection

Step 3
- NSAID/paracetamol+/- antiemetic + triptan
- Rimegepant

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The utility of anti-emetics

NNT for headache freedom at 2hrs

Ibuprofen
7.2

Aspirin
8.1

Aspirin
+Prochlorperazine
≡suma

Paracetamol
12

Paracetamol
+Metoclopramide
≡suma

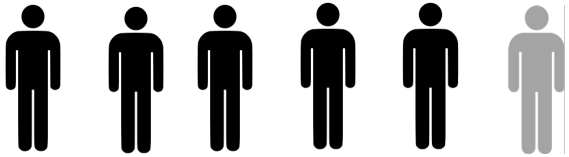
Dr J Anderson Headache Academy 2019

STEP 2

- **Triptan ± anti-emetic***

NNT for headache freedom at 2hrs

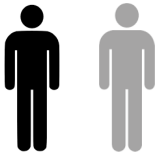
S-triptan 50mg
6.1



S-triptan 100mg
4.7

Z-triptan 5mg
4.5

S-triptan 6 SC
2.3



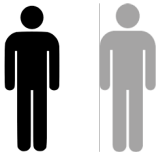
NNT for headache relief at 2hrs

S-triptan 50mg
4.0

S-triptan 100mg
3.5

Z-itriptan 5mg
3.2

S-triptan 6 SC
2.1



Troubleshooting with triptans

- **Triptan Ineffective –** check the patient is taking it early enough, try in at least 3 migraine attacks, think about alternative method of administration
- **Triptan side effects** – consider almotriptan, frovatriptan, naratriptan
- **Triptan effective but having to repeat dose in 2-3 hours** – consider adding NSAID naproxen 500mg or using triptan with slower onset
- **Wanting better 2 hour pain response** - eletriptan 80mg, rizatriptan 10mg or almotriptan 12.5mg
- **Problematic nausea –** change route of triptan. Add antiemetic
- **Failed 2 triptans** – consider rimegepant
- **Over 65 or CVD** - consider paracetamol + metoclopramide* or rimegepant

Where does Rimegepant fit in?

Triptan Non responders

→ **80% patients respond to triptans**

→ Consider timing, dose and non oral routes

Triptan Contra-Indicated

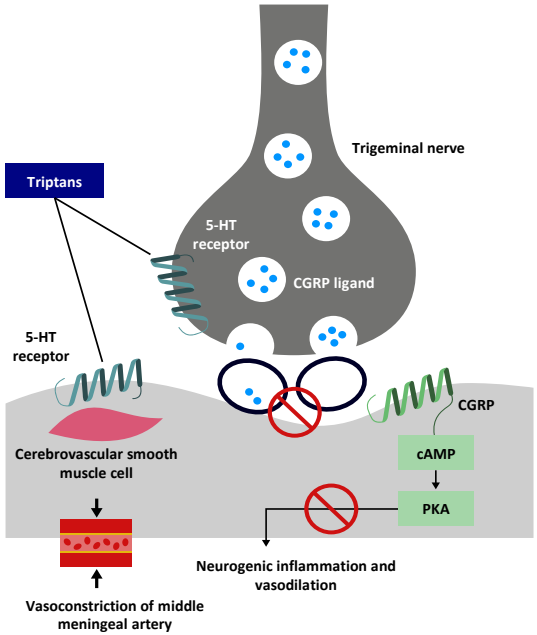
Triptan Intolerant

The mechanisms of action of triptans and gepants[1,2]

Triptan MoA

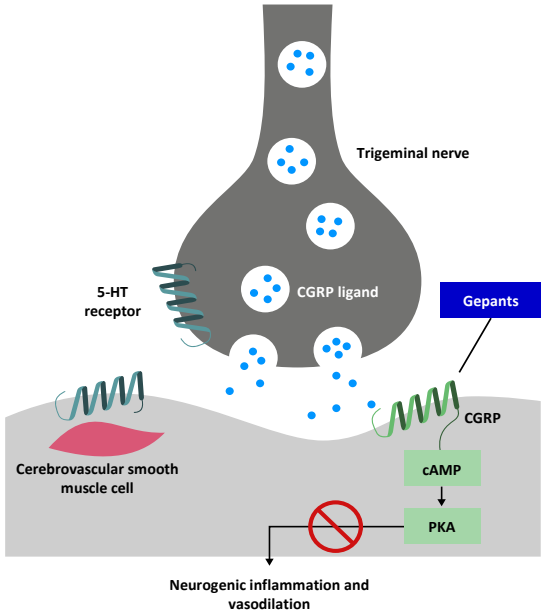
- Triptans are **5-HT$_{1B/1D}$ receptor agonists[3]**
- These 5-HT$_{1B/1D}$ receptors are located on **trigeminal nerves** and **prevent the release of CGRP[3]**
- However, the receptors are also found in **arterial smooth muscle,** which can lead to **vasoconstriction[4]**

Triptan MoA[1,2]



Gepant MoA*

Gepant MoA[1,2]



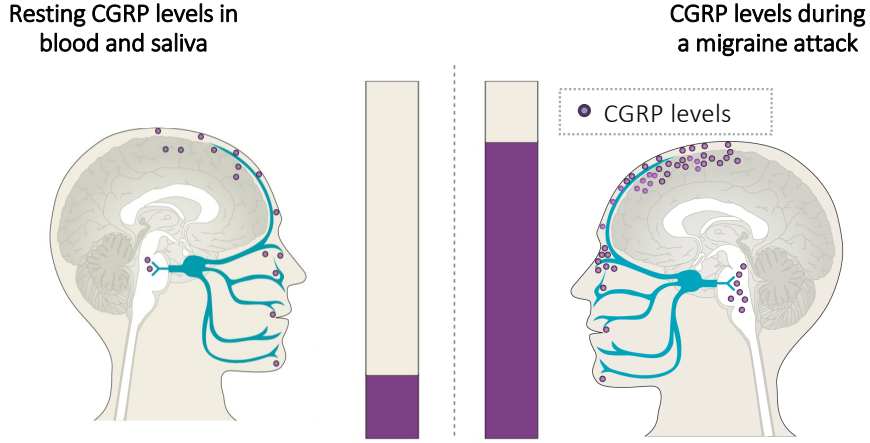
- Gepants **are CGRP receptor antagonists[5]**
- CGRP is a **potent vasodilator,[2]** but gepants are **not active vasoconstrictors[5,6]**

Adapted from Edvinsson L, *et al*. *Nat Rev Neurol* 2018.[1]

5-HT, 5-hydroxytryptamine (serotonin); cAMP, cyclic adenosine monophosphate; CGRP, calcitonin gene-related peptide; MoA, mechanism of action; PKA, protein kinase A.
*Please note, the relationship between pharmacodynamic activity and the mechanism(s) by which Vydura® exerts its clinical effects is unknown.[7]
1. Edvinsson L, *et al. Nat Rev Neurol* 2018;14:338–350; 2. Durham PL. *N Engl J Med* 2004;350:1073–1075; 3. Benemei S, *et al. J Headache Pain* 2017;18:103; 4. De Vries T, *et al. Pharmacol Ther* 2020;211:107528; 5. Ogunlaja O, Goadsby P. *eNeurologicalSci* 2022;29:100420; 6. Tepper D. *Headache* 2020;60:1037–1039;].

What is Vydura (rimegepant)?

Vydura (rimegepant) is a small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist[1,2]



Adapted from Schuster N, Rapoport A. *Nat Rev Neurol.* 2016.[4]

During a migraine attack, plasma CGRP levels increase[3–5]

CGRP is an important mediator of migraine and one of the targets of migraine treatment[3–5]

CGRP, calcitonin gene-related peptide.

1. Vydura (rimegepant) Summary of Product Characteristics for Great Britain; Vydura (rimegepant) Summary of Product Characteristics for Northern Ireland; 2. Croop R, *et al. Lancet*. 2019;394:737–45; 3. Ho TW, *et al. Nat Rev Neurol.* 2010;6:573–82; 4. Noseda R and Burstein R. *Pain.* 2013;154(Suppl 1):S44–53; 5. Schuster N and Rapoport A. *Nat Rev Neurol.* 2016;12:635–650.

Rimegepant is indicated for:[1]

Acute treatment of migraine with or without aura in adults

Recommended dosage is 75 mg Vydura, as needed

and

Preventive treatment of episodic migraine in adults who have at least four migraine attacks per month

Recommended dosage is 75 mg Vydura, every other day

The maximum dose per day is 75 mg[1]

The maximum dose of Vydura is 75 mg every 48 hours when it is concomitantly administered with moderate inhibitors of CYP3A4 or with strong inhibitors of P-gp[1]

1. Vydura® (rimegepant) Summary of Product Characteristics for the United Kingdom.

Rimegepant Prescribing Information: Part1

Licenced Indication

- Rimegepant 75 mg can be considered for patients who have not responded to adequate trials of at least 2 triptans

or

- if triptans are contraindicated or not tolerated or inadequate pain relief with NSAIDs and paracetamol

Acute treatment dosing regimen

- 75mg taken at the onset of a moderate to severe migraine (maximum 10 days per month or on average 2 days per week)
- The maximum dose in 24 hours is 75mg and a second dose should not be taken if ineffective or pain recurs

Rimegepant Prescribing Information: Part 2

Side Effects

- Rimegepant is generally well tolerated.
- Nausea is the main adverse effect in 1.2% of patients.
- Hypersensitivity reactions have been reported but are uncommon occurring in <1%.

Drug Interactions

- If patient is prescribed a strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole) then concurrent administration is not recommended.
- If prescribed with a moderate CYP3A4 inhibitor (erythromycin, fluconazole) a second dose should be delayed for 48 hours

Pregnancy and Breastfeeding

- Rimegepant is not recommended in pregnancy, if planning a pregnancy, or in breastfeeding

Rimegepant Prescribing Information: Part 2

Acute treatment dosing regimen[1]

The recommended dose is 75 mg rimegepant, as needed.

The maximum dose per day is 75mg

Undesirable Effects

The most common adverse reaction was nausea for acute treatment (1.2%).

Hypersensitivity reactions, including serious hypersensitivity, can occur days after administration. If a hypersensitivity reaction occurs, Rimegepant should be discontinued and appropriate therapy should be initiated

Please refer to the Vydura SmPC for full prescribing information

1. VYDURA 75 mg oral lyophilisate - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Rimegepant Prescribing Information: Part 3

Drug Interactions

- If patient is prescribed a strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole) then concurrent administration is not recommended.
- If patient is prescribed a strong CYP3A4 inducer (e.g. phenobarbital, rifampicin, St John's Wort) or a moderate CYP3A4 inducer (e.g. bosentan, efavirenz, modafinil), concurrent administration is not recommended
- If prescribed with a moderate CYP3A4 inhibitor (e.g. erythromycin, fluconazole) or a strong P-gp inhibitor (e.g. cyclosporine, verapamil) another dose should be delayed for 48 hours

Pregnancy and Breastfeeding

- Rimegepant is not recommended in pregnancy, if planning a pregnancy, or in breastfeeding

Please refer to the Vydura SmPC for full prescribing information

1. VYDURA 75 mg oral lyophilisate - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Cardiovascular Safety

BNF and SmPC – no cardiovascular contra-indications listed[1,2]

- The three Rimegepant acute treatment of migraine studies (Study 301, 302and 303)allowed patients with contraindications to triptans (1.0% and 0.7% of the pooled rimegepant and placebo groups respectively) to enrol provided that they met the other inclusion criteria. However, patients with uncontrolled, unstable or recently diagnosed cardiovascular disease were excluded[3].

  Scottish Medicines consortium: **"Due to the assumed absence of vasoconstrictive properties with rimegepant and the apparent favourable cardiovascular risk profile, no cardiovascular contraindications were noted for rimegepant."[3]**

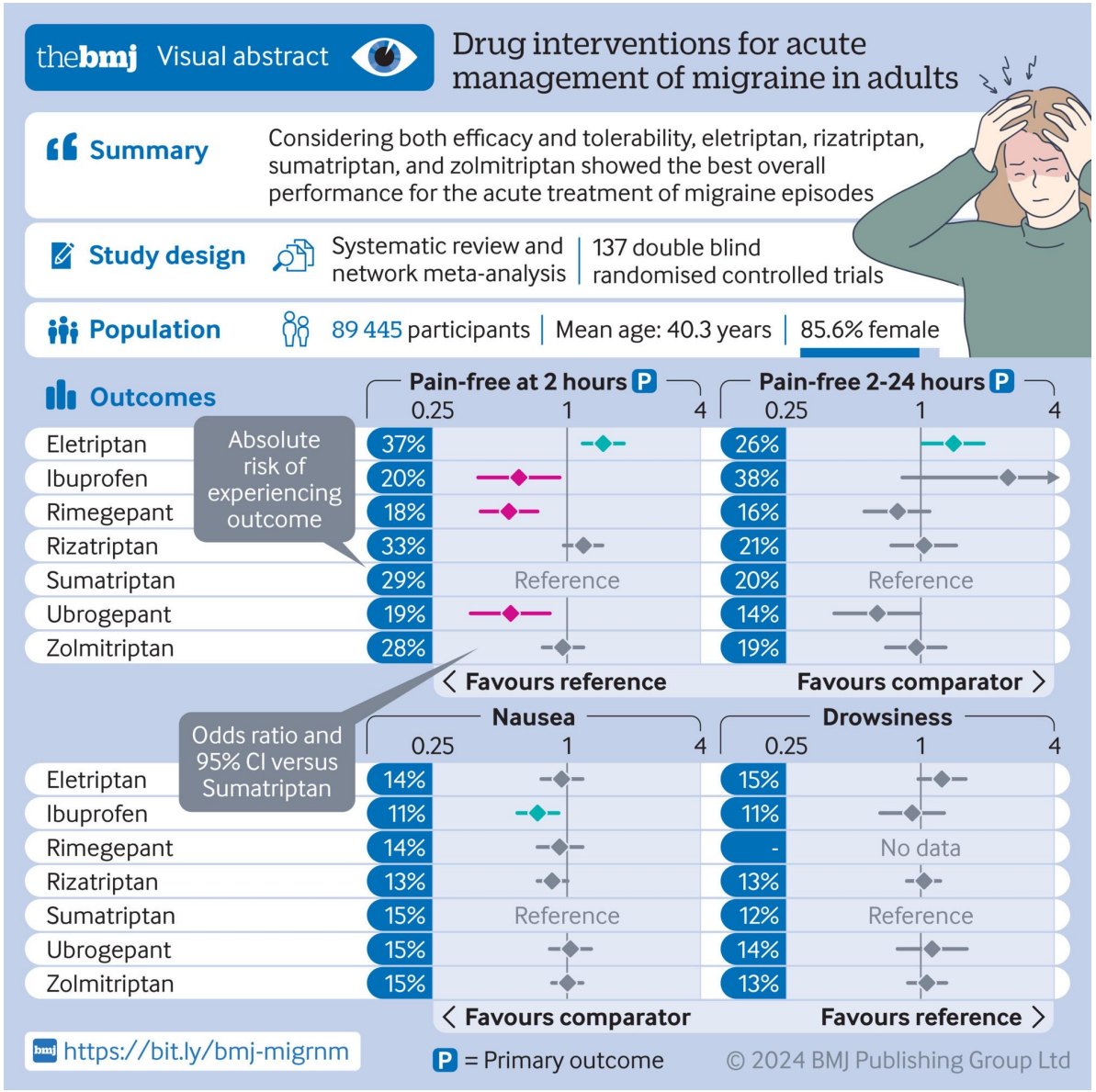
True et al. **Safety of Rimegepant in Adults with Migraine and Cardiovascular Risk Factors: Analysis of a Multicenter, Long-Term, Open-Label Study. Pain Ther (2024) 13:1203–1218**

- Of the 1800 rimegepant-treated subjects, 59.2%, 28.8%, and 12.1%, respectively, had 0, 1, or ≥2 CV risk factors; 7.0% had a moderate to high 10-year CV risk.
- Rimegepant showed favourable safety and tolerability in adults with migraine and CV risk factors, including those with moderate to high CV risk.

Bhardwaj et al. **No clinically relevant electrocardiogram effects of single therapeutic/supratherapeutic rimegepant doses in healthy adults.** Clin Transl Sci. 2024 Mar 5;17(3):e13727

- Both the 75mg-and 300mg (unlicensed) doses of rimegepant had no clinically relevant effect on ECG parameters, including QTcF, heart rate, PR and QRS interval, T-wave morphology, and U-wave presence.

1. https://bnf.nice.org.uk/drugs/rimegepant/
2. VYDURA 75 mg oral lyophilisate - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
3. Scottish Medicines Consortium Advice Rimegepant April 2023 Available at: https://scottishmedicines.org.uk/medicines-advice/rimegepant-vydura-full-smc2521/ Last accessed Oct 2024



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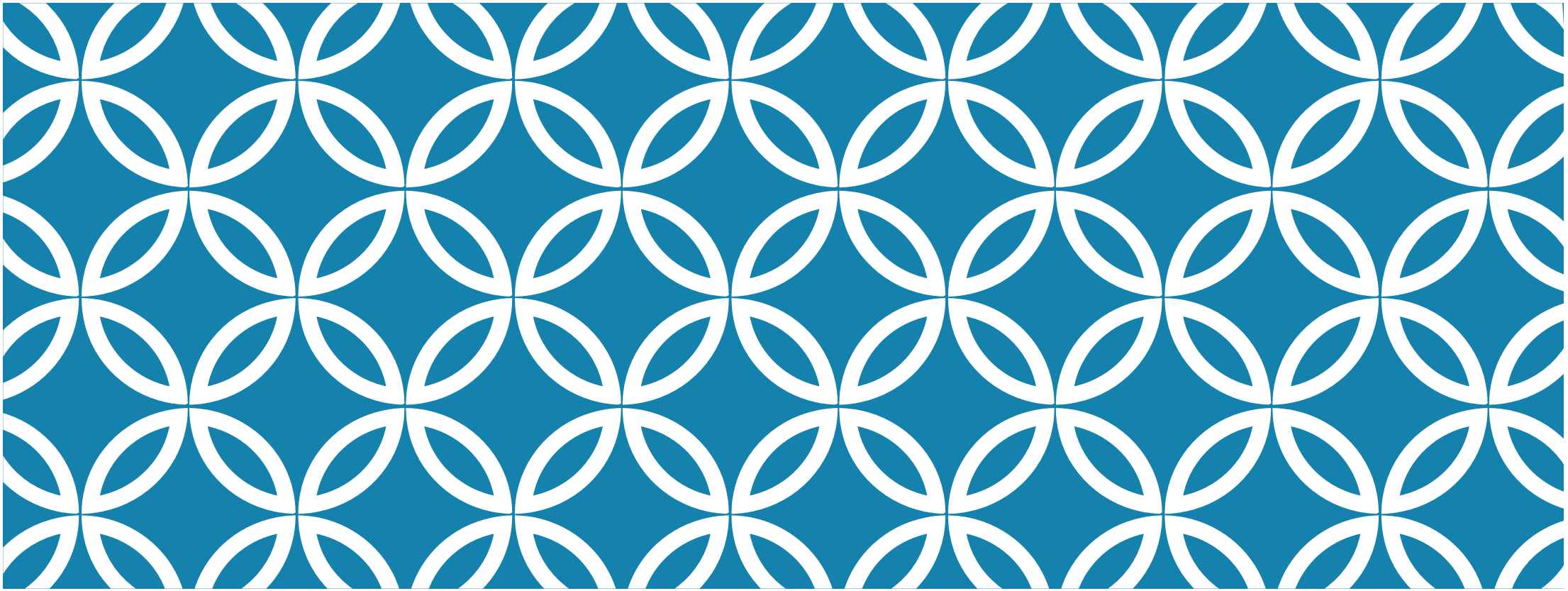
William K Karlsson et al. BMJ 2024;386:bmj-2024-080107



MANAGING MIGRAINE – PREVENTATIVE MEDICATIONS

Martin Harley

Consultant in Neurology

South Eastern Health and Social Care Trust

DISCLOSURES

I have received speaker fees from Teva, Pfizer and Abbvie

I have received conference sponsorship from Teva and Abbvie

WHY IS HEADACHE IMPORTANT?

One of the most common neurological symptoms

Account for 30% GP and 50% Neurology Referrals

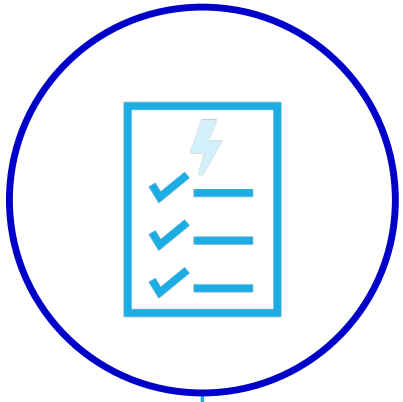
95% of the population at some stage experience headaches

15-19% of Acute Medical Admissions(1), 55% of Neurology in A&E(2)

1. Weatherall M., J RCP Edinb 2006; 36: 196-200

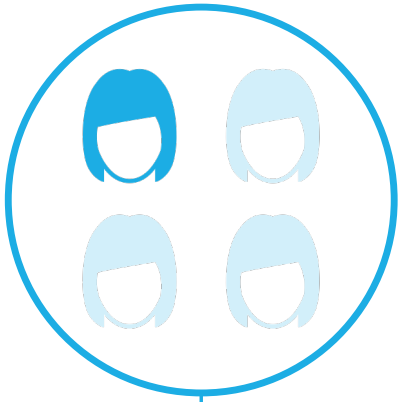
2. Craig J., Patterson V., Roche L., JamisonJ., Accident and Emergency Neurology: time for a reappraisal? Health Trends, 1997, 29, 89-91

MIGRAINE IS COMMON



Migraine is the **third most common** health condition in the world[1]

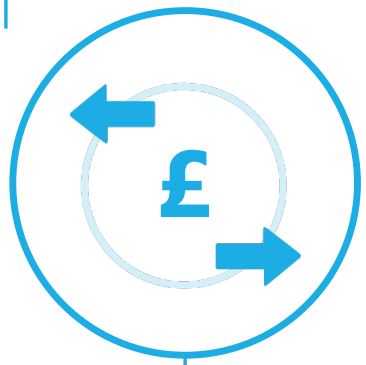
In the UK, more people live with migraine than **diabetes, asthma and epilepsy** combined[2]



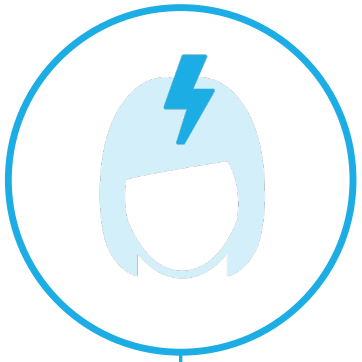
Around **1 in 4 adults** aged 15–49 in the UK are living with migraine[3]

1. Steiner TJ, *et al. J Headache Pain.* 2013;14(1):1; 2. The Migraine Trust. State of the Migraine Nation Dismissed for too long: Recommendations to improve migraine care in the UK. September 2021. https://migrainetrust.org/wp-content/uploads/2021/09/Dismissed-for-too-long_Recommendations-to-improve-migraine-care-in-the-UK.pdf [Last accessed April 2023]; 3. The Migraine Trust. Who is living with migraine in the UK? January 2020. https://migrainetrust.org/wp-content/uploads/2021/08/State-of-the-Migraine-Nation-population-rapid-review.pdf [Last accessed April 2023].

MIGRAINE HAS A LARGE ECONOMIC IMPACT



In the UK, the **direct healthcare costs** of migraine are estimated to be around **£1 billion** per year[1]



Migraine is the **second highest** cause of global disability in the general population*, but takes **first place** in women aged 15–49[†2]

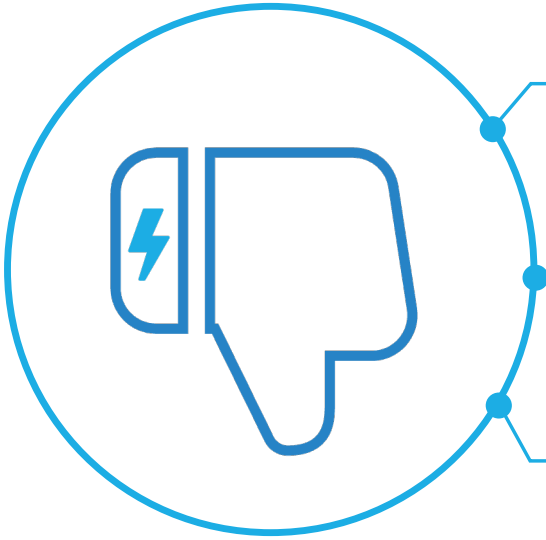
86 million equivalent workdays are lost **per year** in the UK due to migraine-related absenteeism and presenteeism[1]

In the UK, **loss of productivity** due to migraine accounts for an estimated **indirect cost of £8.8 billion** per year[1]

*The level-3 grouping of headache disorders in the GBD Study 2019 includes only specific diseases: migraine and tension-type headache, each with medication overuse headache as a sequela factored in according to the proportion of MOH attributed to it[2]; [†]Expressed as years lived with disability[2]. GBD, Global Burden of Disease; MOH, medication overuse headache.

1. The Work Foundation. Society's headache: The socioeconomic impact of migraine. April 2018. https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/lums/work-foundation/SocietysHeadacheTheSocioeconomicimpactofmigraine.pdf [Last accessed April 2023]; 2. Steiner TJ, *et al. J Headache Pain.* 2020;21(1):137.

MIGRAINE IMPACTS MULTIPLE ASPECTS OF PATIENTS' LIVES



Daily activities, with reduced ability to[1]:

- Contribute to housework
- Take part in social activities

Work productivity and professional lives[2]

Negative effect on relationships with family and friends[1]

Emotional and mental health issues are common in migraine patients

Mood change and anxiety disorders **2–5 times** more common in patients with migraine than in the general population[3]

1. The Migraine Trust. State of the Migraine Nation Dismissed for too long: Recommendations to improve migraine care in the UK. September 2021. https://migrainetrust.org/wp-content/uploads/2021/09/Dismissed-for-too-long_Recommendations-to-improve-migraine-care-in-the-UK.pdf [Last accessed April 2023]; 2. Begasse de Dhaem O, *et al. eNeurologicalSci.* 2022;27:100408;
3. Minen MT, *et al. J Neurol Neurosurg Psychiatry.* 2016;87(7):741–49.

Most headache presenting to GPs is migraine

Tepper SJ, et al. Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. *Headache*. 2004;44(9):856-64.

HOW DOES HEADACHE BREAKDOWN?

In a large (n=97,000) study patients presenting with headache were followed up to find the ultimate diagnosis

Secondary headache	5%
Tension Headache	21%
Migraine	72%
Cluster	2%

MAKING THE DIAGNOSIS

The Landmark study found that when a physician diagnosed migraine, they were correct 98% of the time

When they diagnosed non-migraine headache, they were wrong 94% of the time - the patients did in fact have migraine

Altogether, one in four (25%) did not receive a clinical diagnosis of migraine

The ICHD-3 gives diagnostic criteria www.ichd-3.org

Tepper SJ, *et al*. Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. *Headache*. 2004;44(9):856-64.

MIGRAINE – DIAGNOSTIC CRITERIA

At least five attacks

Each lasting 4 to 72 hours.

The headache should have two or more of the following characteristics:

- Unilateral location
- Pulsating quality
- Moderate to severe pain intensity
- Aggravated by or causing avoidance of routine physical activity.

The headache should be accompanied by one or more of:

- Nausea
- Vomiting
- Photophobia
- Phonophobia.

The headache should not be attributable to another disorder.

SO, WHAT IS MIGRAINE?

Migraine is a neurological condition which features amplification of a number of sensory pathways[1]. Some studies suggest that genetic components contribute to susceptibility of the condition[5]

May be lifelong but varies in impact, severity and frequency throughout life (epigenetics)[2]

Is a spectrum condition; attacks may be mild, moderate or severe[1]

Can lead to attacks which may start at any age; usually in early adulthood[3]

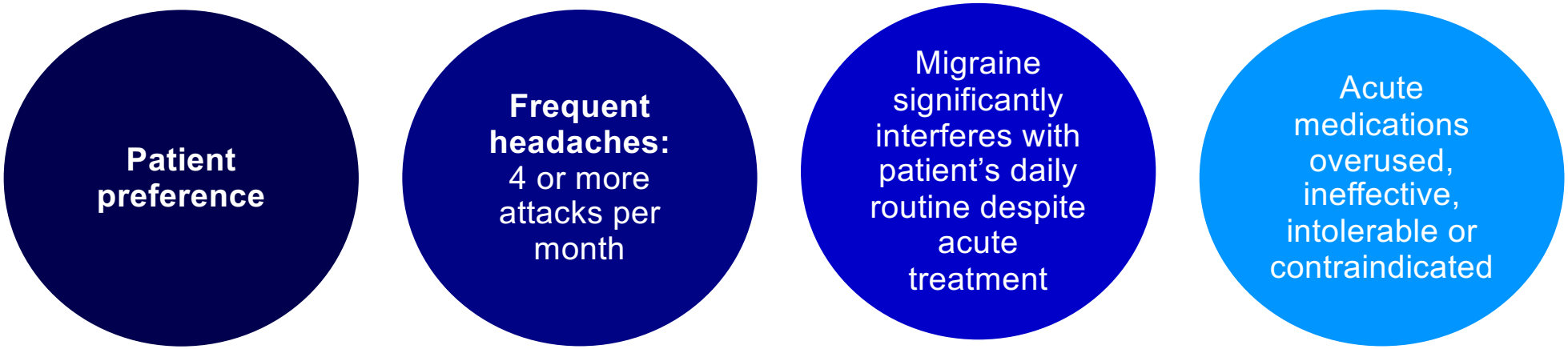
Has a natural history, often eventually improving with age[2]

Migraine is NOT just a bad headache[4]

1. Brennan K., Pietrobon D. A systems neuroscience approach to migraine. *Neuron.* 2018;97(5):1004-1021. 2. Kelman L. Migraine Changes with Age: IMPACT on Migraine Classification. *Headache.* 2006;46(7):1161-71. 3. NHS. Overview: Migraine. Available at: https://www.nhs.uk/conditions/migraine/. Accessed March 2023. 4. Kennedy AL. Flashing lights and poor funding: more than a headache. *Lancet.* 2017 (Radio). 5. Bron et al. Exploring the Hereditary Nature of Migraine. *Neuropsychiatric Disease and Treatment.* 2021;17. 1183-1194.

THE THREE PILLARS

PREVENTIVE TREATMENT: WHEN TO CONSIDER?



Silberstein SD. Preventive Migraine Treatment. *Continuum (Minneap Minn)*. 2015;21(4 Headache):973-89.

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS

Class	Drug	Dose recommendations
Beta-blockers	Propranolol	80–160 mg daily
Tricyclic antidepressants	Amitriptyline	10-75 mg nocte
Angiotensin II receptor blocker	Candesartan	16–32 mg daily
Serotoinin Antagonist	Pizotifen	500 micrograms to 1.5mg daily
SNRI	Venlafaxine	75 - 150 mg daily
Anticonvulsants	Topiramate	50-100 mg daily
	Valproate	600-1500mg daily

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—PROPRANOLOL

- **Mechanism of Action:**
  - **Beta-Adrenergic Blockade:** Inhibits beta receptors in the locus coeruleus, reducing the hyper-excitability of the central nervous system (Singh et al., 2024).
  - **Vascular Regulation:** Prevents vasodilation and modulates thalami-cortical activity, effectively raising the threshold for a migraine attack (EHF, 2023).
  - **Serotonergic Modulation:** Interacts with 5-HT receptors, which may inhibit the trigeminovascular system.
- **Efficacy in Practice:**
  - **Gold Standard:** Often considered the first-line choice for patients without respiratory contraindications.
  - **Reduction Metrics:** Provides a ≥50% reduction in mean monthly migraine days for 50% of patients (Linde & Rossnagel, 2004).

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—PROPRANOLOL

- **Dosing and Titration:**
  - **Start Low:** 10–20 mg BD (or 80 mg Modified Release).
  - **Maintenance:** Typically **80–160 mg daily**. Titrate slowly to the maximum tolerated dose.
- **Safety Profile:**
  - **Contraindications:** Asthma (relative), COPD, bradycardia, or second/third-degree heart block.
  - **Common Side Effects:** Fatigue, cold extremities, sleep disturbance (vivid dreams/insomnia), and exercise intolerance (NHS Grampian, 2025).
  - Ideal for patients with comorbid **hypertension, anxiety, or essential tremor.**

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—AMITRIPTYLINE

- **Mechanism of Action:**
  - **Monoamine Modulation:** Potent inhibition of the reuptake of serotonin ($5-HT$) and norepinephrine, enhancing descending inhibitory pain pathways (Singh et al., 2024).
  - **Neuronal Stability:** Suppression of **cortical spreading depression (CSD)**, the physiological hallmark of migraine aura (EHF, 2023).
  - **Ion Channel Blockade:** Modulation of sodium, calcium, and potassium channels, which may reduce neuronal hyperexcitability (EHF, 2023).
- **Efficacy in Practice:**
  - **Prophylactic Success:** Significantly reduces monthly headache frequency, severity, and duration compared to placebo (Jackson et al., 2010) with ≥50% reduction in mean monthly migraine days for 52% of patients

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—AMITRIPTYLINE

- **Dosing and Titration:**
  - **Start Low:** 10 mg taken at bedtime to improve tolerability and sleep.
  - **Maintenance:** Typically **25–75 mg daily**. Titrate by 10 mg weekly or bi-weekly based on response and side effects.
- **Safety Profile:**
  - **Contraindications:** Recent myocardial infarction, heart block, or narrow-angle glaucoma.
  - **Common Side Effects:** Anticholinergic effects sedation, and weight gain.
  - **Serious Risks:** Cardiac dysrhythmias (prolonged QT interval) and potential increase in suicidal ideation in younger patients.
  - Ideal for patients with comorbid **insomnia, tension-type headache, or fibromyalgia**; screen for cardiac risk factors with a baseline ECG if indicated.

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—CANDESARTAN

- **Mechanism of Action:**
  - **Angiotensin II Blockade:** Acts to reduce oxidative stress and neurogenic inflammation in the cerebral vasculature (Stovner et al., 2014).
  - **Neuroprotection:** May improve endothelial function and blood-brain barrier integrity.
- **Efficacy in Practice:**
  - **Non-Inferiority:** Placebo controlled clinical trials have demonstrate efficacy (Rystad Øie et al, 2025) and comparative studies have shown non-inferiority to propranolol but with a significantly lower side-effect burden (Stovner et al., 2014).
  - **Chronic Migraine:** Useful for both episodic and chronic migraine management.

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS– CANDESARTAN

- **Dosing and Titration:**
  - **Start Low:** 2–4 mg OD.
  - **Titrate:** Double the dose every 2 weeks until **16 mg OD**.
- **Safety Profile:**
  - **Monitoring:** Check **U&Es (Creatinine and Potassium)** at baseline and 1–2 weeks after reaching the maintenance dose.
  - **Contraindications:** Pregnancy (teratogenic), severe renal impairment, or bilateral renal artery stenosis.
  - **Common Side Effects:** Dizziness, orthostatic hypotension, and occasional headache (initial).
  - Excellent choice for patients with **metabolic syndrome or obesity** where beta-blockers or TCAs are undesirable. Worth considering a switch if already on anti-hypertensives.

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—PIZOTIFEN

- **Mechanism of Action:**
  - **Antagonist Activity:** Acts as a potent 5-HT-2 receptor antagonist; also possesses antihistaminic and mild anticholinergic properties.
  - **Vascular Tone:** Reduces the permeability of cranial vessels during the headache phase.
- **Efficacy in Practice:**
  - Most studies are quite old but they indicate good benefit with ≥50% reduction in mean monthly migraine days for 64% of patients (Peet et al, 1977), but evidence is weaker than propranolol or topiramate.
  - Many patient find the side effect profile intollerable

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—PIZOTIFEN

- **Dosing and Titration:**
  - **Initial:** 0.5 mg nocte.
  - **Range:** Increase gradually to **1.5 mg nocte.**
- **Safety Profile:**
  - **Common Side Effects: Significant weight gain** (increased appetite) and **heavy sedation.**
  - **Precautions:** Glaucoma and urinary retention (due to anticholinergic effects).
  - Usage had been decreasing in adults due to metabolic side effects, but still with the MHRA Topiramate guidance there has been a resurgence.

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—VENLAFAXINE

- **Mechanism of Action:**
  - **Dual Reuptake Inhibition:** Inhibits reuptake of both 5-HT and norepinephrine, strengthening descending inhibitory pain pathways (EHF, 2023).
- **Efficacy in Practice:**
  - **Comparative Success:** Studies show efficacy similar to amitriptyline but with potentially fewer anticholinergic effects (Bulut et al., 2004).

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—VENLAFAXINE

- **Dosing and Titration:**
  - **Initial:** 37.5 mg (Modified Release) OD.
  - **Maintenance: 75–150 mg OD**.
- **Safety Profile:**
  - **Contraindications:** Uncontrolled hypertension or high cardiovascular risk.
  - **Common Side Effects:** Nausea (early treatment), dry mouth, sweating, and sexual dysfunction.
  - **Discontinuation:** Requires very slow tapering to avoid withdrawal syndrome.
  - Excellent for patients with **comorbid generalized anxiety disorder or depression**.

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—TOPIRAMATE

- **Mechanism of Action:**
  - **Glutamate/GABA Modulation:** Blocks AMPA glutamate receptors and enhances GABA mediated inhibition (Singh et al., 2024).
  - **Voltage-Gated Channels:** Inhibits Na+ and Ca2+ channels, preventing the initiation of cortical spreading depression.
  - **Enzyme Inhibition:** Weak inhibition of carbonic anhydrase.
- **Efficacy in Practice:**
  - **Evidence Base:** Level A evidence for reducing migraine days with ≥50% reduction in mean monthly migraine days for 49% of patients (Brandes et al, 2004). Particularly useful in chronic migraine, migraine complicated by medication over use and for those in which aura is a prominent feature.

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—TOPIRAMATE

- **Dosing and Titration:**
  - **Start Low:** 25 mg nocte.
  - **Titrate:** Increase by 25 mg increments weekly/fortnightly to **50 mg BD**.
- **Safety Profile:**
  - **Pregnancy: Strict Pregnancy Prevention Programme (PPP).** High risk of cleft lip/palate (MHRA, 2024).
  - **Side Effects:** Paraesthesia (80%), cognitive "fog," taste perversion (carbonated drinks), and weight loss.
  - **Serious Risks:** Acute myopia and secondary angle-closure glaucoma; metabolic acidosis.
  - Ideal for patients with **high BMI**; avoid in those with a history of **kidney stones or depression**.

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—SODIUM VALPROATE

- **Mechanism of Action:**
  - **GABAergic Enhancement:** Increases brain concentrations of GABA by inhibiting its degradation and increasing its synthesis.
  - **Hyperexcitability:** Limits repetitive firing of neurons by inhibiting voltage-gated sodium channels.
- **Efficacy in Practice:**
  - **Robust effectiveness:** Shown to result in a ≥50% reduction in mean monthly migraine days for 48% of patients (Mathew et al, 1995) Has also shown effective for refractory cases where other medications have failed to provide benefit (Shaygannejad et al., 2008).

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS—SODIUM VALPROATE

- **Dosing and Titration:**
  - **Range:** 400 mg to 1000 mg daily (usually divided doses).
- **Safety Profile:**
  - **Regulatory Alerts:** Contraindicated in women of childbearing potential unless no other treatment is possible and a strict PPP is in place. New 2024 risks regarding male fertility/offspring (MHRA, 2024).
  - **Common Side Effects:** Weight gain, tremor, hair loss (reversible), and nausea.
  - **Serious Risks:** Hepatotoxicity and pancreatitis; baseline and periodic LFTs required.

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS – DECISION AID

Medication	Preferred If...	Avoid If...
Amitriptyline	Insomnia, Tension-type headache, Depression, Fibromyalgia	Obesity, Cardiac conduction issues, Glaucoma
Propranolol	Hypertension, Anxiety, Essential tremor, Hyperthyroidism	Asthma, COPD, Bradycardia, PVD, Depression
Candesartan	Hypertension, Metabolic syndrome, Obesity	Pregnancy, Renal artery stenosis, Hyperkalaemia
Topiramate	High BMI (Weight loss), Epilepsy	Pregnancy, Kidney stones, Glaucoma, "Brain fog"
Venlafaxine	Comorbid mental health indications, Menopausal vasomotor symptoms	Uncontrolled hypertension, High CV risk
Sodium Valproate	Comorbid neuropathic pain, Refractory cases	Female of childbearing potential, Liver disease
Pizotifen	Pediatric patients (sometimes)	Obesity/Weight concerns, Severe drowsiness

NON-SPECIFIC ORAL MIGRAINE PREVENTIVE TREATMENTS – DECISION AID

Which is a very long winded way to say that which ever drug you chose has about a 50% chance of reducing your patients mean monthly migraine days by a half or more.

We aim for this 50% or more reduction (in episodic migraine) as this is benchmark set by most studies however it is important to individualise patient responses. For some a medication may be successful if it prevents disability or results in an intensity reduction that permits them to function.

It is also important to consider dose increase or medication change if patients haven't gotten the response that **they** need from medication.

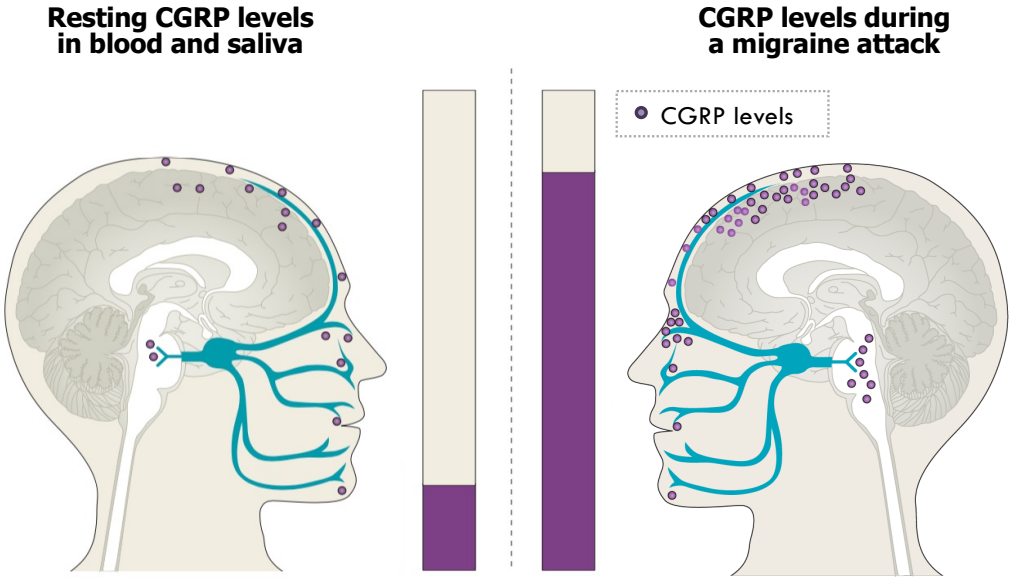
MIGRAINE SPECIFIC PREVENTIVE TREATMENTS

Class	Drug	Indication (s)	Standard recommended dose
Botulinum toxin	OnabotulinumtoxinA	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)	155–195 units by injection to 31–39 sites every 12 weeks
CGRP monoclonal antibodies	Erenumab	Prophylaxis of migraine in adults who have at least 4 migraine days per month	70 mg or 140 mg SC every 4 weeks
	Fremanezumab		225 mg SC once monthly or 675 mg SC every 12 weeks
	Galcanezumab		240 mg SC loading dose, then 120 mg SC once monthly
	Eptinezumab		100 mg or 300 mg IV every 12 weeks
CGRP receptor antagonist	Rimegepant	• Preventive treatment of episodic migraine in adults who have at least four migraine attacks per month	75 mg orally every other day
	Atogepant	• Prophylaxis of migraine in adults who have at least 4 migraine days per month	60mg orally once daily

WHAT ARE CGRP BASED THERAPIES?

CGRP is an important mediator of migraine and one of the targets of migraine treatment[3–5]

Plasma CGRP levels increase during a migraine attack[3–5]



Adapted from Schuster N, Rapoport A, 2016.[5]

CGRP is a pain-signalling neuropeptide and potent vasodilator[3]

- Released from trigeminal sensory afferents and the spinal trigeminal nucleus[4]

Studies have shown that CGRP[3,6]**:**

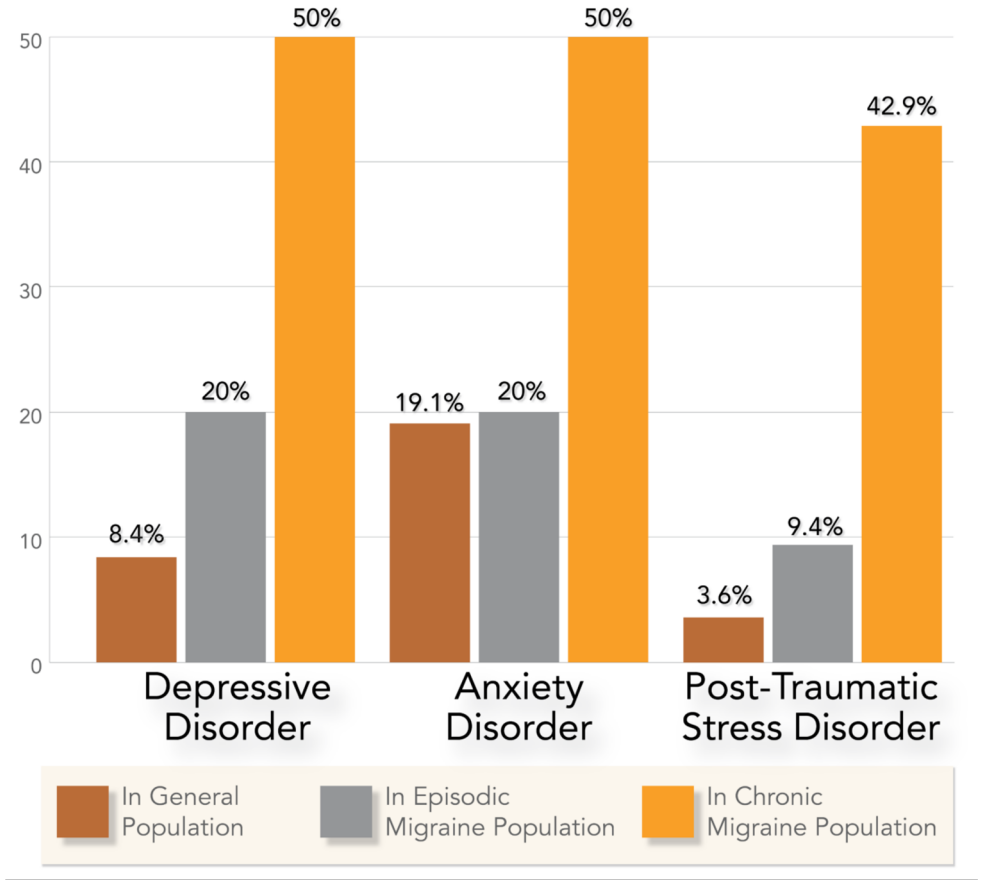
- Plasma levels are elevated during and outside of migraine attacks in people with migraine
- Infusion into patients with migraine can trigger a migraine attack

CGRP, calcitonin gene-related peptide.

2. Croop R, *et al. Lancet*. 2019;394:737–45; 3. Ho TW, *et al. Nat Rev Neurol* . 2010;6(10):573–82; 4. Noseda R and Burstein R. *Pain.* 2013;154(Suppl 1):S44–53; 5. Schuster N and Rapoport A. *Nat Rev Neurol.* 2016;12(11):635–50; 6. Ashina M, *et al. Pain.* 2000;86(1–2):133–38.

Medication	Mechanism	Dosing	Efficacy (≥50% Reduct.)	Super-Responder (≥75% Reduct.)	Discontinuation Rates (Trial vs Real-World)
Botox	Presynaptic ACh & CGRP inhibitor	155–195U every 12 wks	~47% (Chronic)	23%	Trial: <4% Real-World: 14%
Rimegepant	CGRP receptor antagonist	75 mg EOD	~49% (Episodic)	25%	Trial: <3%. No Real-World data but generally tolerated
Atogepant	CGRP receptor antagonist	60 mg at night	56% – 61%	38%	Trial: ~4%. No Real-World data but significant GI side effects
Galcanezumab	CGRP ligand mAb	120 mg monthly	~60% (Episodic)	34%	Generally well tolerated with occasional GI side effects causing discontinuation
Fremanezumab	CGRP ligand mAb	225 mg monthly	~57% (Episodic)	34%	
Erenumab	CGRP receptor mAb	140 mg monthly	~50%	26%	

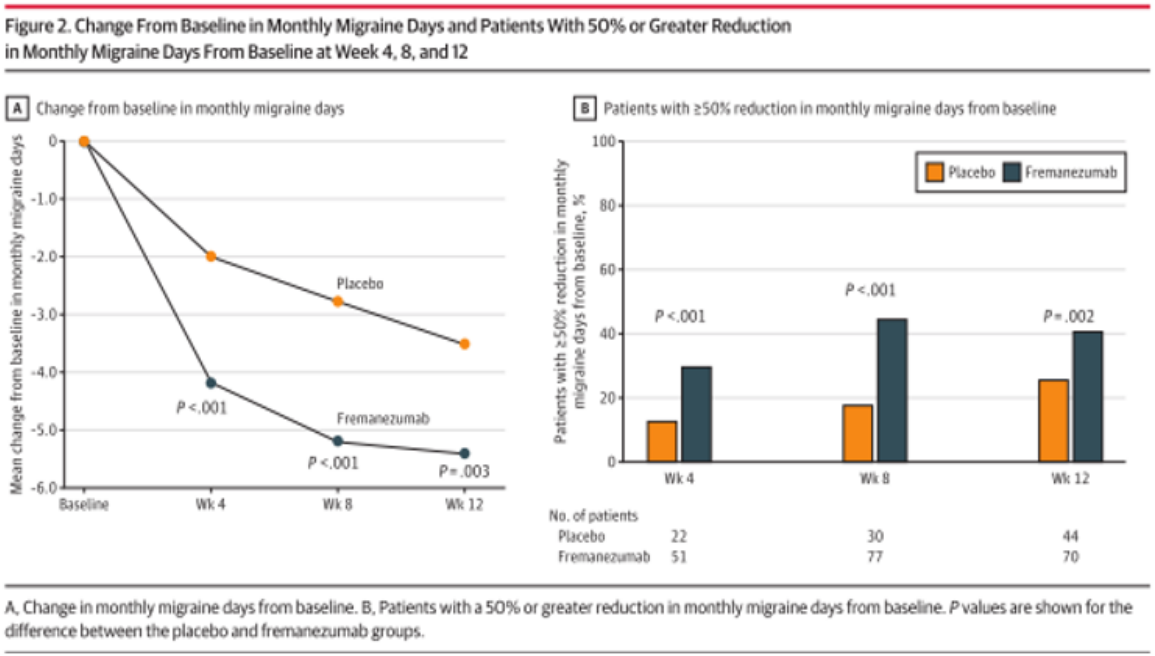
SPECIAL CASES – COMORBID DEPRESSION



SPECIAL CASES – COMORBID DEPRESSION

The UNITE Randomised Clinical Trial

- Efficacy and safety of fremanezumab (n=175) *vs* placebo (n=178) in adults with migraine and comorbid major depressive disorder (MDD).
- Parallel-group, RCT with 12-week double-blind period and 12-week open-label extension.
- Primary endpoint: mean change from baseline in monthly migraine days during the 12-week double-blind period.
- Secondary endpoint: patients with ≥50% reduction from baseline in monthly migraine days over 12 weeks.



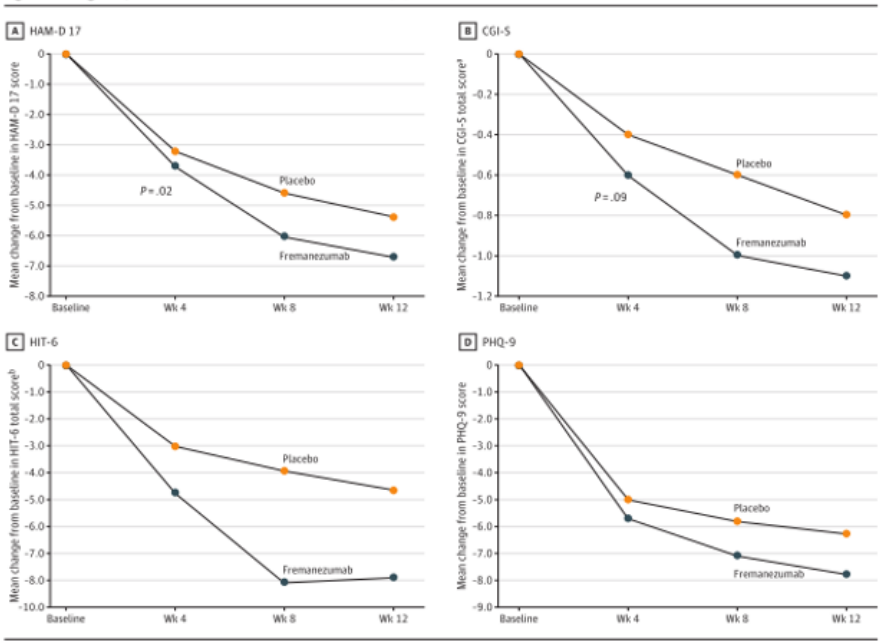
Adapted from Lipton RB *et al. JAMA Neurol* 2025; 82(6): 560-569

SPECIAL CASES – COMORBID DEPRESSION

The UNITE Randomised Clinical Trial

- Further secondary end points: mean change from baseline in depressive symptoms at week 8 measured by HAM-D 17; mean change from baseline in patient reported outcome scores at weeks 4 & 8 (CGI-S) and week 12 (CGI-S and HIT-6); safety and tolerability outcomes.
- Key exploratory endpoints: change from baseline in depressive symptoms at week 4 (PHQ-9 and HAM-D 17), week 8 (PHQ-9), week 12 (PHQ- and HAM-D 17), and week 24 (HAM-D 17).
- 70/176 patients (40%) in the fremanezumab group and 48/177 (27%) in the placebo group reported ≥1 adverse event during the double-blind period, most of which were mild or moderate in severity. Tolerability comparable to previous pivotal trials.

Figure 3. Change in Questionnaire Scores From Baseline at Week 4, 8, and 12



A, Hamilton Depression Rating Scale–17 Items (HAM-D 17). B, Clinical Global Impression Severity of Illness (CGI-S). C, 6-Item Headache Impact Test (HIT-6). D, 9-Item Patient Health Questionnaire (PHQ-9). *P* values are shown for the difference in mean change from baseline values between the placebo and fremanezumab groups.

[a]Reductions of 2 or more points from baseline, or a score of 3 or greater indicates a clinically meaningful minimal change.

[b]Reductions of 8 or more points indicate a clinically meaningful minimal change.

Adapted from Lipton RB *et al. JAMA Neurol* 2025; 82(6): 560-569

SPECIAL CASES – MENSTRUATION RELATED MIGRAINE

Medication	Class	Evidence-Based Dosing	Level of Evidence	Clinical Notes
Frovatriptan	Triptan	2.5 mg BID	Level A (Strongest)	26h half-life provides superior protection; lowest "rebound" rates.
Naratriptan	Triptan	1 mg BID	Level B	Well-tolerated; slower onset but sustained effect.
Zolmitriptan	Triptan	2.5 mg BID/TID	Level B	Effective in reducing severity and frequency.
Naproxen	NSAID	550 mg BID	Level B	First-line if patient also has dysmenorrhea (cramps).
Mefenamic Acid	NSAID	500 mg TID	Clinical Practice	Often used where menorrhagia (heavy bleeding) is a factor.
Magnesium	Supplement	360 mg daily	Level C	Start from Day 15 of cycle; safest for low-risk profiles.

The Triptan medications should be taken form 2 days before and until 3 days after bleeding is expected to start
I generally avoid hormonal manipulation unless this is indicated for other reasons.
Both Gepant medications are in clinical trials looking at this indication.

SPECIAL CASES – PREGNANCY AND LACTATION

Propranolol

- **Evidence:** Long-standing safety data; considered one of the safest preventatives in pregnancy.
- **Safety Profile:** Not associated with increased risk of major congenital malformations.
- **Late Pregnancy Risks:** Potential for **Neonatal Beta-Blockade** (bradycardia, hypoglycemia, and respiratory distress) and **Intrauterine Growth Restriction (IUGR)**.

Amitriptyline Evidence: Generally considered low-risk, particularly at the low doses (10–50 mg) used for migraine (compared to higher antidepressant doses).

- **Safety Profile:** Most large-scale studies show no significant increase in the risk of major birth defects.
- **Late Pregnancy Risks:** High-dose use near term may lead to **Neonatal Withdrawal Syndrome** (irritability, jitteriness, and feeding difficulties).

SPECIAL CASES – PREGNANCY AND LACTATION

Medication	Excretion into Breast Milk	Safety Status	Clinical Notes
Propranolol	Low (highly protein-bound)	Compatible	Generally considered the first-line choice. Monitor infant for bradycardia or lethargy.
Amitriptyline	Low / Minimal	L2: Probably Safe	Low doses used for migraine are unlikely to affect the infant. Monitor for sedation.
Candesartan	Unknown (likely low)	L3: Caution	Limited data.
Topiramate	Significant (up to 10-20%)	L4: Not Recommended	
Sodium Valproate	Low (approx. 1-10%)	L2: Probably Safe	The Valproate PPP make this a very unlikely scenario.
Venlafaxine	Moderate	L3: Caution	High metabolite levels in milk. Monitor infant for irritability or poor sleep.
CGRP mAbs	Extremely Low (Large molecule)	L3/L4: Limited Data	Molecules are likely too large to pass into milk in significant amounts, but data is currently sparse.
Gepants	Unknown but theoretical risk of crossing into milk	L4: Not Recommended	(Rimegepant, Atogepant). Insufficient data; currently avoided in breastfeeding.

SPECIAL CASES – PREGNANCY AND LACTATION

- Trigeminal nerve stimulation (Cefaly)
- Remote electrical stimulation (Nerivio)

SPECIAL CASES – MENOPAUSE

In women with migraine peri-menopause can result in worsening of migraine symptoms.

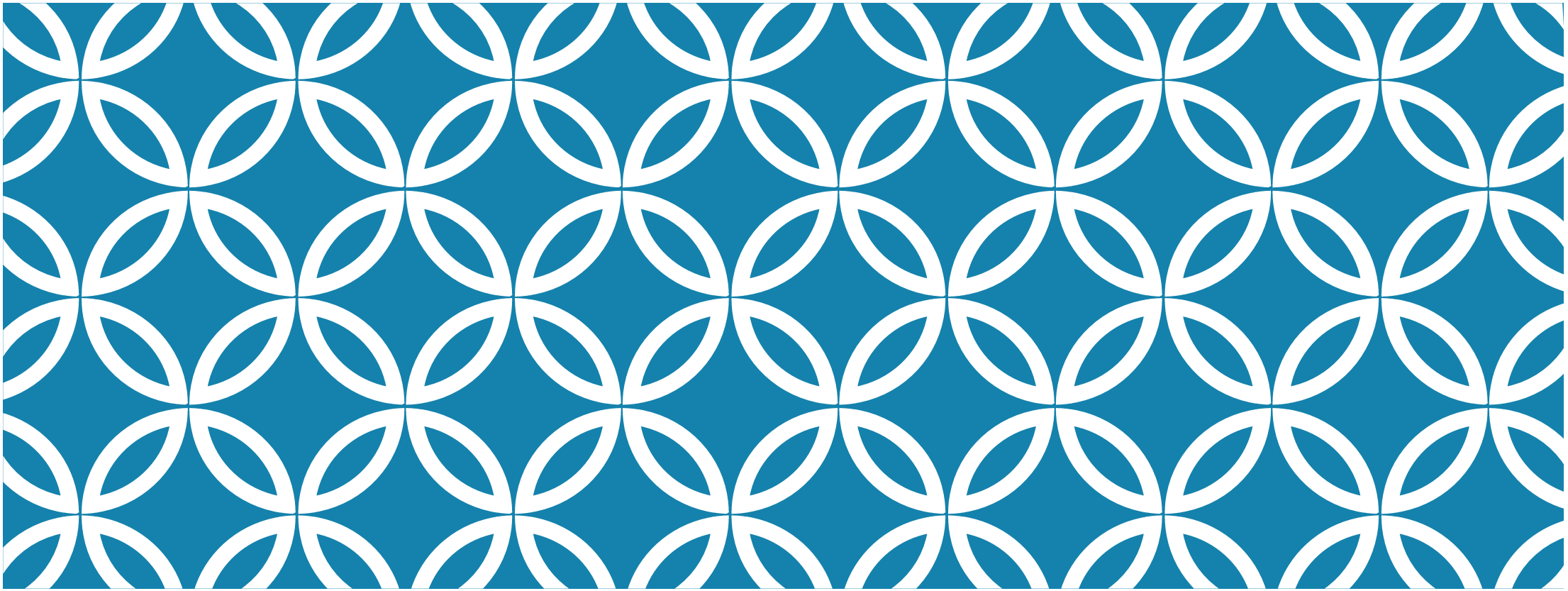
While conventional migraine medications can be of benefit there is also value in managing with HRT if there are no contraindications.

Migraine with or without aura does not contraindicate HRT use.

In terms of HRT regime choice it is best to use non-oral estrogen (patch or gel). The lowest oestrogen dose that effectively controls vasomotor symptoms should be used.

Where progestogen is required continuous delivery is recommended, with preparations such as levonorgestrel intrauterine system , transdermal norethisterone (as in combined patches) or micronised progesterone.

Women with migraine and vasomotor symptoms who do not wish to use HRT or in whom estrogens are contraindicated may benefit from venlafaxine.



QUESTIONS?