

[diagnosis and treatment of migraine]



Migraine is the most common neurological condition in the world and the most frequently seen disabling headache in primary care. In Ireland, approximately 10-15% of the population suffer from migraine, indicating that there are over 400,000 sufferers in the country. Only about half of these people are managing their migraine adequately.

The introduction of the 5-HT_{1B/1D} agonists (Triptans) in the 1990's has revolutionised the treatment of migraine and lessened the heavy burden for thousands of people across the country. However, migraine is still an extensively underdiagnosed and undertreated condition and the impact that it can have on the individuals quality of life can be huge.

It is this impact that distinguishes migraine from other headache disorders. It is common for patients to say that the condition has taken control of their lives. Many claim that at its height, migraine is the worst pain they have ever experienced.

The management of migraine in Primary Care can be quite challenging, largely due to the widespread variability in clinical presentation, impact and response to treatments. Nevertheless, the vast majority of patients presenting with migraine can be diagnosed and managed through Primary Care. Only a minority need referral to specialist services such as the Headache/Migraine Clinics in Cork and Dublin.

Migraine

Migraine is a neurological disorder characterised by episodic attacks of disabling headache often with associated autonomic and neurological symptoms. Attacks vary in their frequency, duration, severity and number of associated symptoms.

Migraine is estimated to cost the Irish Economy €45 million in lost productivity per annum

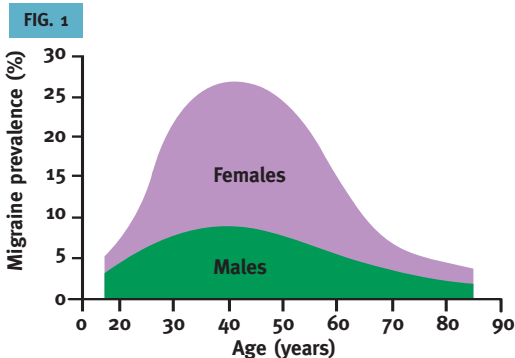
Minimum of 200,000 days are lost from work per annum in Ireland due to Migraine

Average migraineur loses 3-5 days per annum and the equivalent of another 4 days in reduced effectiveness

The World Health Organisation recently classified Migraine as the 19th leading cause of disability worldwide and the 12th leading cause of disability among women.

Epidemiology of Migraine

Migraine affects 10 – 15% of the adult population. About 11% of children are affected with it being equally common in boys and girls. At puberty, there is a rapid rise in incidence among women with adult women being three times more commonly affected. Its peak prevalence occurs at around 40 years (see FIG 1). 25% of people with migraine will have experienced their first attack before the age of 10 and over 90% will have experienced their first attack before the age of 40. It is rare for new cases to occur after the age of 40. In post-menopausal women and beyond middle age in men, the prevalence of migraine decreases so that by the age of 60 it has frequently disappeared. For a minority however, it can continue into old age. The frequency at which migraine attacks

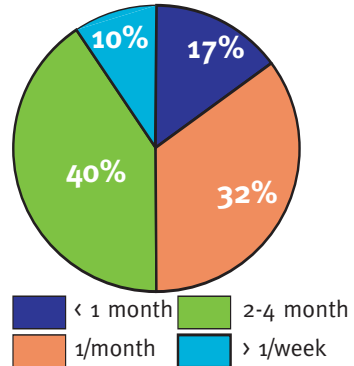


Staffa JA, Lipton RB, Stewart WF, *Rev Contemp Pharmacother* 1994;5:241-252.

occur varies enormously. Some patients experience 1-2 attacks per year, whilst the

average sufferer gets 1-2 attacks per month and up to 10% of sufferers get 1 attack per week. See FIG 2.

FIG. 2 Average Frequency of Migraine Attacks.



Adapted from Stewart WF; Shechter A, Lipton RB. Migraine heterogeneity - Disability, Pain intensity and attack frequency and duration. *Neurology* 1994; 44 (Suppl 4) 24-39

Diagnosis of Migraine

In 1988, The International Headache Society published diagnostic guidelines for migraine and other types of headache. It proposed 7 major subcategories (see below). Of these subcategories, Migraine with Aura and Migraine without Aura account for almost all patients.

- 1.1 Migraine without Aura
- 1.2 Migraine with Aura
- 1.3 Ophthalmoplegic Migraine
- 1.4 Retinal Migraine
- 1.5 Childhood Periodic Syndromes
- 1.6 Complications of Migraine
- 1.7 Migrainous disorders not fulfilling the above criteria

1.1 Migraine without Aura

To arrive at a diagnosis of Migraine without Aura, the I.H.S. lists the following criteria:

- A. At least five headaches fulfilling B-D**
- B. The headaches last for 4-72 hours (treated or untreated), patients being symptom free between attacks**
- C. The headaches have at least 2 of the following features:**
 - 1. Unilateral location**
 - 2. Pulsating in nature**
 - 3. Moderate to severe intensity**
 - 4. Aggravation by movement or routine physical activity**
- D. During the headache, at least one of the following is present**
 - 1. Nausea or Vomiting**
 - 2. Photophobia**
 - 3. Phonophobia**

Headache classification Committee of the International Headache Society. Classification and Diagnostic criteria for Headache disorders, Cranial Neuralgias and Facial Pain. Cephalalgia 1988;8(suppl 7):19-28

1.2 Migraine with Aura:

The diagnosis of Migraine with Aura is based on the aura and not on the headache. (See also Page 7)

The following criteria are defined.

- A. At least 2 attacks fulfilling B**
- B. At least 3 of the following characteristics are present**
 - 1. One or more fully reversible aura symptoms indicating focal cerebrocortical or brainstem dysfunction.**
 - 2. At least one symptom develops gradually over more than 4 minutes or two or more symptoms occur in succession.**

- 3. No aura symptom lasts longer than 60 minutes, but if more than one aura symptom is present, the duration is proportionately increased.**
- 4. The Headache follows the aura with a symptom-free interval of less than 60 minutes, but may also begin before or simultaneously with the aura.**

Headache classification Committee of the International Headache Society. Classification and Diagnostic criteria for Headache disorders, Cranial Neuralgias and Facial Pain. Cephalalgia 1988;8(suppl 7):19-28

No single headache feature and no single non-headache symptom are absolutely required for diagnosis. Migraine diagnosis using the criteria is quite flexible and subjective. In addition to the above inclusive features, a process of exclusion should also take place prior to diagnosis to rule out potential secondary headaches. CT scanning of the brain is indicated when secondary causes are suspected based on the patients history or any abnormality on neurological examination.

There are a number of distinguishable subcategories of Migraine with aura. These include:

Familial Hemiplegic Migraine (FHM)

FHM is a rare condition of recurrent headaches associated with hemiparesis. An additional prerequisite for diagnosis of FHM is that that at least one first degree relative is affected as well. Hemiplegic Migraine may also occur in non-familial (sporadic) form.

Basilar Artery Migraine (BAM)

BAM is another rare form of migraine in which the aura symptoms originate from the brainstem, giving rise to diplopia, ataxia, dysarthria, vertigo, tinnitus and/or changes in consciousness and cognition

Migraine Aura without headache

This is a relatively common condition in which aura symptoms such as fortification spectra, scotomas, paraesthesiae, dysphasia and other symptoms of cortical or brain stem origin may occur without any subsequent headache. In older patients, this needs to be distinguished from Transient Ischaemic Attacks which carry a higher risk of subsequent vascular disease.

1.3 Ophthalmoplegic Migraine

About 1 in 5000 people with migraine suffer from Ophthalmoplegic migraine. The condition is associated with acute attacks of oculomotor nerve palsy with accompanying dilation of the pupil. Ptosis and Diplopia are common features. In this setting, the differential diagnosis includes an intracranial aneurysm or chronic sinusitis complicated by a mucocele. The ophthalmoplegia normally outlasts the headache by days or weeks. The condition occurs more commonly in children, especially boys.

1.4 Retinal Migraine

Consists of repeated reversible attacks of monocular scotoma or blindness lasting less than 60 minutes and associated with headache. The headache usually follows the attack but can be simultaneous or absent. It is the eye, rather than the visual field that is affected. Ischaemic, embolic disease and other organic causes must be ruled out before diagnosis.

1.5 Childhood Periodic Syndromes (Childhood Migraine)

Studies show that about 11% of children experience migraine. It is frequently of shorter duration and less severe. Gastrointestinal symptoms, abdominal discomfort, motion sickness, and fatigue are commonly more eminent than headache symptoms. Children often experience one or more “Migraine equivalents”- symptoms of nausea, vomiting, mood changes, photophobia and phonophobia that are unaccompanied by headache. If these symptoms are occurring in children without an organic explanation, then that is a strong indication of Abdominal Migraine. It has been linked to migraine because of its functional nature, its simultaneous occurrence with migraine or migraine occurring elsewhere in the family. In addition, Abdominal Migraine often precedes the onset of typical migraine, so is considered to be a migraine forerunner.

Other established migraine forerunners are:

Cyclic Vomiting Syndrome

Characterised by recurrent, prolonged attacks of severe nausea, vomiting and prostration with no apparent cause. Vomiting occurs at frequent intervals (5-10 times an hour at the peak) for a few hours to 10 days (1-4 days most commonly). The episodes tend to be similar to each other in symptoms and duration. It is most common from the ages of 3-7 years.

Benign Paroxysmal Vertigo

Benign paroxysmal vertigo of childhood consists of sudden vertigo and dizziness spells without hearing loss or tinnitus. The spells last minutes to hours. Nausea, vomiting, flushing, and visual disturbances can also occur. It is most commonly seen in children between 1 and 4 years old. Many children develop more typical migraine in their teens.

Paroxysmal Torticollis

Paroxysmal torticollis of infancy consists of head-tilt spells that may be associated with nausea, vomiting, pallor, agitation, and ataxia. There is no hearing loss or tinnitus.

Alternating Hemiplegia of Childhood

Infantile attacks of hemiplegia, affecting each side alternately. The nature of the disorder is unclear, though a relationship with migraine is suggested on clinical grounds.

Migraine in children goes into remission in about 60% of cases, though it can recur in later life in about 20% of these. The earlier the onset of migraine in childhood, then the increased likelihood of it continuing or re-emerging in adult life.

1.6 Complications of Migraine

There are 2 recognised sub-types of migraine that fall under this category. Status Migrainosus occurs when a patient fulfills the criteria for Migraine with or without aura, but when the headache lasts for longer than 72 hours. Headache free periods of ≤ 4 hours may occur. Migrainous Infarction (Complicated Migraine) is a migraine attack complicated by ischaemic stroke, leading to aura symptoms which are not fully reversible within 7 days.

Chronic Daily Headache (CDH)

Chronic daily headache is an umbrella term referring to a group of headache disorders characterised by headaches that occur more than 15 days a month, with an average untreated duration of more than 4 hours a day and existing for at least 6 months.

The condition develops insidiously over time and patients frequently have a past medical history of migraine or other primary headache. Patients may also have a possible history of neck or head injury. Co-morbid conditions include stress, anxiety states and depression and are important predisposing risk factors.

The overuse of analgesics, particularly the paracetamol/ codeine preparations can lead to the development of dependence. Clinically these headaches are generalised, non-throbbing and mild to moderate in severity. Patients with a past history of migraine may continue to experience full blown episodic migraine attacks.

Because CDH is resistant to treatment, it can be a difficult condition to manage. Guiding principles involve:

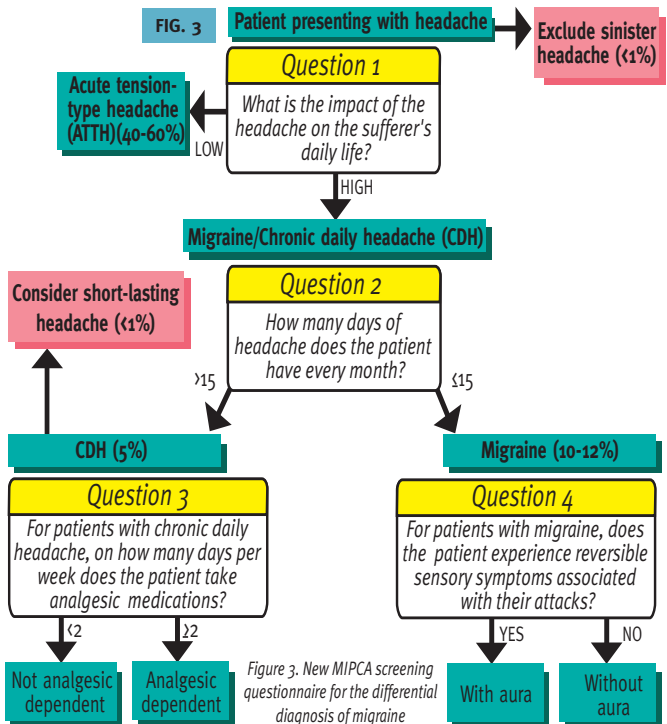
Investigations: Some patients will require a CT scan because the changed pattern and increased frequency of headaches will require secondary causes to be ruled out.

Detoxification: Many patients consume in excess of 40-50 paracetamol / codeine tablets or other analgesics weekly. In patients with rebound headache attributable to medication overuse, a detoxification programme can be implemented, aiming at a 10% weekly reduction in the consumption of the medication. Initially the headaches may worsen due to the rebound phenomenon and patients need to be warned of this possibility. The use of analgesics should be limited to twice per week. Long-acting N.S.A.I.D.s are an alternative analgesic.

Prophylactic therapies: Low-dose tricyclic antidepressants are the first line choices. Other preventative options include sodium valproate, beta-blockers, calcium antagonists, and more recently the S.S.R.I.'s. The objective is to raise the threshold for pain at central brainstem locations by actions on the adrenergic and nonadrenergic receptor sites.

Physical Measures such as physiotherapy of the neck may be beneficial if head or neck injury is involved.

Diagnostic Screening Model



AJ Dowson, S Lipscombe, J Sender et al. New guidelines for the management of migraine in primary care. *Curr Med Res Opin.* 2002.

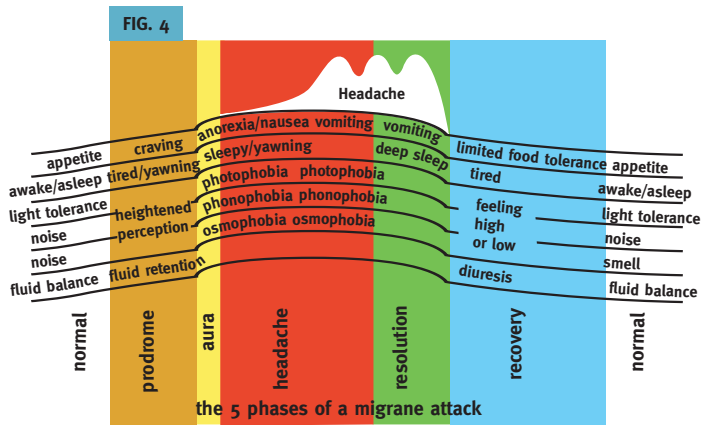
FIG. 4

Clinical Features of Migraine

Migraine is a clinical syndrome characterised by four distinct phases:

- 1) The prodromal phase.
- 2) The aura phase.
- 3) The headache phase
- 4) The postdromal phase.

see FIG 4



The **prodromal** or premonitory symptoms are experienced by approximately 50% of patients, and precede the headache by a number of hours. These symptoms include alteration in mood, tiredness, difficulty in concentration, yawning, cravings for certain foods, fluid retention, altered perception of heat and cold, and loss of appetite. These symptoms give the patient a subjective insight towards an impending attack, though some patients are not always aware of these symptoms or may mistake them for migraine 'triggers'

The **aura** is a transient complexity of reversible, focal neurological symptoms that affects 10-30% of migraineurs. Not all patients with Migraine with Aura will experience aura symptoms with all attacks. Aura symptoms develop over 5-20 minutes but can last up to 1 hour. They usually precede the headache, but may coincide with or continue into the early stages of the headache phase. The most common aura

symptom is visual (99%) consisting of fortification spectra, flashing lights, zig-zag lines and scotoma. In addition 33% of aura patients experience unilateral sensory parasthesia, often following the visual aura. This usually begins as numbness in the hand and migrates up the arm and jumps across to involve the face, lips and tongue. Less frequent aura symptoms are dysphasia and motor weakness.

The **headache** phase is the most disabling feature of a migraine attack and is the most common reason for consultation. There is huge variability in the severity and duration of the headache. The duration ranges from 4-72 hours and may be described as either moderate or severe in nature. The pain is usually gradual in onset and frequently is present on awakening in the morning. At onset the headache may be bilateral but as it progresses it becomes unilateral in 70-80% of patients, and can extend from the periorbital and frontal areas backwards to the temporo-parietal and occipital regions and can even extend to the shoulder area.

As the headache intensifies, patients describe it as throbbing, pounding or pulsating in character and is exacerbated by physical activity or simple head movement. The headache can alternate from one side to the other in different attacks. The headache is almost always accompanied by other symptoms, which generally intensify in tandem with the headache. Nausea accompanies the headache in 70-90% and leads to vomiting in 20-50%. Vomiting may occur early or late in the headache phase and when it occurs after the headache is well established, it may result in a precipitous easing of the headache. Some migraineurs are aware of this and will induce vomiting to gain relief. Other associated symptoms are photophobia, phonophobia and osmophobia. See FIG 5.

The **postdromal** or resolution phase follows the headache. Typically, the sufferer continues to complain of symptoms of tiredness, sore muscles, food intolerance, malaise, alteration in mood, and decreased energy and requires a period of rest until recovery is complete. Immediately after an attack, a minority of sufferers feel energised, euphoric and can return to normal activities at once. The Postdromal phase may last for up to 48 hours.

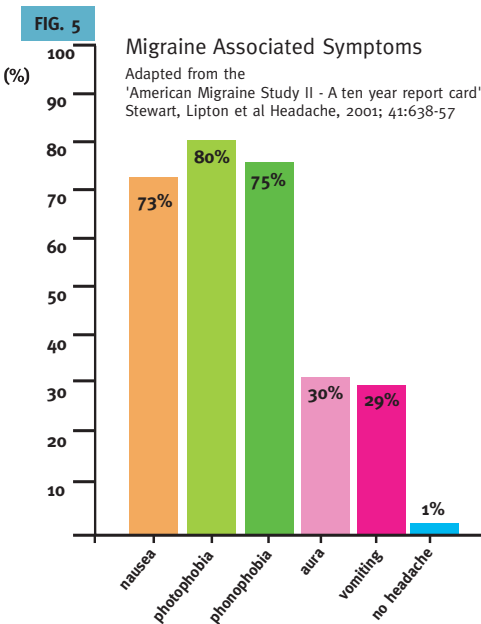
Causes of Migraine

In recent years, the causes of migraine have become clearer, though they are still not completely understood. A number of factors are involved:

1. Genetic Factors

Migraine has been long observed to run in families and studies have shown that 60% of patients have a positive family history with the mother being the most commonly affected relative. If both parents suffer from migraine, each off-spring has a 70% risk of inheriting the condition and a 45% risk if one parent suffers.

Migraine with aura seems to be strongly associated with genetic factors, while Migraine without aura is determined by a combination of genetic and environmental factors.



Recent evidence has shown that a mutation in the gene for the voltage-dependent calcium ion channel on Chromosome 19 is implicated in hemiplegic migraine and this has led to further research into genetic factors.

2. Trigger Factors

Internal or external precipitating (or trigger) factors are implicated in 30-40% of attacks. A wide range of potential trigger factors exist. The most common are listed on the

COMMON TRIGGER FACTORS

Dietary Factors

- e.g. chocolate, cheese, red wine, citrus fruits, MSG etc.
- Lack of food; irregular meals
- Caffeine withdrawal

Sleep Related

- Sleep deprivation or disturbance
- Irregular patterns
- Excessive sleep

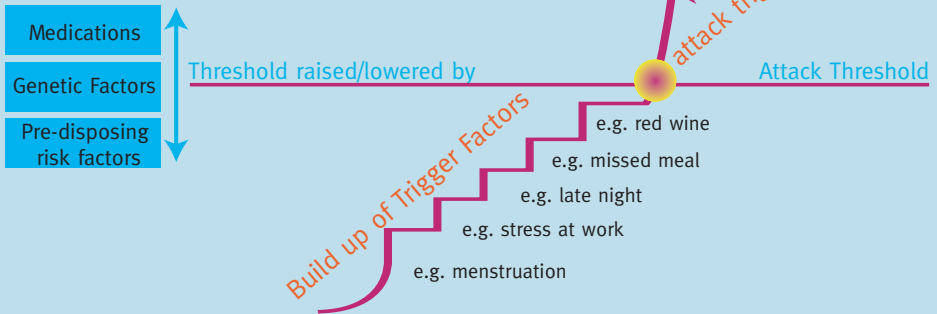
Emotional triggers

- Anxiety
- Stress
- Relaxation after stress
- Excitement

Physical triggers

- Over-exertion
- Travel
- Change of routine
- Too much/ too little exercise
- Smoking/ Passive smoking

FIG. 6 Threshold Theory of Migraine



Adapted from MacGregor EA 1996 -Menstrual Migraine: towards a definition, Cephalalgia 16:11-21

right. Identifying trigger factors for migraine is through association and recognising a cause/effect relationship between the trigger and the subsequent development of an attack. The individual, with the aid of a migraine diary (included in pack) should be able to identify trigger factors when present. Frequently it is a combination of triggers that will result in the patient crossing the 'threshold'. See FIG 6.

Hormonal Factors

- Menstrual Cycle (± 2 days of menstruation; around ovulation)
- Oral Contraceptives
- Menopause
- HRT

Environmental Factors

- Flickering lights
- Sunlight/ Bright lights
- Heat
- High altitude
- Loud noise
- TV/ VDU screens
- Strong smells
- Meteorological changes
- Barometric Changes

Physiological Factors

- Neck/ Back injury
- Head trauma
- High Blood pressure

3. Predisposing factors

Research has shown that migraineurs can have certain metabolic abnormalities that may predispose them to migraine. Some of the factors identified include dysfunction and instability in the autonomic nervous system; changes in ovarian hormone levels and changes to platelet structure and function.

Pathophysiology of Migraine

At least 3 mechanisms are involved in the pathogenesis of migraine.

- *Extracranial arterial vasodilation*
- *Extracranial neurogenic inflammation*
- *Lowered inhibition of central pain transmission*

On reaching the Migraine threshold, a wave of depolarization spreads across the cerebral cortex from occipital to frontal regions at a rate of 2-3 mm/min, resulting in brain ion dysfunction and secondary vasoconstrictor vascular events. These changes account for the progression and variety of symptoms that occur during these phases.

The pain sensitive structures responsible for headache are the extracranial arteries, the proximal parts of the intracranial extracerebral arteries, the pial vessels, the meninges, and the large dural venous sinuses. The sensory innervation is from the ophthalmic division of the trigeminal nerve and the upper segments of the cervical cord (C2-C3). During the headache phase the

trigeminovascular system is activated. On activation, there is depolarisation of the trigeminal ganglion which gives rise to a central transmission of painful information and a retrograde release of vasocative neuro-peptides (C.G.R.P., neurokinin and substance P) from the perivascular nerve terminals of the ophthalmic division of the trigeminal nerve. Centrally, the painful sensory information is transmitted upwards to the thalamus by second order neurones and onwards to the higher centres where pain is perceived. Peripherally, the neuropeptides have local vascular effects. Vasodilatation and plasma extravasation are mediated via C.G.R.P. and neurokinin/substance P respectively.

Migraine patients have low circulating levels of plasma 5-HT in between attacks and during an attack there is a release of endogenous 5-HT from platelets. This is confirmed by increased levels of the breakdown product, 5 Hydroxyindolacetic acid in the urine.

In the absence of a cure for migraine, the aims of migraine management at Primary care level are:

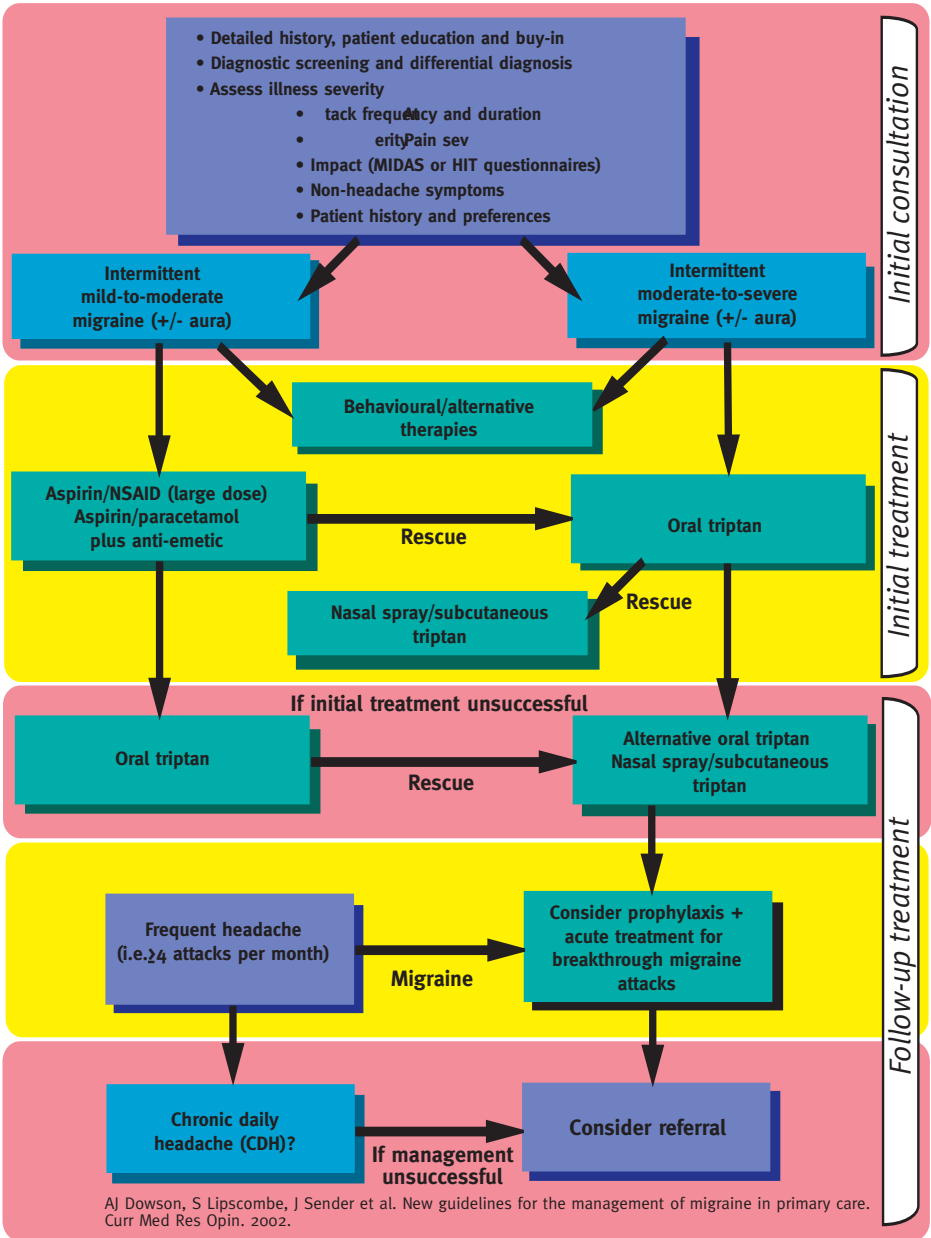
The successful treatment of the migraineurs acute attack.

The prevention and limitation of future attacks.

To encourage migraine sufferers to continue with their care.

The identification and referral of the minority of patients who need specialist services.

FIG. 7 The new MIPCA algorithm for the management of migraine in primary care



AJ Dowson, S Lipscombe, J Sender et al. New guidelines for the management of migraine in primary care. *Curr Med Res Opin.* 2002.

Migraine Management in Primary Care

In recent years, the traditional stepped care model of managing migraine has been largely superceded by evidence based, individualised criteria such as the Migraine in Primary Care Advisors (MIPCA) guidelines from the UK (see FIG 7) as the approach of choice in the management of migraine.

The main features of this model are:

- Patient reassurance and an explanation of the condition should be provided and the patient encouraged to buy into the management of their own migraine. People with headache disorders are often motivated to understand their condition. They should be made aware that although primary headache cannot be cured, it can be effectively managed.
- A careful history assessment and diagnosis should be conducted.
- The impact that migraine has on the patient should be considered when evaluating the patient.
- Each patient should have an individual treatment plan, based on factors such as headache frequency, duration and severity, non-headache symptoms, the impact it has on the patients life and the patients own history and preference.
- Migraine specific treatments should be provided from the start if necessary. Rescue medication is recommended in case the initial therapy fails.

The Migraine Diary

The diagnosis of migraine will sometimes require more than one consultation. The use of a headache/ migraine diary (enclosed in pack) is now standard practice for both diagnosis and management.

The diary will yield vital information on the pattern of the headache and associated symptoms from one attack to the next.

It also gives important information on the identification of trigger factors and the severity, duration and impact of attacks.

The diary is a useful tool for encouraging patients to become actively involved in the management of their migraine.

Finally the diary monitors on-going treatment changes, in both the acute and preventative approaches.

Additional diaries can be obtained free of charge by calling the Association on 1850 200 378 or downloaded from our website at www.migraine.ie

Non Pharmacological treatments

Self-Management

Migraineurs should be encouraged to assume responsibility for the management of their own condition. Part of this involves recognising that drug treatments can be augmented by self-help approaches. The identification and subsequent avoidance of trigger factors has been shown to decrease the frequency at which migraine attacks occur.

It is a good starting point in tailoring a treatment plan towards the individual migraineur's needs. Other useful general tips a sufferer can employ include:

- Join the Migraine Association of Ireland
- Learn about the condition
- Try to control stress
- Use a migraine diary to assess the effectiveness of treatments
- Keep regular patterns of eating and sleeping
- Exercise regularly
- Learn to recognise trigger factors and prodromal symptoms
- The appliance of heat, cold or light pressure to the head during an attack can ease the pain
- Be prepared for an attack

Complementary treatments:

The use of complementary or alternative treatments is widespread among people with migraine. Individually, patients may respond to one or a combination of these therapies though there is little evidence based medicine to support any statistical benefit. The most beneficial non-pharmacological approaches observed in clinical practice are:

Relaxation / Biofeedback: Stress is a common contributing factor and is in itself a trigger factor for migraine. These techniques reduce the “fight/ flight” response and limit the neurochemical changes that occur in response to stress.

Behaviour / cognitive: This approach relates to giving insight into the nature of headaches, altering negative feelings

towards treatments and the ability to gain control of symptoms. Behavioural modifications include regular sleep, regular exercise, regular meals, avoidance of trigger factors, reduction of caffeine and alcohol intake and the introduction of a stress management programme.

Feverfew: The herbal remedy feverfew (*tanacetum parthenium*) may be effective as migraine prophylaxis, though its safety profile needs to be evaluated further. Feverfew is contraindicated during pregnancy.

Pharmacotherapy for Migraine

Pharmacological treatment of migraine can be given in 2 ways:

- Acute treatment for symptomatic relief
- Prophylactic treatment to prevent future attacks

Because only a minority of migraineurs suffer from frequent attacks, acute treatment is likely to be sufficient for most patients.

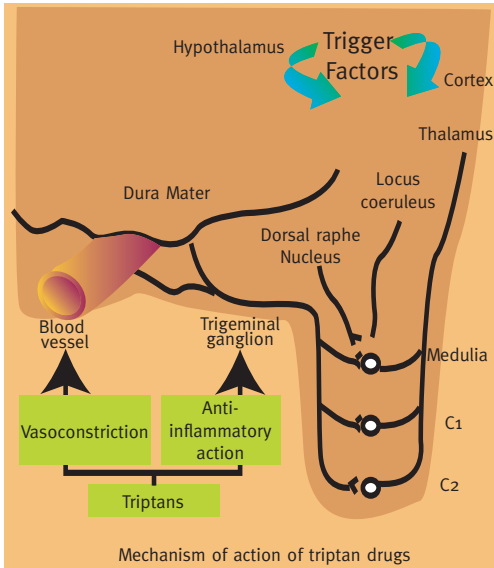
Acute Treatment

By the time patients consult their doctor, most will have already tried over-the-counter preparations.

Factors determining the doctor's choice of therapy will be influenced by:

- The effectiveness of previously tried or prescribed medication.

FIG. 8



Adapted from Goadsby PJ, Olesen J; Diagnosis and Management of Migraine. *Br Med J* 1996; 312:1279-1283

- The severity of an attack, whether it is mild-moderate or moderate-severe.
- The circumstances in which a migraine attack occurs e.g. on the way out to work in the morning.
- Individual requirements of the patient.

In acute therapy the key concerns to be addressed from the patients perspective are:

- *The efficacy of the treatment*
- *The time to onset of action*
- *The consistency of response from one attack to the next and*
- *The tolerability of the medication*

Analgesics:

Up to a third of migraineurs effectively manage their attacks without needing to consult their G.P. The vast majority at some time have self-medicated with over-the-counter (O.T.C.) preparations. Preparations such as paracetamol, aspirin or ibuprofen can be very effective particularly if taken early in the headache phase. Although generally well tolerated, frequent use can lead to the development of rebound headache which can ultimately lead to chronic daily headache.

Simple analgesics are often combined with other medications to improve their efficacy in migraine treatment. If nausea is a symptom, then the concomitant use of the pro-kinetic drugs Domperidone or Metoclopramide will relieve the nausea and also prevent the gastric stasis associated with migraine which slows absorption. Combined preparations such as paracetamol/codeine preparations are effective for some, but there is an inherent risk of developing codeine dependency. Codeine is also a major cause of rebound headache.

Triptans

The triptans are 5-HT_{1B/1D} receptor agonists and are a refinement of the original non-specific 5-HT, ergot preparations, which they have now largely replaced. They can be prescribed in patients (both those with and

PHARMACOLOGICAL PROFILE OF THE TRIPTANS

TRIPTAN	FORMULATION	DOSAGE	HEADACHE RELIEF * PERCENT	TMAX** HRS	HALF LIFE HRS	BIOAVAILABILITY PERCENT
Almotriptan	Oral	12.5 mg	64%	1.4 – 3.8	3.2 – 3.7	70
Frovatriptan	Oral	2.5 mg	36-46% (56-65% after 4 hrs)	2 - 4	25	24 – 30
Sumatriptan	Oral	50 mg	50-61%	2.5	2.5	15
	Oral	100 mg	56-62%			
	Nasal	20 mg	55-64%			
	Subcutaneous	6mg	81-82%			
Zolmitriptan	Oral	2.5 mg	62-65%	2 - 2.5	2.5 – 3	40 - 48
	Oral	5 mg	59-67%			
	ODT	2.5 mg	63%			
	Nasal	5 mg	70%			

* Headache relief is standardised to mean the percentage of patients who have gone from severe or moderate to mild or absent pain within 2 hours

** Time to maximum concentration

without aura) between the ages of 18 - 65 years. In patients with moderate to severe migraine attacks the triptans are now considered first line treatments, particularly if the circumstances of the attack imply an inability to carry out routine activities or the cancellation of pre-arranged commitments. There are four triptans currently available in Ireland

- *Almotriptan 12.5mg orally.*
- *Frovatriptan 2.5mg orally*
- *Sumatriptan 100mg /50mg orally; 20mg/40mg intranasally; 6mg subcutaneously (on a named patient basis).*
- *Zolmitriptan 2.5mg orally (conventional and orally disintegrating formulation)*

The triptans have potent agonist activity at the 1B/1D receptor sites. The specificity of these drugs to these receptor sites limits

their side effect profile and makes them well tolerated. See TABLE 1.

The triptans have three sites of action:

- They cause vasoconstriction of the dilated meningeal, dural, extracerebral, and pial blood vessels by stimulating the 5-HT_{1B} receptors located on these blood vessels,
- They inhibit the release of C.G.R.P., substance P and neurokinin from the peripheral end of the trigeminal nerve by stimulating the 5-HT_{1D} receptor sites located on the pre-synaptic nerve terminals.
- They have a high affinity for the 5-HT_{1D} located centrally in the region of the trigeminal nucleus caudalis in the brainstem. This last site of action modulates in-coming nociceptive or painful sensory information from the

periphery and inhibits its upward transmission to the thalamus and higher brain centres where pain is perceived.

Clinical features of the Triptans

All of the triptans share a number of clinical features:

- Effective for moderate to severe migraine.
- Relief of both headache and non-headache symptoms without need for an anti-emetic.
- When taken orally, efficacy starts within 1 hour and 60% or more of patients report relief within 2 hours. When taken intranasally or subcutaneously, onset of action may be as fast as 15 minutes.
- Headache recurrence rate of about 30% within 24 hours following an initial dose. When this occurs further doses of the prescribed triptan should be repeated.
- Well tolerated. Common adverse events include nausea, drowsiness, fatigue, dizziness, paraesthesia, and the sensation of heaviness in the chest wall, throat and limbs.
- Contraindicated for patients with risk factors for cardiovascular disease due to the potential for vasoconstriction.
- Contraindicated in patients with uncontrolled hypertension and pregnant or lactating women.
- Triptans are contraindicated with lithium.

Evidence suggests that no one triptan is substantially superior to another, especially in oral format. The important question is not which one is better relative to another, but which one will give headache relief to the patient. Despite their advantages, triptans do not respond in all patients and in clinical practice it is not possible to predict who will or will not respond. However, it has been shown that if a patient doesn't respond to one triptan, they may still respond to an alternative triptan. An evaluation of each patient as to his or her clinical needs should drive the choice of triptan. Evaluation of efficacy for a particular patient should be based over three consecutive attacks with the aid of a migraine diary.

Prophylactic drug therapies

Preventative or prophylactic treatment is indicated in patients that

- Experience 2 or more attacks per month and are unresponsive to the acute treatments.
- Suffer from concomitant co-morbidities.
- Suffer from a medical illness precluding first line acute therapy.
- Demonstrate regular patterns to their attacks.

The role of prevention is to achieve a reduction in the frequency, severity and duration of attacks. Effective prophylaxis can achieve up to a 50% reduction in the frequency in approximately 50% of

migraineurs*. Patients should be started on the lowest dose of a prophylactic medicine and increased gradually if required. Preventative therapies need to be taken daily and often 8–12 weeks will elapse before a benefit is observed. Patients are maintained on preventatives for at least 6–9 months before reduction and gradual withdrawal is considered. While on a course of prophylactic treatment, patients still need to have access to an effective acute treatment to deal with breakthrough attacks. The preventative therapies are thought to mediate their benefit by antagonism of central serotonergic receptors, by regulation of calcium ion channels, and by enhancement of central antinociceptive mechanisms. This results in raising the threshold for both cortical spreading depression and trigeminovascular activation.

Beta-Blockers

The Beta-Blockers have been used for prophylaxis for more than 25 years and continue today to be the drug of first choice unless contraindicated in patients with asthma or peripheral vascular disease. It is believed that Beta-Blockers mode of action is antagonism at the central 5-HT₂ receptor. Propranolol 80mg (long acting) is the starting dose and can be titrated up to 320mg. Propranolol has been shown to lead to a ≥50% reduction in attack frequency* in 35-60% of patients, though it has no impact

on the severity or duration of attacks that actually occur. Other Beta-Blockers known to confer benefit are atenolol and metoprolol. Side effects include fatigue, arterial hypotension, nightmares and depression.

Pizotifen

Pizotifen is a 5-HT₂ antagonist and anti-histamine which has been shown to reduce attack frequency* by ≥50% in 35-50% of patients. The dose is 0.5mg – 3mg and is best taken as a single dose in the evening. It is frequently used in childhood and adolescent migraine. Side effects include increased appetite with associated weight gain and drowsiness.

Calcium Antagonists:

Flunarizine is a calcium antagonist with a long half-life. It is a good alternative if Beta-blockers are contraindicated. The dose is 10mg daily at bedtime and is frequently prescribed for patients with prolonged aura or for patients who frequently awaken with migraine. Side effects can be severe and include sedation and Parkinsonian symptoms after long-term use due to anti-dopaminergic actions. Verapamil is licensed in the U.S. for migraine prophylaxis but it doesn't have a licence in Ireland.

Tricyclic Anti-Depressants:

Low dose tricyclic anti-depressants such as amitriptyline are widely prescribed, though

not licensed, for migraine prophylaxis. They are most beneficial in those who suffer from concurrent tension type or chronic daily headache and in those for whom migraine and depression are co-morbid. Side effects include dry mouth, arterial hypotension and urinary retention.

Anti-Convulsants

Recent clinical trials have shown sodium valproate to reduce attack frequency* by $\geq 50\%$ in 45-50% of cases. It was also shown to be generally well tolerated, with the most common side effects being mild to moderate nausea, dyspepsia, dizziness and diarrhoea. Gabapentin may also be useful in clinical practice, especially in treating transformed migraine. Topiramate has been the subject of recent clinical trials which also proved positive.

** 'Reduction in frequency' is defined as a 50% or greater reduction in attack frequency*

Other prophylactic measures:

Other agents used, though clinical trial data is lacking, include magnesium supplementation and SSRI's. Clonidine, the alpha-blocker, is now seldom used due to its demonstrated lack of efficacy. In menstrual migraine, the use of N.S.A.I.D.s may be very effective when prescribed pre-emptively to prevent an attack.

Management of Childhood Migraine

Paracetamol with or without an anti-emetic is the recommended treatment for children. The prophylactic drug of choice is Pizotifen. Non pharmacological interventions such as relaxation exercises, biofeedback, lifestyle management and behavioural therapies can also greatly reduce the frequency of children's attacks.

The Combined Oral Contraceptive & Migraine:

The use of the Combined Oral Contraceptive is not contraindicated in migraine patients. However, Combined Oral Contraceptives often aggravate migraine especially if it is menstrually related. If, the frequency or the severity of attacks increases, then the C.O.C. (Combined Oral Contraceptive) should be discontinued.

Smoking, particularly in migraine with aura patients, is absolutely contraindicated, in those patients seeking advice regarding the Combined Oral Contraceptive. These migraineurs are at increased risk of stroke because of the synergistic effect of migraine with aura, cigarette smoking and the C.O.C.

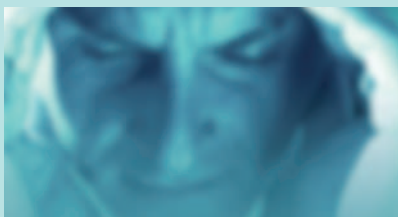
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The Migraine Association of Ireland

The Migraine Association of Ireland was formed in 1994 with 3 main goals:

- 1. To provide information, support and reassurance to migraine sufferers in Ireland.*
- 2. To raise awareness of the condition in the general population and in the population of the health profession.*
- 3. To support research into the condition of Migraine and seek out better treatments for people with migraine.*

Our patient services include:

- Support & Reassurance available via our Helpline
- Regular newsletter
- Regular e-mail newsletter
- Information leaflets and publications
- Advice available from the Specialist Migraine nurse
- On-line information at www.migraine.ie.
- Public information seminars and awareness campaigns.
- We also support research into migraine in Ireland and we were the catalyst in the setting up of Irelands two Headache/Migraine clinics.

‘Your **No.1**
resource for the
latest on
Migraine’

Sources for data used in the publication of this booklet are available upon request