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## Introduction and Background

Glossary	
5-HT	5-hydroxytryptamine (serotonin)
Bruxism	Excessive teeth grinding or jaw clenching
Diplopia	Double vision
Hypoaesthesia	Absent or reduced sensitivity to cutaneous stimulation
Nystagmus	Involuntary eye movement
Oculogyric crisis	Spasmodic attack that is marked by fixation of the eyeballs in one position usually upward
Paraesthesia	A sensation of pricking, tingling or creeping on the skin
Phonophobia	Intolerance of noise
Photophobia	Intolerance to light; painful sensitivity to strong light
Status migrainosus	A debilitating migraine that lasts for more than 72 hours
Tenesmus	A distressing but ineffectual urge to evacuate the rectum or urinary bladder
Trismus	Spasm of the muscles of mastication

These guidelines aim to form evidence-based recommendations for the drug treatment of migraine attacks and of migraine prophylaxis. Non-drug management (e.g. behavioural modification) will not be included in this COMPASS Therapeutic Note, although it is regarded as an important part of migraine management. For example, regular aerobic exercise alone can reduce headache frequency by around 40%.<sup>1</sup> Medication overuse headache (MOH) is a potential complication when managing migraine. For this reason, MOH will be discussed within this COMPASS Therapeutic Note. Tension headache, however, will not be covered.

Migraine is a highly prevalent, disabling and under-treated condition.<sup>2</sup> It is a primary episodic or chronic headache disorder that is characterised by attacks comprising various combinations of headache and neurological, gastrointestinal and autonomic symptoms.<sup>3,4</sup> Migraine can, in most cases, be successfully managed in primary care.

### Classification of migraine

Although various schemes preceded it, the 1998 classification of the International Headache Society,<sup>5</sup> known as the International Classification of Headache Disorders (ICHD), was the first to be widely adopted.

This has been revised since, and a third edition is now close to being finalised. A beta version has been published ahead of the final version, ICHD-3 (beta).<sup>6</sup> ICHD-3 (beta) is the international standard.<sup>6</sup> It classifies migraine as:<sup>6</sup>

- **Migraine without aura** (formerly called “common migraine”) – occurring in 75% of people.
- **Migraine with aura** (formerly called “classic migraine”) – occurring in 20% of people. This includes retinal migraine.
- **Chronic migraine** – headache occurring for more than 15 days a month for more than three months, which, on at least 8 days per month, has the features of migraine headache.
- **Probable migraine** – with or without aura
- **Episodic syndromes that may be associated with migraine** – e.g. cyclical vomiting syndrome, abdominal migraine, benign paroxysmal positional vertigo (BPPV).
- **Complications of migraine** (chronic migraine, status migrainosus, migrainous infarction, migraine-triggered seizure, medication overuse headache).<sup>7</sup>

### Pathophysiology of migraine

During a migraine attack, nerve activation results in the dilatation of meningeal blood vessels that, in turn, causes pain, further nerve activation and inflammation.<sup>8</sup> Because neural events are linked to vascular changes, migraine is considered a neurovascular headache disorder.<sup>7</sup> Migraine is a disorder of sensory processing, which explains the numerous non-headache features of migraine.

### How big is the problem?

Migraine is one of the most frequent headache disorders.<sup>9</sup> It is three times more common in women than in men; prevalence in women is approximately 18% and in men 6%.<sup>3</sup> The first attack is often in childhood and over 80% have had their first attack by the age of 30.<sup>10</sup> In anyone over the age of 50 who experiences “migraine” for the first time, an alternative pathology should be considered, although rarely found. There is a family history in 70-80% of people with migraine.<sup>7</sup>

The prevalence of migraine in children between the ages of three and eight years is about 3% and in adolescents between 10-19%.<sup>11</sup> Childhood onset migraine is more common in boys than in girls.<sup>12</sup> The mean age of onset of migraine is 7.2 years for boys and 10.9 years for girls.<sup>13</sup> Migraine headaches can have adverse effects on the lives of children and adolescent sufferers. These include impaired school performance, poor attendance and diminished participation in extracurricular activities and social life.<sup>11,14</sup> In primary care, a practice of 2000 patients can expect about 5 new cases of migraine per year and 40 consultations for existing migraine.<sup>10</sup> These numbers, however, may be misleading as many sufferers do not consult their GP.<sup>7</sup>

In the UK, an estimated 190,000 attacks are experienced every day, with three quarters of people affected reporting disability. As a result, it has been estimated that over 100,000 people are absent from work or school because of migraine every working day.<sup>15</sup> The cost to the UK economy may exceed £1.5 billion per annum.<sup>7</sup> According to the World Health Organization (WHO), in the Global Burden of Disease Study (updated in 2013), headache is the third highest cause of years lost due to

disability, substantial personal suffering, impaired quality of life and financial cost.<sup>16</sup>

### Keeping a headache diary

Keeping a headache diary for a minimum of eight weeks is a useful tool for the management of any patient with migraine. A headache diary helps:

- Eliminate recall bias with respect to headache timing and characteristics.
- Identify the type or types of headache experienced.
- Identify possible trigger factors.

Ask the patient to record the following for each headache they experience:

- Frequency, duration and severity
- Any associated symptoms
- All prescribed and over-the-counter medications taken to relieve headache
- Possible precipitants
- Relationship of headache to menstruation.<sup>17</sup>

The Migraine Trust has migraine diary templates that can be printed and completed by the patient or carer: <https://www.migrainetrust.org/living-with-migraine/coping-managing/keeping-a-migraine-diary/>.

### Features of migraine (see TABLE ONE)

Patients with migraine typically give an account of recurrent, episodic, moderate or severe headaches (which may be unilateral and/or pulsating) lasting 4 to 72 hours, associated with gastrointestinal symptoms, during which they limit activity and prefer a dark and quiet room. They are free from symptoms between attacks.<sup>18</sup>

A typical migraine attack can consist of four phases:<sup>4</sup>

#### 1. The premonitory phase

This occurs in 20 to 60% of those with migraine. The premonitory phase is different from an aura and occurs hours to days before the headache. Common features are depression, tiredness, difficulty concentrating, irritability, a stiff neck and food cravings.<sup>19,20</sup> In fact, cravings for certain foods can sometimes be mistaken for triggers, as the patient associates them with being followed by a migraine.

#### 2. The aura

The migraine aura consists of focal neurological symptoms that precede, accompany or (rarely) follow an attack. Aura usually develops over 5 to 20 minutes, lasts for less than 60 minutes, can be visual, sensory or motor, and can involve language or brainstem disturbances.<sup>5</sup> Headache usually follows within 60 minutes of the end of the aura.<sup>7</sup>

Aura in migraine usually presents with a positive neurological sign (e.g. tingling, pins and needles, seeing flashing lights). This differentiates migraine aura to stroke symptoms where negative neurological signs are present (e.g. numbness and loss of vision).<sup>21</sup>

#### 3. The headache

The typical headache is unilateral (although bilateral in 30-40% of cases), of gradual onset, throbbing, aggravated by movement and having pain of moderate to severe intensity. Anorexia is common. Nausea is common and occurs in approximately 50% of patients.<sup>22</sup> Sensory hypersensitivity results in patients seeking a dark, quiet

room.<sup>23</sup> Blurry vision, nasal stuffiness, anorexia, hunger, tenesmus, diarrhoea, abdominal cramps, polyuria, facial pallor, sensations of heat or cold or sweating might occur. Depression, fatigue, anxiety, nervousness, irritability and impairment of concentration are common.<sup>7</sup>

#### 4. The resolution

After the headache, the patient often feels tired, washed out, irritable or listless, and can have impaired concentration, scalp tenderness or mood changes.<sup>7</sup>

#### Childhood migraine – features

In children, headache is often bilateral, attacks are usually shorter (2 to 72 hours) and photophobia may be inferred from their behaviour.<sup>24,25</sup> Apart from these differences, the ICHD-3 (beta) criteria for migraine are the same for children as for adults.<sup>6,7</sup>

In both adults and children, the diagnosis of migraine is based on the typical patient's history and a normal neurological examination.<sup>9</sup> At least five attacks must have occurred before the diagnosis can be established.

#### Features indicative of a more sinister pathology

Evaluate people who present with headache and any of the following features, and consider the need for further investigations and/or referral:

- Worsening headache with fever
- Sudden-onset headache reaching maximum intensity within 5 minutes
- New-onset neurological deficit
- New-onset cognitive dysfunction

- Change in personality
- Impaired level of consciousness
- Recent (within the past 3 months) head trauma
- Headache triggered by cough, valsalva or sneeze
- Headache triggered by exercise
- Orthostatic headache
- Symptoms suggestive of giant cell arteritis
- Symptoms and signs of acute narrow angle glaucoma
- A substantial change in headache characteristics.<sup>17</sup>

#### Aims / goals of migraine management

Patients need to understand that cure is not a realistic aim. The shared objective should be control of symptoms so that the effect of the illness on a person's life is minimal.<sup>18</sup>

As soon as a clinical diagnosis of migraine is made and disability and comorbidities have been assessed, the next task is to develop an individualised treatment plan.<sup>26</sup> This plan usually has a number of goals that vary in priority with the patient's headache characteristics and treatment preferences. The plan usually includes educating patients about their illness and its management (e.g. mechanisms, trigger recognition and lifestyle changes), acute treatment and preventative treatment. Lifestyle modification is a major factor in the management of migraine and should not be overlooked.



#### Patient information on lifestyle modification:

[www.migrainetrust.org](http://www.migrainetrust.org) or [www.migraine.ie](http://www.migraine.ie)

**TABLE ONE: Features of migraine**<sup>27</sup>

Migraine without aura	Migraine with aura	Chronic migraine
Headaches last 4 to 72 hours and have at least two of the following features: <ul style="list-style-type: none"> <li>• Unilateral</li> <li>• Pulsating /throbbing</li> <li>• Moderate to severe pain</li> <li>• Pain aggravated by movement.</li> </ul> In addition there is at least one of: <ul style="list-style-type: none"> <li>• Nausea</li> <li>• Vomiting</li> <li>• Photophobia and phonophobia</li> </ul>	One or more of the following reversible aura symptoms: <ul style="list-style-type: none"> <li>• Visual</li> <li>• Sensory</li> <li>• Speech and/or language</li> <li>• Motor</li> <li>• Brainstem</li> <li>• Retinal</li> </ul> Headache begins around the time the aura finishes and has similar features to migraine without aura.	Headache occurring on 15 or more days per month for more than three months, which, on at least 8 days per month, has the features of migraine headache.
Probable migraine	Episodic syndromes that may be associated with migraine	Complications of migraine
Migraine-like attacks missing one of the features required to fulfil all criteria for a subtype of migraine (see above criteria) and not fulfilling criteria for another headache disorder.  Migraine attacks often do not achieve all characteristics necessary for a migraine attack diagnosis but nevertheless respond to specific migraine treatments.	A group of disorders, occurring in patients who have migraine with / without aura, or who have an increased likelihood to develop migraine. Historically noted to occur in childhood, but may also occur in adults. Additional conditions that may occur in these patients include motion sickness, periodic sleep disorders including sleep walking, sleep talking, night terrors and bruxism.	These include: <ul style="list-style-type: none"> <li>• Status migrainosus</li> <li>• Persistent aura without infarction</li> <li>• Migrainous infarction</li> <li>• Migraine aura-triggered seizure</li> </ul>

For full details, see HIS Classification ICHD-3 beta <https://www.ichd-3.org/1-migraine/>

# Management of Acute Migraine

The objective of acute migraine therapy is to restore the patient's ability to function by rapidly and consistently alleviating pain and associated symptoms.<sup>28</sup> Acute treatment can be subdivided into non-specific agents such as aspirin, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), and migraine-specific treatments (triptans).

Previously a 'stepped approach' was used in the management of acute migraine, whereby monotherapy with simple analgesics was used first-line and failure during three separate migraine episodes would be the criterion for progressing to the next step. Current thinking is to use a stratified care, whereby treatment is based on the patient's level of disability and symptoms. Mild symptoms might be treated with simple analgesics, while more severe symptoms might be treated with a triptan. Evidence suggests that combination treatment with a triptan and either paracetamol or an NSAID is more effective compared to monotherapy. A triptan and NSAID is a more effective combination than a triptan and paracetamol.<sup>3</sup>

The following approach is recommended:<sup>3</sup>

- Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol. For young people aged 12 to 17 years, consider a nasal triptan in preference to an oral triptan.<sup>17</sup>
- If monotherapy is preferred, offer an oral triptan, or NSAID, or aspirin (900mg every 4 to 6 hours when necessary up to a maximum of 4g daily), or paracetamol 4g daily.
- Consider adding an anti-emetic (such as metoclopramide, domperidone or prochlorperazine) even in the absence of nausea and vomiting – *however, see MHRA Warnings with metoclopramide and domperidone (page 6).*
- Do **not** offer ergots or opioids for acute treatment of migraine.<sup>17</sup>

## Analgesics

Ibuprofen and naproxen have a low risk of contributing to MOH and therefore may be considered as first-line options (taking into account the person's risk factors for NSAIDs).<sup>3</sup>

Analgesics are best taken in soluble or orodispersible formulations<sup>29,30</sup> and early in the attack when absorption may be least inhibited by gastric stasis.

In all cases, use a non-delayed release formulation of analgesic +/- domperidone or metoclopramide to promote gastric emptying.

Diclofenac suppositories 100mg (up to 200mg in 24 hours) are an option for pain if vomiting is preventing absorption.<sup>3</sup>

A full discussion on the contraindications, adverse effects, monitoring issues and interactions of NSAIDs is beyond the scope of this guidance. However, in brief, consider the following prescribing issues for NSAIDs:

- Patient co-morbidity (including cardiovascular risk assessment).
- NSAIDs commonly cause GI adverse effects. Do not give without gastroprotection if there is a history of peptic ulceration.
- NSAIDs can worsen asthma, hypertension, renal

impairment, and heart failure.

### Doses of NSAIDs used in acute migraine

- Ibuprofen 400mg to 600mg every 4 to 6 hours; no more than 4 doses in 24 hours.<sup>3</sup>
- Tolfenamic acid rapid release 200mg, repeated once if necessary after 1 to 2 hours.<sup>3</sup>
- Naproxen 750mg to 825mg with a further 250mg up to twice in 24 hours.<sup>3</sup>
- Diclofenac-potassium 50mg to 100mg, repeated up to a total of 200mg in 24 hours.<sup>3,126-128</sup>

**NB: Use should be restricted to no more than 2 days per week to avoid MOH.**

### Are there any analgesics that are *less* suitable in the management of acute migraine?

#### Paracetamol

In adults, paracetamol *alone* is often ineffective.<sup>31</sup>

#### Opioid analgesics

These should be avoided for the following reasons:<sup>16</sup>

- They have no proven pain relieving effect in migraine.
- They can cause nausea and vomiting which can exacerbate existing problems.
- They reduce gastric motility, which can decrease the uptake of other drugs.
- They have an addictive potential and are implicated in medication overuse headache.<sup>32-34</sup>

#### Analgesics in children:

Simple analgesics or NSAIDs often are quite effective in children and adolescents with mild to moderate migraine.<sup>9,12</sup> Ibuprofen or paracetamol have been shown to be effective in treatment of childhood migraine.<sup>35,36</sup>

### Prescribing notes — Analgesics

- Start acute treatment early in the attack.
- Where possible, use soluble or orodispersible formulations.
- Do NOT use modified-release formulations.
- Consider using combination preparations; MigraMax<sup>®</sup> (aspirin 900mg and metoclopramide 10mg)<sup>37,38</sup> and Paramax<sup>®</sup> (paracetamol 500mg and metoclopramide 5mg) are available as dispersible granules. These are the only dispersible forms of metoclopramide available.
- Recommended analgesic doses for acute migraine are typically greater than standard doses to achieve rapid therapeutic levels against a background of gastric stasis. An initial approach may be to ensure that the dose taken is adequate and that analgesics are carried by the patient at all times, and taken as soon as the onset of an attack is recognised.<sup>33</sup>
- Aspirin-containing preparations should NOT be given to children under 16 years of age (association with Reye's syndrome).
- Codeine and codeine-containing preparations are particularly **UNSUITABLE** in migraine. (Note: Migravele<sup>®</sup> tablets contain codeine).



## Anti-emetics

The role of anti-emetics in acute migraine is two-fold:

1. Anti-emetics treat commonly occurring GI symptoms, such as nausea and vomiting.
2. During an acute migraine attack, gastric stasis may result in delayed or wholly suppressed absorption of drugs. Anti-emetics like metoclopramide and domperidone are able to speed up gastric emptying and should be taken as soon as possible at the beginning of the attack.<sup>39-41</sup>

For nausea and vomiting in adults:

- Metoclopramide 10mg up to three times a day, or
- Prochlorperazine buccal tablet 3 to 6mg,<sup>42</sup> dissolved between gum and cheek up to twice in 24 hours, or
- Domperidone 10mg, up to four times a day.

Buccal prochlorperazine tablets can be useful if vomiting is preventing drug absorption.<sup>3</sup>



### MHRA warnings with metoclopramide and domperidone

#### Metoclopramide

- Metoclopramide can cause acute dystonic reactions, especially in patients under 20 years of age.
- It can be prescribed for short-term use (**up to 5 days**) for the symptomatic treatment of nausea and vomiting associated with acute migraine.
- See [MHRA Drug Safety Update August 2013](#) for further information.

#### Domperidone

- Domperidone is associated with a small increased risk of serious cardiovascular side-effects.
- Treatment is not recommended for longer than **one week** (maximum of 10mg three times a day).
- Domperidone is now contraindicated in those with underlying cardiac conditions and other risk factors.
- See [Drug Safety Update May 2014](#) for more information.

**Metoclopramide and domperidone should NOT be given to children.**

## Triptans

The development of the selective 5-HT<sub>1B/1D</sub> receptor agonists, or “triptans”, in the latter part of the 20<sup>th</sup> century revolutionised the treatment of migraine. Seven triptan medications are now available. Studies have shown an improvement in headache in 30 to 40% of patients within 60 minutes of administration of a triptan. This increases to 50 to 70% after two hours.<sup>43-46</sup>

### How do triptans work in migraine?

Triptans selectively stimulate 5-hydroxytryptamine (5HT<sub>1</sub>, also known as serotonin) receptors. Specifically, triptans act on the 5-HT<sub>1B</sub> and the 5-HT<sub>1D</sub> receptors; these are not necessarily responsible for starting a headache but are important in stopping one.<sup>43</sup>

### What are the contraindications to the use of triptans?

Triptans should not be given to people with:<sup>47</sup>

- Uncontrolled or severe hypertension
- Coronary heart disease or cerebrovascular disease
- Coronary vasospasm.

NB: triptans are not licensed for people aged over 65 years, although they are used in practice. Especially if they have been previously used and found to be effective, there is no reason to stop prescribing them.<sup>3</sup>

### At what stage of an acute migraine should a triptan be taken?

It is important that a triptan is taken once the headache has started but the pain is still mild.<sup>48</sup>

Unlike analgesics, triptans should not be taken too early. Triptans are less effective if taken during the aura phase of a migraine.<sup>49,50</sup>

### Common problems encountered using triptans:

#### 1. The initial dose of triptan is ineffective

If the first dose of triptan is ineffective, a further dose is unlikely to be effective and should not be taken during that attack. The exception to this is zolmitriptan, where an additional dose can be tried after two hours even if the first was unsuccessful.<sup>3</sup>

Non-response has been attributed to a variety of factors, including:<sup>51</sup>

- Low and inconsistent absorption
- Use of the triptan too early or too late in the attack.
- Inadequate dose
- Individual biological variability.

Evidence from trials confirms the common clinical observation that patients with a poor response to one triptan can benefit from another in subsequent attacks.<sup>52</sup> Ideally, each triptan should be tried in three attacks before it is rejected for lack of efficacy.<sup>18</sup>

Not only a different triptan but also dosage and a different route of administration should be considered.<sup>18</sup>

#### 2. The patient experiences relief of their headache but has unacceptable side-effects

Try using a lower dose of triptan e.g. rizatriptan 5mg or eletriptan 20mg [unlicensed]. Alternatively, use a triptan known to have fewer adverse effects. Naratriptan, frovatriptan and almotriptan are reputed to be the triptans with highest tolerability.<sup>44,53</sup>

#### 3. The chosen triptan initially relieves pain but the headache returns within 24 hours

This is known as “headache recurrence” or “headache relapse” and is a significant problem with all triptans. Headache recurrence is defined as a recurring or worsening of headache after pain-free or mild pain has been achieved with a drug within 24 hours.<sup>54,55</sup> Up to 40% of people taking an oral triptan experience headache recurrence.<sup>56,57</sup>

### What can be done about headache recurrence?

There is good evidence that a second dose of triptan is effective for headache recurrence.<sup>18</sup>

In most people, it is the sensible option, with a minimum of two hours between doses and within the total daily dose limitation for the particular triptan. But in some people, relapse appears to be a manifestation of rebound, and repeated dosing can give rise to repeated rebound over several days.<sup>58</sup> There is no clear consensus on the best management of these people, but

**naproxen 500mg or tolfenamic acid 200mg**<sup>59</sup> may be preferable for the first or second relapse.

For patients who consistently relapse, there is some evidence that naratriptan,<sup>53</sup> eletriptan<sup>60</sup> and frovatriptan<sup>53</sup> are associated with relatively low relapse rates.<sup>9</sup>

#### 4. More than two triptans are ineffective

Consistent lack of response to triptans is rare, as 79-89% of patients respond in at least one of three treated attacks.<sup>44</sup> Therefore:

- Review the diagnosis.
- Review compliance and determine whether drugs are being used correctly.
- If the diagnosis is correct and drugs are being used correctly but are not effective, try combining a triptan with standard analgesia with or without an anti-emetic, and if migraines are very frequent consider using prophylactic drug treatment.

#### 5. The person is nauseated or cannot swallow tablets

Try:

- Sumatriptan injection, or
- Sumatriptan nasal spray, or
- Zolmitriptan nasal spray, or
- Rizatriptan dissolvable wafer, or
- Zolmitriptan orodispersible tablets.

#### 6. The person is vomiting

Sumatriptan injection or zolmitriptan nasal spray can be considered. (Note: intranasal sumatriptan is not recommended if there is vomiting, as it is absorbed through the oral route. Intranasal zolmitriptan may be a better option as about 30% of the drug is absorbed through the nasal mucosa).<sup>3</sup>

#### 7. The chosen triptan does not work for every migraine attack

This is to be expected. Efficacy in only two of three attacks is regarded as good.<sup>9</sup>

#### Are there important differences between the triptans?

The triptans are a very homogeneous group of drugs. Meta-analyses comparing triptans have shown that all oral triptans are generally effective and well tolerated.<sup>33,44,61</sup> In addition, there is no evidence that any particular triptan is safer to use than another.<sup>3</sup>

However, there are small but clinically significant differences which might suggest the use of one agent over another in individual patients:

- **Comparative efficacy** – there is a high degree of variability in individual response to specific triptans. If a particular triptan is not effective in an individual, another can be tried.
- **Onset of action** – sumatriptan subcutaneous has the fastest onset of action (about 10 minutes) and naratriptan the slowest (up to 4 hours).<sup>62,63</sup>
- **Consistency** – rizatriptan 10mg, eletriptan 80mg and almotriptan 12.5mg have the highest likelihood of consistent success.<sup>44</sup>
- **Adverse effects** – if a particular triptan is poorly tolerated it can be switched; in particular, almotriptan, naratriptan or frovatriptan may cause fewer adverse effects.
- **Availability of different formulations.**
- **Cost.**

As well as these differences, patient characteristics and preferences vary, and individual responses to a triptan cannot be predicted. Thus, it is possible to say that differences between triptans are small, but they may be important for some patients. Hence, treatment should be individualised for each person.

#### What is the first-line choice of triptan?

The Northern Ireland Formulary recommends sumatriptan 50mg as the first-line choice. The 100mg dose has more adverse effects and is only marginally more effective.

If the first dose of a triptan fails to help, alternative medication should be considered. If treatment with sumatriptan proves to be inadequate, assess compliance and consider:

- Increasing to a dose of sumatriptan 100mg (if not used already)
- Prescribing a second-line triptan (almotriptan is the second choice triptan in the NI Formulary)
- Subcutaneous sumatriptan in severe migraine or where vomiting precludes oral treatment or where oral triptans have been ineffective.

#### What are the adverse effects associated with the triptans?

The adverse effects associated with the triptans can be divided into two main groups:

1. Common, mild, but annoying effects.
2. Rare but potentially serious adverse effects.

##### 1. Mild adverse effects

The so called “triptan sensations” include warm/hot sensations, tightness, tingling, flushing and feelings of heaviness or pressure in areas such as the face, limbs, and occasionally the chest. Such sensations can mimic angina and cause considerable alarm. However, when patients are forewarned about these sensations, they cause less distress should they occur.<sup>3,33,64,65</sup> It is advised that the triptan is discontinued if there are particularly intense sensations or chest pain, as this could be due to coronary vasoconstriction.<sup>3</sup> Other adverse effects are generally mild and self-limiting for all triptans. They include nausea, dizziness, somnolence, dry mouth and drowsiness.<sup>3</sup>

##### 2. Potentially serious effects

The main concern with all triptans is their potential for coronary vasoconstriction. There are theoretical concerns that this may increase the likelihood of myocardial infarction, but extensive experience with these drugs, especially sumatriptan, have shown this is very rare.<sup>33</sup> A long-term, post-marketing review concluded that triptans were very safe as long as they were not used in people with cardiovascular disease or major risk factors for cardiovascular disease.<sup>66</sup>

#### Which type of triptan formulation is most popular?

Although oral absorption of drugs is delayed during migraine attacks, most patients prefer oral formulations; they account for more than 90% of all triptan prescriptions.<sup>52</sup>

#### Can triptans be used in children?

With the exception of sumatriptan 10mg nasal spray, which can be used from the age of 12 years, none of the

triptans are licensed for use in patients under the age of 18 years.<sup>67-78</sup> However, BNF-C provides dosing information for sumatriptan (by mouth, subcutaneous injection and intranasally) and zolmitriptan (by mouth and intranasally) in children. See BNF-C for full details.

### Which drugs are known to interact with triptans?

The following clinically significant interactions are recognised:<sup>3,67-80</sup>

- **Macrolide antibacterials and antifungal agents** – eletriptan should not be used concomitantly with clarithromycin, erythromycin, itraconazole or ketoconazole as these result in increased plasma concentrations of eletriptan.
- **SSRIs / SNRIs** – the weight of evidence suggests that the concurrent use of triptans and SSRIs is normally uneventful, but adverse reactions do occur occasionally. Caution and close monitoring are advised when two such agents are used together.
- **MAOIs** – the oral triptans are metabolised by the monoamine oxidase pathway, and therefore should not be administered with MAOIs.
- **Propranolol** – when rizatriptan is given to patients taking propranolol, the maximum rizatriptan dose should be 5mg (or alternatively use another triptan).
- **Selegiline** – contraindicated due to risk of serotonin syndrome.
- **Linezolid** – contraindicated with triptans.
- **Ergotamine** – ergotamine should not be taken concomitantly with a triptan.
- **St John's wort** – increased serotonergic effects when triptans are given with St John's wort – avoid concomitant use

*\*See BNF for full details of drug interactions with triptans\**

### Availability of over-the-counter sumatriptan

Sumatriptan 50mg tablets can be obtained without prescription at community pharmacies (available as a generic or Imigran® Recovery) for designated patients aged 18 to 65 years. The obvious concern with triptans is the likelihood of use by those with coronary risk factors and the possibility that this may lead to significant numbers of coronary events. For this reason, pharmacists are required to give advice at point-of-sale. In addition, advice to patients at the time of purchase is essential to ensure that sumatriptan is administered appropriately. Otherwise, it is likely that OTC sumatriptan will be used for headaches that are not migrainous, or too early or too late for best effect. See Panel ONE for guidance on supply of sumatriptan without prescription.

### What is status migrainosus?

Status migrainosus is a debilitating migraine attack lasting for more than 72 hours.<sup>3</sup> It is a common reason for visits to the emergency department.<sup>81</sup> Such attacks are often more severe and refractory to home rescue medication, making them more challenging to treat.<sup>81</sup>

Status migrainosus is usually treated aggressively in secondary care, e.g. with greater occipital nerve (GON) block or a reducing dose of corticosteroids, to prevent the person developing chronic migraine.

Following discharge, modifications in the patient's rescue plan need to be made to avoid such visits in the future.<sup>81</sup> NSAIDs are preferable to specific anti-migraine drugs in status migrainosus.<sup>18</sup> In primary care, a high reducing

dose of naproxen is a useful first-line strategy: 500mg three times a day for 3 days and then 250mg three times a day for 3 days.



### Prescribing notes: Triptans

- Do not prescribe triptans with other migraine drugs such as ergotamine.<sup>82</sup>
- Recommend that a triptan is taken when the headache starts rather than at the time of the aura.<sup>82</sup>
- Orodispersible tablets and wafers may be useful if swallowing is a problem.<sup>3</sup>
- Nasal sprays give rapid relief.<sup>3</sup>
- Subcutaneous injection (sumatriptan) gives the most rapid relief.<sup>3</sup>
- Triptans are contraindicated in patients with ischaemic heart disease, uncontrolled hypertension, or risk factors for coronary heart disease and cerebrovascular disease.<sup>82</sup>
- Reduce the dose of rizatriptan to 5mg if the person is taking propranolol, as plasma levels of rizatriptan are almost doubled by propranolol.<sup>9</sup>
- Patients should be asked about any OTC triptan use during GP consultations.



### Panel ONE: Royal Pharmaceutical Society of Great Britain Guidance: Sumatriptan OTC.<sup>83</sup>

OTC sumatriptan is indicated for the acute treatment of migraine attacks with or without aura in adults aged 18 to 65 years. (Patients over the age of 50 who are experiencing their first ever migraine attack need to seek medical advice).

- It should only be used where there is a clear diagnosis of migraine. Patients should have an established pattern of migraine attacks.
- It should not be used prophylactically.

Advice from pharmacists to anyone purchasing sumatriptan should include:

- Take a single tablet as soon as possible after the onset of a migraine headache.
- If the first dose of sumatriptan is ineffective, a further dose is unlikely to be effective and should not be taken.
- However, if symptoms return after initial relief, a second dose can be taken after two hours.
- Sumatriptan can cause drowsiness. Use caution with driving or operating machinery.
- Do not take St John's Wort preparations along with sumatriptan.

The following individuals should not be supplied with sumatriptan:

- Anyone with a history of cardiovascular disease or those at high risk of cardiovascular disease.
- Those under the age of 18 or over 65.
- Patients over the age of 50 who are experiencing their first ever migraine attack.
- Pregnant or breast-feeding women.



# Medication Overuse Headache

## What is medication overuse headache?

Medication overuse headache (MOH) is a chronic headache (occurring on more than 15 days each month) that develops or worsens with frequent use of any drug treatment for pain in people who have tension-type headache (TTH) or migraine.<sup>84</sup>

While typically it develops with drug treatment of episodic migraine or TTH, it may occur in people with migraine or TTH who take analgesics for other painful conditions,<sup>84</sup> e.g. back pain. It is rare in people who do not have migraine or TTH.<sup>84</sup>

## How common is MOH?

MOH is a common complication of migraine and TTH. It is estimated that 1 in 50 adults suffer from MOH.<sup>85</sup> It is five times more common in women than in men.<sup>18</sup>

## What are the features of MOH?

MOH is often at its worst on awakening in the morning and increases after physical exertion. Associated nausea and vomiting are rarely pronounced.<sup>18</sup>

## What causes MOH?

The exact mechanism of medication overuse headache is unknown, but it is generally believed to involve a disturbance of central pain systems. Frequency of dosing is important: low daily dosing carries a greater risk than larger intermittent dosing.<sup>85</sup>

## Does the risk of developing MOH differ between drug treatment?

Yes, the risk of developing MOH varies with different symptomatic treatments. The risk is considered to be:

- Highest with opioids and triptans
- Intermediate with paracetamol and aspirin
- Lowest with NSAIDs.<sup>86</sup>

Note: caffeine can also increase the risk of MOH if taken for > 15 days per month.

## When should MOH be suspected?

It is recommended to be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for 3 months or more:

- Triptans, opioids, ergots or combination analgesic medications (usually simple analgesics plus opioids or caffeine) on 10 days per month or more, or
- Paracetamol, aspirin or an NSAID, either alone or in any combination, on 15 days per month or more.<sup>17</sup>

## How should MOH be managed?

A thorough explanation should be provided to the person, including why they have developed MOH and what to expect during and after withdrawal.<sup>84</sup>

The only effective treatment is to stop the drugs. People should be advised to stop taking all overused acute headache medications for at least one month and to stop abruptly rather than gradually.<sup>17</sup>

## What to expect when withdrawing overused medication

- Headache symptoms are likely to get worse before they improve. Withdrawal headache typically lasts

between 2 and 10 days.

- There may be associated withdrawal symptoms such as nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety and nervousness. These typically settle within 7 days but may take up to 3 weeks to fully resolve.<sup>84</sup>

## Can adjunctive therapy help with withdrawal symptoms?

Providing that a NSAID is not the overused medication, the British Association for the Study of Headache (BASH) recommend that withdrawal headache can be managed with naproxen. This should be taken regularly, whether symptoms are present or not, to help break the habit of responding to pain with medication.<sup>18</sup> BASH suggests that naproxen can be taken for 3 to 4 weeks and then stopped abruptly or as a tapering dose over 6 weeks.<sup>18</sup> An anti-emetic can be considered for people who experience vomiting during withdrawal.<sup>87</sup>

## What follow-up is required?

The patient should be reviewed after 4 to 8 weeks of stopping the overused medication to:

- Review the diagnosis of MOH.
- Assess the need for further management of any underlying headache disorder.<sup>87</sup>

## How should patients be managed moving forward?

Overused medications may be re-introduced, with explicit restrictions on their use.<sup>84</sup>

Prophylaxis for primary headache disorders should be considered. The choice of prophylactic treatment will depend on the underlying primary headache disorder<sup>84</sup> – see later section on *Prophylaxis of migraine*.

## When should a person be referred to secondary care?

Most people with MOH can be managed in primary care.<sup>84</sup> However, consider referral for people with MOH who:

- Have MOH caused by an opioid (gradual withdrawal may be necessary).
- Have significant co-existing conditions, including:
  - Psychological problems (such as anxiety or depression)
  - Physical problems, e.g. angina or diabetes
  - Pregnancy
  - Painful conditions requiring continued symptomatic treatment.
- Have had previous unsuccessful attempts at withdrawal of overused medication.
- Are poorly motivated to stop symptomatic treatments.<sup>84</sup>



### Patient information

Patient information on MOH is available on the Patient.info website:

<https://patient.info/health/medication-induced-medication-overuse-headache>



# Prophylaxis of Migraine

To minimise the impact of the illness on their lives, people with frequent, severe or disabling migraine headaches may benefit from taking a drug to *prevent* attacks. On average, two thirds of patients will have a 50% reduction in headache frequency with most preventative drugs.<sup>88</sup> Therefore, even when prophylaxis of migraine is successful, the patient will, in most cases, still suffer some attacks,<sup>89</sup> so, when indicated, prophylactic therapy is used **in addition** to acute therapy, not in place of it.<sup>18</sup>

## When is it appropriate to consider introducing prophylaxis?

Preventive treatment may be considered if:

- Migraine attacks are causing frequent disability (e.g. two or more disabling attacks per month).
- The person is at risk of medication overuse headache (MOH) due to frequent use of acute drugs. (NB: rule out MOH before starting preventive treatment. If MOH is suspected, then the appropriate management is drug withdrawal rather than prevention.)
- Standard analgesia and triptans are contraindicated or ineffective.
- Migraine is of an uncommon type, e.g. hemiplegic migraine, or migraine with prolonged aura. Consider referral or seek expert advice.<sup>3</sup>

## How should prophylaxis be introduced, and for how long should it be continued?

Preventive drugs take time to work, and it is important that the person continues to take them during the first few weeks so their effectiveness can be assessed (provided there are no intolerable adverse effects).<sup>3</sup> Each preventative drug should be started at a low dose and then increased to an acceptable maximum. The person should allow 4 to 6 weeks at the maximum tolerated dose before assessing effect.

If the drug is effective, it should be used for 4 to 6 months.<sup>3,90</sup>

## How is a prophylactic drug judged to be effective?

Migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by at least 50% within three months. For therapy evaluation, a migraine diary is mandatory.<sup>9</sup>

## What agents are recommended for migraine prophylaxis?

According to NICE, the benefits and risks of prophylactic treatment for migraine should be discussed with the person, taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life.<sup>17</sup>

The evidence-base for efficacy is good for beta-blockers and topiramate, adequate for amitriptyline, but poor for other prophylactic drugs.<sup>18</sup>

### First-line choices

First-line agents for migraine prophylaxis are **topiramate** or **propranolol**.<sup>17</sup>

Amitriptyline may be considered as an alternative (note: will not be suitable for all patient groups).<sup>192</sup>

Atenolol may be better tolerated than propranolol in some

cases and may be considered as an alternative to propranolol.<sup>16</sup>



### Beta blockers in people with asthma and COPD

- Propranolol is a non-cardioselective beta-blocker and is contraindicated in people with asthma and chronic obstructive pulmonary disease (COPD).<sup>3,18</sup>
- Atenolol is a cardioselective beta-blocker. It should usually also be avoided in people with asthma and COPD. However, when there is no alternative, it may be given with caution and under specialist supervision. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.<sup>47</sup>



### Topiramate in women and girls of childbearing potential

- Topiramate is associated with a risk of foetal malformations and can impair the effectiveness of hormonal contraceptives (topiramate is an enzyme-inducing drug).
- Women and girls of childbearing potential should therefore be offered suitable contraception if needed before prescribing.<sup>17</sup>
- Preferred methods of contraception include:
  - progestogen-only injection or
  - levonorgestrel-releasing intrauterine system or
  - copper intrauterine system.Alternatively, a combined oral contraceptive with a minimum 50 micrograms (30 micrograms + 20 micrograms) ethinyloestradiol monophasic pill during treatment and for a further 28 days with a continuous or tricycling regimen plus a pill-free interval of 4 days can be considered.<sup>91</sup>

## Doses used in migraine prophylaxis

### Topiramate<sup>3</sup>

- Initially 25mg at night for 1 week, then increase in steps of 25mg at weekly intervals.
- The usual dosage is 50mg to 100mg daily in 2 divided doses (maximum daily dosage 200mg).

### Propranolol<sup>3</sup>

- Initially 80mg daily (either 40mg twice a day, or 80mg modified-release once a day taken in the morning or the evening).
- The dose may be increased to 160mg daily (maximum daily dose 240mg, either in divided doses or as a single modified-release dose).

### Atenolol<sup>18</sup>

- Unlicensed for migraine prophylaxis.
- Usual dosage range is 25mg to 100mg twice daily.

### Amitriptyline<sup>18</sup>

- Unlicensed for migraine prophylaxis.
- Usual dosage range is 10mg to 150mg daily, taken either at bedtime or 1 to 2 hours before bedtime.

### What monitoring is required for topiramate?

- Topiramate lowers serum bicarbonate levels, with the potential to cause metabolic acidosis. Monitor serum bicarbonate levels after 2 weeks of therapy and every 3 months in people with conditions which put them at increased risk of metabolic acidosis, e.g. renal disease, severe respiratory disorders, diarrhoea, surgery, ketogenic diet, certain drugs.<sup>3</sup>
- Caution in renal impairment: reduce the starting and maintenance dose by half. Increase the length of the titration intervals, as a longer time to reach steady-state at each dose may be required.<sup>3</sup>
- Caution in moderate to severe hepatic impairment as clearance of topiramate is decreased.<sup>3</sup>

### What are important adverse effects with topiramate?

- **Gastrointestinal** – decreased appetite, taste disturbance, nausea, vomiting, diarrhoea, constipation and weight loss.
- **Psychiatric** – slowness of thought, depression, expressive language disorder, irritability, fatigue, somnolence and insomnia.
- **Neurological** – abnormal coordination, impaired attention, seizures, dizziness, dysarthria, hypoaesthesia, lethargy, memory impairment, paresthesia and tremor.
- **Visual disturbances** – diplopia, nystagmus, and blurred vision. Topiramate has been associated with acute myopia with secondary angle-closure glaucoma, typically occurring within one month of starting treatment. Seek specialist advice and stop topiramate as rapidly as feasible.<sup>3</sup>

### Agents used in prophylaxis but with limited / uncertain efficacy

Several drugs are in regular use for migraine prophylaxis despite limited evidence to support their use. They may be effective for some people, however due to a lack of evidence to support their use, NICE does not recommend their use.<sup>3</sup>

**Pizotifen** (an antihistamine and serotonin antagonist structurally related to the tricyclic antidepressants)<sup>47</sup> has been widely used for many years, but with little clinical trial evidence of efficacy. It is associated with unwanted adverse effects which limit its use. It should now be superseded by other agents.<sup>3,18</sup>

Despite this, over 27,000 prescription items were dispensed in NI last year at a cost of nearly £300,000.<sup>52</sup>

Other drugs, such as **coenzyme Q10** and **candesartan**, show potential benefit from RCTs, but more evidence is needed before recommendations can be made.<sup>18</sup>

#### Riboflavin

Riboflavin (400mg once a day) may be effective in reducing migraine frequency and intensity for some people.<sup>17</sup> This can be purchased over the counter.

### People already established on prophylaxis treatment

For people who are already having treatment with another form of prophylaxis and whose migraine is well controlled, continue the current treatment as required.<sup>17</sup>

### What if migraine prophylaxis fails?

- Review the diagnosis.
- Review compliance with treatment (often poor,

especially with multiple daily doses).

- Review other medication, especially for medication overuse.
  - Consider using a combination of agents.
- If prophylaxis still fails to have measurable benefit, discontinue it.<sup>18</sup>

### When and how should migraine prophylaxis drugs be stopped?

If prophylactic drugs are successful in reducing the frequency of migraines, drugs should be continued for at least 4 to 6 months.<sup>3,92</sup> Review the need for preventive treatment at 6 months and consider reducing or stopping treatment.<sup>3</sup> Migraine is cyclical, with periods of acute exacerbation followed by 'benign' periods, therefore prolonged administration of a preventive drug is usually not appropriate.<sup>3</sup>

### Migraine prophylaxis in children

Initiation of preventive treatment in primary care is not generally recommended for children. Specialist advice should be sought.<sup>3</sup>

There is little formal evidence of efficacy of prophylactic drugs in children. For the few children who need prophylaxis, paediatric headache specialists employ the full range of treatments used in adults, often with benefit. **Beta-blockers** are often viewed as one of the first-line agents. Propranolol has been found to be effective for the prevention of migraine in children and adolescents.<sup>13,93</sup> However, the results obtained are inconsistent.<sup>94-96</sup> Timolol, atenolol, metoprolol and nadolol may be alternative choices.<sup>12</sup>

**Antidepressants** may also be useful. Amitriptyline<sup>124,125</sup> and other tricyclics are widely employed, and selection is generally a matter of personal preference and experience. There are no comparative data. Topiramate is effective in paediatric migraine prophylaxis,<sup>97,98</sup> but is not licensed under the age of 16.<sup>99</sup>

#### Summary – Migraine Prophylaxis

- It may take 1 to 3 months for the full effect of the preventative drug to be seen.
- Propranolol and topiramate are the first-line choices of prophylactic migraine drug, and are licensed for this indication.
- Evidence for other agents used is mixed, and they often have intolerable side-effects.
- On average, most patients will have a 50% reduction in headache frequency with most preventative drugs.
- If the drug is effective it should be used for 4 to 6 months then slowly tapered off over 2 to 3 weeks.

# Menstrual Migraine

## What is menstrual migraine?

A decrease in oestrogen levels can trigger migraine in some women.<sup>100</sup>

**Menstrually-related migraine** is diagnosed when migraine without aura regularly occurs between 2 days before and 3 days after the start of menstruation but there may be additional attacks at other times of the cycle.<sup>3</sup> About 60% of women with migraine have menstrually-related migraine.<sup>3</sup>

**Pure menstrual migraine** is diagnosed when migraine attacks occur only with menstruation.<sup>3</sup> Less than 10% of women with migraine have pure menstrual migraine.

Correct diagnosis of true menstrual migraine is essential for successful *preventive* management. The diagnosis is clinical and confirmed by diary card evidence over three months.<sup>3,18</sup>

## How should menstrual migraine be managed?

*Acute* treatment of menstrual attacks of migraine is the same as for non-menstrual attacks, i.e. usually involving a combination of a triptan plus NSAID/paracetamol +/- an anti-emetic.<sup>18,101</sup>

When acute therapy is insufficient to reduce disability from menstrual migraine, *prophylactic* therapy may be considered.<sup>101</sup> Hormonal or non-hormonal migraine prevention can be tried.<sup>3</sup> Choice depends on the individual woman's type of migraine, regularity of menstruation, other menstrual problems and need for contraception.<sup>101</sup>

It is important that preventive drugs are tried for at least three cycles, at the maximum tolerated dose, whilst effectiveness is established.<sup>3</sup>

## Non-hormonal prophylaxis treatment

### NSAID

Start the NSAID at the onset of menstruation and continue until the last day of bleeding. This option is particularly valuable in migraine occurring with menorrhagia and/or dysmenorrhoea.

Note: mefenamic acid is no longer an NI Formulary choice due to concerns that it is more likely to cause seizures in overdose than other NSAIDs (mefenamic acid has a low therapeutic window, which increases the risk of accidental overdose).<sup>102,103</sup> Naproxen taken at a dose of 500mg twice daily may be used instead.<sup>101</sup>

### Triptan

Where migraine is predictable, consider treatment with a triptan:

- Frovatriptan (2.5mg twice a day) or
- Zolmitriptan (2.5mg twice or three times a day) starting 2 days before the expected onset of migraine [not licensed].<sup>3,16,211</sup>

## Hormonal treatment

### Hormonal contraceptives

Hormonal contraceptives are useful if contraception is desired. **Do not routinely offer combined hormonal contraceptives (CHC) to women who have migraine with aura.**<sup>17</sup> Depending on how severe the aura is, some

specialists will recommend contraception if the patient is a non-smoker and rarely experiences aura.

The following hormonal options are available:

- A CHC continuously for 9 weeks rather than 3 (tri-cycling), followed by the usual 7-day pill-free interval (results in fewer bleeds per year)<sup>3,7</sup> or continuous use of a CHC until breakthrough bleeding occurs, followed by a 4- to 7-day pill-free interval may be adopted.<sup>3</sup>
- Oral desogestrel (the only progesterone pill to inhibit ovulation), sub-dermally implanted etonogestrel (Nexplanon®) or injectable depot progestogens.<sup>3</sup>

### Oestrogen supplements

Oestrogen supplements are an option, but are not licensed for this indication. They are rarely needed as women can reduce the number of periods they have by long-cycle or continuous CHC, or by reducing the hormone-free interval.

## What are cautions to the use of the COC in women with migraine?

Headache is a common side-effect of COCs and many women report onset of migraine after starting them. Others report improvement of pre-existing migraine.<sup>104</sup> There is concern that migraine and COCs are both independent risk factors for stroke in young women.

COCs are therefore contraindicated in:<sup>3,18,105-108</sup>

- All women with migraine with aura (any age).
- Migraine without aura with more than one additional risk factor for stroke, including age over 35.
- Increasingly frequent attacks of migraine without aura (may be prodromal of a cerebrovascular event).

NB – the risk calculator QRISK® has been updated for 2017. QRISK®3 contains additional risk factors for heart disease and stroke, including migraine.<sup>109</sup>

If acute migraine with aura develops whilst taking a COC, the COC should be stopped immediately and advice on alternative contraception given.

## What should be recommended if a woman on a COC experiences migraine without aura during the pill-free interval?

Consider:<sup>3</sup>

- Alternative contraception methods if the COC is now contraindicated.
- Changing to a COC with a lower dose of the same progestogen.
- Changing to a pill with the lowest available dose of a different progestogen.
- Tri-cycling: take the pill continuously for three packs (nine weeks) followed by a 7-day pill-free interval, so that the number of menstrual bleeds are reduced.



# Migraine in Pregnancy and Lactation

In general, women can be reassured that migraine does not have any adverse effects on the outcome of pregnancy in otherwise healthy women.<sup>110-112</sup>

If headaches present for the first time during pregnancy or postpartum, a diagnostic evaluation should be carried out and the possibility that the headache is related to a complication of pregnancy considered; severe preeclampsia / eclampsia always needs to be excluded in women over 20 weeks of gestation.<sup>113</sup>

## Does pregnancy alter the pattern of migraine?

Pre-existing migraine usually improves during pregnancy: studies suggest that around 60 to 70% of women with migraine experience improvement in migraine during pregnancy; in around 20% attacks disappear completely. If migraine has not improved by the end of the first trimester it is likely to continue throughout pregnancy and postpartum.<sup>114</sup> Women with pre-existing migraine without aura generally report improvement or cessation of migraine during pregnancy. In contrast, women who have pre-existing migraine with aura are more likely to continue to have attacks during pregnancy.<sup>3,19</sup>

## How should an acute migraine attack in pregnancy or breastfeeding be managed?

Drug treatment should be limited in pregnancy and breastfeeding. Non-pharmacological measures should be adopted first: identification of avoidance of triggers, relaxation techniques, sufficient sleep. Medication may be required for headaches that are severe and associated with nausea and vomiting.<sup>115</sup>

If treatment is considered essential, the lowest effective dose should be prescribed for the shortest period of time.<sup>3</sup> It is important that adequate fluid is given to prevent dehydration.<sup>195</sup>

## Pregnancy

Where medication is required for acute attacks, paracetamol is the drug of choice throughout pregnancy.<sup>17</sup> A triptan or a NSAID may be considered after a full discussion with the woman about the potential risks and benefits associated with the use of each medication during pregnancy.<sup>17</sup>

### Simple analgesics

- Paracetamol is the analgesic of choice in pregnancy.<sup>3</sup>
- If a NSAID is needed, ibuprofen is the preferred NSAID in pregnancy.<sup>3</sup>
- NSAIDs should be avoided in the third trimester.<sup>3</sup> There is some concern also in the first trimester, but information is limited.<sup>115</sup>
- Aspirin should be avoided early in pregnancy, in women attempting to conceive and in the third trimester.<sup>3</sup>

### Triptans

- Sumatriptan is the preferred triptan in pregnancy.<sup>115</sup>
- Meta-analysis of the available data suggests that there is currently no evidence of an increased risk for major malformation following in utero exposure to triptans. However, as the majority of data relate to use of sumatriptan, evidence for other, less frequently used triptans is lacking, and until further data become

available the possibility of an increased risk cannot be excluded.<sup>195</sup>

### Anti-emetics

If nausea and vomiting are problematic, consider prescribing an anti-emetic [unlicensed]. Cyclizine and promethazine are the anti-emetics of choice when pregnant.<sup>3,115</sup>

## Lactation

Where medication is required for acute attacks, paracetamol is the drug of choice in breastfeeding.<sup>3</sup> Ibuprofen may also be considered.<sup>116</sup> Aspirin should not be used when breastfeeding.<sup>3</sup>

If simple analgesics are insufficient to treat symptoms, sumatriptan is the triptan of choice. Although there is limited data on the safety of triptans in breastfeeding, adverse effects in breastfed infants would not be expected, especially given their short-term use.<sup>116</sup>

Cyclizine, promethazine metoclopramide and prochlorperazine are all probably safe to use short-term when breastfeeding.<sup>3,116</sup>

## Can migraine prophylaxis be used during pregnancy or breastfeeding?

The frequency and severity of migraine attacks decrease in the second and third trimesters of pregnancy for the majority of women (note: it can worsen in the first trimester, so women should be advised that this should improve in the second and third trimesters).

Drugs for the prevention of migraine are not recommended in pregnancy or breastfeeding. If preventive treatment is needed, this should be discussed with a specialist.<sup>3</sup>



### Prescribing notes – Pregnancy and Lactation

- NSAIDs should be avoided in the third trimester because of the risk of premature closure of the ductus arteriosus.<sup>3</sup>
- Aspirin should be avoided early in pregnancy, in women attempting to conceive, and in the third trimester.
- Prescribe the lowest effective dose for the shortest time.<sup>3</sup>
- Sumatriptan is the preferred triptan in pregnancy.<sup>3</sup>
- Prophylactic medication should not be routinely used.

# Migraine, HRT and the Menopause

## Should a woman with migraine be prescribed HRT?

HRT is not specifically contraindicated in women with migraine. There is no evidence that the risk of stroke is affected by the use of HRT in women with migraine, with or without aura.<sup>105</sup>

However, migraine itself is now incorporated into the risk calculator QRISK<sup>®</sup>3 <https://qrisk.org/three/>.

The menopause itself commonly exacerbates migraine. Migraine symptoms can be relieved with HRT. In practice, a number of women on HRT find their migraine becomes worse, although this is often no more than a problem of formulation or dosage.<sup>18</sup>

The following should be considered:

- Percutaneous or transdermal oestrogens are less likely to have a detrimental effect on migraine than oral formulations.<sup>117,118</sup> This is probably the result of the more stable serum hormone levels associated with non-oral routes.<sup>119</sup>
- If migraine is associated with oestrogen withdrawal, consider using a continuous preparation instead of a cyclic preparation.<sup>120</sup>
- Migraine associated with oestrogen may respond to a change in the type of oestrogen or to a

reduction in dose.

- Migraine associated with cyclic progestogens may respond to reducing the number of days on which progestogen is given. However, it must be given for a minimum of 12 days to protect the endometrium.<sup>121</sup>

## What should be done if a woman suffers a migraine attack for the first time whilst taking HRT?

Any new-onset headache should be carefully evaluated for secondary causes, as although migraine may occasionally develop for the first time during the perimenopause, it is unusual for migraine to begin post-menopause.<sup>122</sup>

There are no data regarding risk associated with developing a first attack of migraine with aura when using HRT. There is the concern that transient ischaemic attacks (TIAs) may be misdiagnosed as aura since it is not always easy to distinguish between the two conditions.<sup>123</sup>

On a practical basis, once TIAs have been excluded, the dose and route of delivery of oestrogen replacement should be assessed to provide the lowest effective dose necessary to control menopause symptoms.<sup>7</sup>

## Migraine Resources

**Migraine in Primary Care Advisors (MPCA)**  
([www.mipca.org.uk](http://www.mipca.org.uk)) – an independent charity working through research and education to set standards for the care of headache sufferers. MPCA is a group of physicians, nurses, pharmacists, and other healthcare professionals dedicated to the improvement of headache management in primary care.

**British Association for the Study of Headache**

([www.bash.org.uk](http://www.bash.org.uk))

### Migraine Action

([www.migraine.org.uk](http://www.migraine.org.uk)) – aims to bridge the gap between the sufferer and the medical world by providing unbiased information on all aspects of migraine, its causes, diagnosis, and treatment.

### Migraine Trust

([www.migrainetrust.org](http://www.migrainetrust.org)) – seeks to empower, inform, and support those affected by migraine while educating health professionals and actively funding and disseminating research.

### Migraine Association of Ireland

(<http://www.migraine.ie/>)

### European Association of Neurological Societies

([www.eans.org](http://www.eans.org)) – an organisation that unites and supports neurologists across the whole of Europe.

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Please note that every effort has been made to ensure that the content of the COMPASS Therapeutic Notes is accurate at the time of publication. Readers are reminded that it is their responsibility to keep up-to-date with any changes in practice.

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### 1) Migraine:

- |   |   |   |   |
|---|---|---|---|
| a | Across the whole population, migraine is more common in females.            | T | F |
| b | Migraine with aura is the most commonly reported type of migraine.          | T | F |
| c | There is a family history of migraine in up to 80% of people with migraine. | T | F |
| d | Numbness and loss of vision are common features of migraine with aura.      | T | F |

### 2) Migraine management:

- |   |   |   |   |
|---|---|---|---|
| a | Combination treatment with a triptan plus either NSAID or paracetamol is considered first line treatment for migraine attacks for adults. | T | F |
| b | Analgesics, such as aspirin and ibuprofen, should be taken early in a migraine attack.  | T | F |
| c | Codeine is particularly useful in migraine management.  | T | F |
| d | Metoclopramide and domperidone are safe to use on a long-term basis.  | T | F |

### 3) Triptans:

- |   |   |   |   |
|---|---|---|---|
| a | Triptans should be taken during the aura phase of a migraine.                             | T | F |
| b | If the patient is vomiting, sumatriptan nasal spray may be useful.                        | T | F |
| c | In patients taking propranolol, the dose of rizatriptan should be reduced.                | T | F |
| d | Each triptan should be tried in three attacks before it is rejected for lack of efficacy. | T | F |

### 4) Medication overuse headache:

- |   |  |   |   |
|---|--|---|---|
| a | Is thought to occur in approximately 1 in 50 adults.   | T | F |
| b | Risk of developing medication overuse headache is thought to be highest with naproxen.   | T | F |
| c | People should be advised to gradually withdraw the analgesic(s) thought to be responsible for the medication overuse headache. | T | F |
| d | Overused medications may be re-introduced, with explicit instructions on their use.  | T | F |

### 5) Migraine prophylaxis:

- |   |  |   |   |
|---|--|---|---|
| a | On average, prophylactic agents will take 1 to 3 weeks for their full effect to be seen.                   | T | F |
| b | Beta-blockers or topiramate are considered to be first-line choices for migraine prophylaxis.              | T | F |
| c | A person on migraine prophylaxis should not require agents for acute migraine attacks.                     | T | F |
| d | Pizotifen has been used for migraine prophylaxis for many years and has a good evidence base for efficacy. | T | F |