

## MANAGEMENT OF MIGRAINE

- ✦ Migraine is a common disorder with significant impact on quality of life and work productivity; it is particularly prevalent in women.
- ✦ Many migraineurs do not attend their GP due to poor expectation of an effective treatment.
- ✦ Most migraine attacks can be managed effectively with analgesics and 5HT agonists.
- ✦ Prophylaxis should be considered for patients experiencing more than two attacks per month, or who are refractory to symptomatic treatment.

### INTRODUCTION

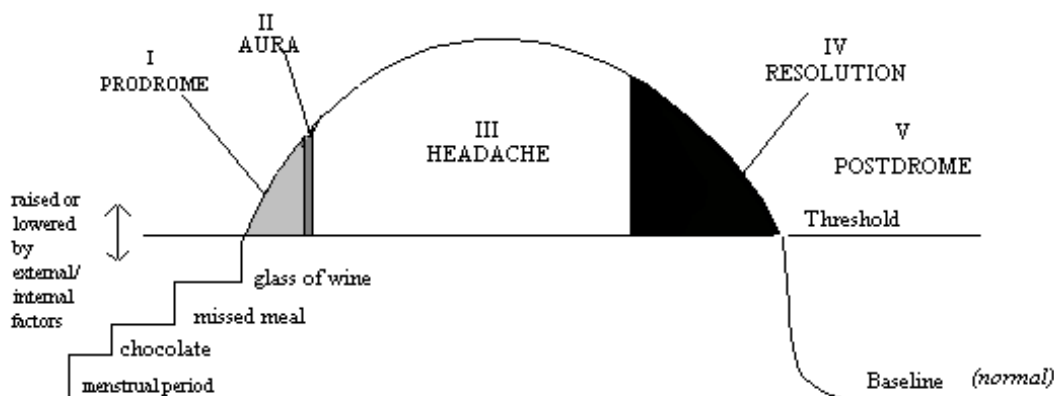
Migraine is a chronic episodic disorder characterised by recurrent headache often accompanied by nausea, vomiting and sensitivity to light and noise. It is a common debilitating condition which affects an estimated 5 - 18 percent of women and 6 percent of men, but most do not attend their GP mainly due to poor expectation of effective management.<sup>1-5</sup> In 75 percent of patients the first attack occurs before the age of twenty.<sup>6</sup> Frequency and severity of attacks are subject to marked inter-patient and intra-patient variability.<sup>6,7</sup> The median attack frequency is 1.5 per month although 10 percent of patients have weekly attacks.<sup>8</sup> The impact of migraine on quality of life and its socioeconomic burden are considerable.<sup>9,10</sup> Correct diagnosis and appropriate prescribing are essential to reduce the individual and economic impact of this disorder.<sup>11,12</sup>

### AETIOLOGY

The exact mechanism underlying migraine is unknown.<sup>6,13,14</sup> A neurovascular reaction to external or internal influences in the environment based on a genetic influence which lowers the headache threshold is postulated.<sup>1,6,15,16</sup> Recognised **trigger factors** for migraine are listed in **Table 1**. A combination of triggers is usually needed to reach the threshold for migraine (see **Fig 1**).<sup>4,17-9</sup>

**Table 1: Trigger factors for migraine** (examples in brackets)

Specific foods (cheese, chocolate, citrus fruit)	Environmental factors (weather changes)
Specific drinks (coffee, tea, alcohol, red wine)	Head and neck pains (eyes, sinuses, jaw pain)
Lack of food (dieting, missed meals)	Exercise (physical exercise, over-exertion)
Sleep irregularity (lack of / too much)	Smoking/substance misuse/excessive analgesia
Hormonal factors (menstruation, oral contraception)	Emotional factors/relaxation after stress



**Fig. 1 The Phases of Migraine** (adapted from Dr. Blau's diagram)

### DIAGNOSIS

Diagnosis is based on headache characteristics and associated symptoms.<sup>1,19-21</sup> Up to five distinct phases may be evident during an attack as illustrated in **Fig 1**.<sup>1,6,17,20</sup> Most migraineurs will experience at least 2 phases.<sup>1</sup> The two main migraine types are **common migraine** (migraine without aura: 80-90%) and **classical migraine** (migraine with aura: 10-20%), the diagnostic criteria for which are summarised in **Table 2**.<sup>5,10,22,23</sup> Rarer forms of migraine (e.g. hemiplegic migraine, basilar migraine, ophthalmoplegic migraine) are more difficult to differentially diagnose from sinister pathologies and should always be referred for specialist opinion.<sup>4</sup>

**Table 2: Diagnostic criteria for common and classical migraine**

<p><b><u>Migraine without aura (80-90%)</u></b></p> <ul style="list-style-type: none"> <li>• At least 5 attacks which fulfil the following: <ul style="list-style-type: none"> <li>♦ Attacks lasts 4-72 hrs (treated/untreated)</li> <li>♦ At least two of the following headache features <ul style="list-style-type: none"> <li>♦ unilateral location</li> <li>♦ pulsating</li> <li>♦ moderate to severe pain aggravated by movement</li> </ul> </li> </ul> </li> <li>♦ At least one of the following <ul style="list-style-type: none"> <li>♦nausea                 ♦photophobia</li> <li>♦vomiting             ♦phonophobia</li> </ul> </li> </ul>	<p><b><u>Migraine with aura (10-20%)</u></b></p> <ul style="list-style-type: none"> <li>• At least two attacks with a minimum of 3 of the following: <ul style="list-style-type: none"> <li>♦ one or more aura symptoms</li> <li>♦ aura symptoms lasting 4-60 minutes</li> <li>♦ gradual development of aura over &gt;4 mins, or several symptoms in succession</li> <li>♦ headache accompanies aura or follows it within 1 hour</li> </ul> </li> </ul>
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## TREATMENT

**Non-pharmacological** approaches (e.g. stress management, relaxation therapy), avoidance of known trigger factors and a regular lifestyle with adequate sleep, exercise, regular meals and cessation of smoking is the simplest approach.<sup>1,16,19</sup> Migraine attacks are often preceded by hypoglycaemia and so food may be helpful, providing the patient is not nauseous.<sup>17</sup> A migraine **diary card** can help identify trigger factors; this also actively involves patients in their care.<sup>6,7</sup> The majority of migraineurs will however require pharmacological intervention. Drug treatment may be **acute** (symptomatic) or **prophylactic** (preventative), depending on the frequency and severity of attacks (see **Table 3**); some patients will require both approaches.<sup>13</sup>

**Table 3: Acute and prophylactic management of migraine**

ACUTE	PROPHYLACTIC
<p><b>If up to two attacks per month:</b></p> <ul style="list-style-type: none"> <li>→ simple analgesics (e.g. paracetamol, ibuprofen)</li> <li>→ antiemetic (e.g. domperidone) given prior to analgesic</li> <li>→ if unresponsive, a 5HT<sub>1</sub> agonist</li> <li>—</li> </ul>	<p><b>If &gt;two attacks per month, consider prophylaxis:</b></p> <ul style="list-style-type: none"> <li>→ beta-blocker e.g. propranolol, atenolol</li> <li>→ pizotifen or alternative agent</li> <li>→ if one agent is not effective try another</li> <li>→ continue for at least 3 months to see effect</li> <li>→ provide breakthrough medication as for acute</li> </ul>

## ACUTE TREATMENT

Acute treatment options include **analgesics, anti-emetics, triptans** and **ergotamine**. Choice of drug should be tailored to the individual. Patients should be advised to take medication early in the symptom experience and to carry their medication with them at all times.<sup>4,10</sup> Symptomatic treatment should be used for 2-3 days of the week at most.<sup>19</sup>

## ANALGESICS

Simple analgesics (**aspirin, paracetamol**) and NSAIDs (**ibuprofen, naproxen, diclofenac**) are used most frequently. Patients will often have tried over the counter (OTC) preparations of these before presenting to their GP.<sup>4,21</sup> In up to 60 percent of cases analgesics are ineffective; this is often due to use of sub-therapeutic doses.<sup>4,24</sup> Soluble or effervescent preparations may be more effective as they are more rapidly absorbed.<sup>5,22,24</sup> Compound preparations containing codeine should be avoided as they can lead to analgesic overuse and chronic daily headaches.<sup>4,13,16</sup> The addition of caffeine and spasmolytics add to expense but not benefit.<sup>6</sup> A prokinetic anti-emetic given prior to an analgesic, will promote absorption (see below). Suppositories should be considered if there is associated vomiting.<sup>7</sup> The main **side-effect** of analgesics is gastrointestinal (GI) irritation. NSAIDs should be **avoided** in patients with a history of hypersensitivity, GI ulceration or bleeding disorders.<sup>25</sup> NSAIDs enhance the effects of anticoagulants, antagonise antihypertensives (e.g. ACEIs, thiazides) and can precipitate lithium toxicity.<sup>26</sup> Excessive consumption of analgesia may cause **rebound analgesic headache**. Pharmacists should counsel patients accordingly.

## ANTIEMETICS

Migraine attacks are accompanied by gastrointestinal stasis.<sup>2,4,29</sup> **Metoclopramide** given prior to an analgesic will promote absorption and hence efficacy by increasing gut motility as well as relieving associated nausea and vomiting. **Domperidone** is preferable in children, the elderly and young women, because of the risk of acute dystonia with metoclopramide in these patient groups.<sup>9,22,24</sup> It is also less likely to cause drowsiness.<sup>25</sup> Suppositories may be preferable if vomiting is prominent.<sup>22</sup> Combination products are available containing cyclizine and buclizine; these are **not** recommended as they have no effect on gut motility which will slow once the migraine is established, limiting their effectiveness.

## TRIPTANS

Sumatriptan is a selective 5HT<sub>1B/1D</sub>-receptor agonist with vasoconstrictor properties. It is highly effective, relieving headache and associated symptoms in 74–83 percent of patients within 4 hours of an oral dose.<sup>1,4,6</sup> The subcutaneous version is more efficacious and has a faster onset of action, although it is not yet available in Ireland.<sup>16,22</sup> The initial dose of sumatriptan is 50 mg orally with further doses if symptoms recur, to a maximum of 300 mg in 24 hours.<sup>28</sup> Sumatriptan is reasonably well tolerated. **Side-effects** include nausea and vomiting, taste disturbance, dizziness, vertigo, drowsiness, heaviness and non-ischaemic chest tightness.<sup>6,30,31</sup> Sumatriptan interacts with MAOIs, SSRIs and lithium and concomitant administration should be avoided.<sup>25,28</sup> It should not be taken within 72 hours of ergotamine due to additive vasoconstrictor effects.<sup>28</sup>

The main **disadvantages** of sumatriptan are cost and headache recurrence; approximately 40 percent of patients will experience a recurrent attack within 24 hours, although this usually responds to a further dose. Headache recurrence is lower with the new triptans, **zolmitriptan** and in particular **naratriptan**.<sup>30,32</sup> The recently launched zolmitriptan has a more rapid action than sumatriptan although comparative trials are lacking. Naratriptan, not yet available in Ireland, has advantages of good oral bioavailability and longer duration of action.<sup>30,32,33</sup> Newer triptans are also under development and a "triptan war" is predicted.<sup>32,33,34</sup> **Contra-indications** to triptan therapy include any condition associated with the risk of stroke or coronary heart disease, arrhythmias and uncontrolled hypertension.<sup>1,6,27</sup> Triptans are not recommended for the elderly, in pregnancy or lactation.<sup>1,25</sup>

## ERGOTAMINE

Ergotamine is a potent vasoconstrictor with serotonin (5HT<sub>1</sub>) and alpha-adrenergic activity, used for many years in the management of migraine.<sup>6,7,9</sup> Due to its unpredictable efficacy and tolerability, use of ergotamine has largely been superseded by sumatriptan.<sup>4</sup> Carefully used, it can be effective in resistant cases refractory to NSAIDs and triptans. Oral absorption is poor (<1 percent), but may be potentiated by caffeine (combination preparations are available).<sup>24,35</sup> **Side-effects** are frequent, often severe and can last for hours.<sup>8</sup> They include nausea, vomiting, abdominal cramps, muscle aches, cold extremities, paresthesia and malaise.<sup>3,6,27</sup> Coronary, cerebral and limb ischaemia are uncommon but hazardous effects and these can be potentiated by beta-blockers. Chronic daily headaches, ergotism with thrombosis and gangrene can occur with overuse and patients must be counselled accordingly.<sup>25</sup> Treatment should be limited to two doses weekly, with 4 days between doses.<sup>1,25</sup> **Contra-indications** to ergotamine include cardiovascular disease, cerebral disease, pregnancy and concomitant beta-blocker therapy.<sup>8,25</sup>

## PROPHYLACTIC TREATMENT

Indications for prophylaxis include: two or more migraine attacks per month, severe and debilitating attacks, failure of, or contra-indications to, acute treatments.<sup>25,36</sup> Drugs used in migraine prophylaxis include; beta-blockers, pizotifen, methysergide, tricyclic antidepressants (TCAs) and sodium valproate. Calcium antagonists (except flunarizine) and clonidine have also been used, but are not recommended.<sup>12,36</sup> Prophylaxis only provides a 50 percent improvement in migraine; this should be explained to the patient.<sup>3,19,28,37</sup> Reasons for treatment failure include unacceptable side-effects, poor compliance, prescribing of sub-therapeutic doses, or treatment for too short a period.<sup>24</sup> At least 3 months of treatment is needed to establish activity. Choice of drug should be tailored to the patient according to side-effect profile, contra-indications and co-existing morbidities.<sup>16</sup>

## BETA-BLOCKERS

Beta-blockers (e.g. **propranolol**, **metoprolol**, **atenolol**), with the exception of agents with intrinsic sympathomimetic activity (e.g. oxprenolol) are effective; cardioselective agents generally have a better side effect profile.<sup>36,37,38</sup> The major **side-effect** limiting use in the young migraneur is lethargy.<sup>25</sup> Beta-blockers are **contra-indicated** in asthmatics, myocardial insufficiency and Raynaud's disease and should be avoided in diabetes. Concomitant administration with ergotamine must be avoided. Compliance may be improved using once-daily preparations such as atenolol. Beta-blockers are particularly useful if there is associated hypertension or anxiety.<sup>28</sup>

## PIZOTIFEN

Pizotifen is an antihistamine and a 5HT-antagonist, effective at a dose of 1.5-3 mg daily<sup>3,16</sup> Common **side-effects** are weight gain and sedation. It should be taken at night to minimise day time drowsiness.<sup>36</sup> Weight gain is unacceptable to many patients, particularly women.<sup>4</sup> Drowsiness may be reduced by starting with 0.5 mg at night and increasing gradually over 4 weeks.<sup>36</sup> **Contra-indications** include obesity and glaucoma.<sup>28,36</sup> Pizotifen may be useful where poor appetite and insomnia are problems.

#### METHYSERGIDE

Methysergide is an ergot derivative with 5HT<sub>2</sub>-antagonist activity, very effective in the prophylaxis of migraine.<sup>28,36</sup> The dose used is 1-2 mg *tds*. It is seldom used in clinical practice because of the risk of retroperitoneal, pleural and pericardial fibrosis, rare but serious **side-effects** associated with prolonged therapy (> 6 months).<sup>6,12,36</sup>

#### TRICYCLIC ANTIDEPRESSANTS (TCAs)

TCAs are unlicensed for use in migraine. **Amitriptyline** and **dothiepin** are effective and particularly useful if there is associated depression, tension-type headache or insomnia.<sup>4,16</sup> Amitriptyline initially 10 mg at night, increasing gradually to 75 mg is recommended.<sup>7,36</sup> Migraineurs are particularly sensitive to the anticholinergic **side-effects** of TCAs; these often improve after several weeks. **Contra-indications** to TCAs include heart block, post MI and closed-angle glaucoma.<sup>28</sup>

#### SODIUM VALPROATE

Sodium valproate, although unlicensed in migraine, has been proven to reduce frequency, duration and severity of attacks.<sup>35,36</sup> The effective dosage range for migraine is 400 - 700 mg daily. **Side-effects** include weight gain, GI disturbance, tremor, hair loss and rarely hepatotoxicity.<sup>36</sup> **Contra-indications** include hepatic disease and thrombocytopenia. Women of child-bearing age should be informed of its teratogenic potential and use effective contraception.<sup>16,35</sup> Valproate is particularly useful in migraine associated with tension-type headache. Platelets and LFTs should be monitored in the early stages of treatment.<sup>36</sup>

#### CALCIUM ANTAGONISTS

Flunarizine is the **only** calcium antagonist with proven benefit in migraine. The recommended dose is 10 mg daily.<sup>7,36</sup> **Side-effects** include sedation and weight gain and so it is useful in patients who are anorexic or have insomnia.<sup>36</sup> Dihydropyridines e.g. nifedipine, nimodipine are ineffective in migraine and may exacerbate headache.<sup>12,35,36</sup> Verapamil is sometimes used but efficacy is unconvincing.<sup>24,36</sup>

#### ALTERNATIVE THERAPIES

Many patients are keen to explore alternative therapies e.g. reflexology, yoga, acupuncture, homeopathy, chiropractic and herbal remedies. Feverfew (*Tanacetum parthenum*) is a herbal treatment shown in controlled trials to be an effective preventative treatment.<sup>22</sup> It is thought to work by prostaglandin inhibition.<sup>7</sup> It must be **avoided** in pregnancy as it can stimulate uterine muscle.<sup>17,39</sup>

#### MIGRAINE IN SPECIAL POPULATIONS

Certain patient groups require special consideration when prescribing drugs for migraine. These are summarised below (see **Table 4**).

**Table 4 Management of migraine in special populations**

Patient Group	Comment
Oral contraceptive users	Although migraine is not a contra-indication to oral contraceptives, women with focal, severe or crescendo symptoms should not take the combined pill. <i>See NMIC Bull 1998; Vol.4 No.1</i>
Pregnant Women	Non-pharmacological approaches should be tried first. Drugs should be avoided, if possible, in the first trimester. Sumatriptan and ergotamine are contra-indicated. Migraine generally improves during pregnancy. <i>See NMIC Bull 1997; Vol.3 No.4</i>
Breast-feeding	Paracetamol, ibuprofen, diclofenac, naproxen, domperidone and sumatriptan are compatible with breast-feeding. <sup>26,24</sup> In terms of prophylaxis, amitriptyline and valproate are considered safe. <sup>26</sup>

Children	Migraine is common in children (5-10%), particularly in males; the common presentation is abdominal pain and nausea, rather than headache. <sup>42,43</sup> Many anti-migraine drugs are not suitable for children (e.g. aspirin, sumatriptan); paracetamol and ibuprofen are the drugs of choice. Pizotifen and propranolol (providing not asthmatic) are used for prophylaxis.
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## COSTS OF TREATMENT

Comparative costs of some preparations used in the treatment of migraine are given in **Table 5**. Costs refer to either the minimum effective stat dose (**acute**) or cost of 28 days of treatment (**prophylactic**).

**Table 5: Comparative costs of some drugs used in the management of migraine**

ACUTE			PROPHYLACTIC		
Drug	Dose (mg)	Cost per dose (£)	Drug	Dose (mg)	Cost for 28 days (£)
Paracetamol	1000	0.05	Atenolol	50	3.88
Ibuprofen	600	0.09	Pizotifen	1.5	8.12
Domperidone	10	0.19	Methysergide	3	7.50
Sumatriptan	50	4.52	Amitriptyline	10	0.33
Zolmitriptan	2.5	4.51	Sodium valproate	400	3.97
Ergotamine	2	0.62	Flunarizine	10	27.02

(prices June '98)

*The Irish Migraine Association (IMA) provides on-going education and support. Details available from the IMA at Carmichael House, 4 North Brunswick Street, Dublin 7. Tel. 01-8724137.*

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Additional references (21-43) available on request