The Challenges of Headache and Migraine Management in Community Pharmacies

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Introduction

Headache is a common symptom which has a lifetime prevalence of > 90% of the population. In many patients headache is a self-limiting complaint and can be successfully self-medicated with simple over-the-counter analgesics. However, in clinical practice, headache requires careful evaluation and a diagnosis, differentiating between primary (benign) and secondary (potentially sinister) disorders.

In addition migraine is a disabling disorder and is ranked 3rd by World Heath Organisation in terms of its impact on individuals and quality of life. In recent years treatment advances in both acute and preventative therapies have transform the management of migraine. The local pharmacist is ideally placed to identify migraine patients particularly those who find migraine disabling and difficult to manage.

Diagnosis

A careful history and examination will identify those who require investigations and delineate between primary and secondary causes (fig 1).

Headache warning symptoms or ''red-flags'' which are worrisome and require further investigation for secondary causes include:

- Thunderlcap headache which is an abrupt onset of a severe headache which reaches maximal intensity within 1 minute.

Primary Headache Disorders	Secondary Headache Disorders
1.Tension Type Headache	1. Subarachnoid Haemorrhage
2. Migraine With and Without Aura	2. Brain tumour headache
3. Chronic Daily Headache	3. Giant cell arteritis
4. Cluster Headache	4. Post-Traumatic Headache
5. Short-Lasting Stabbing Headaches	5. Medication-Overuse-Headache
6. Trigeminal Neuralgia	6. Idiopathic Intracranial Hypertension
7. Trigeminal Autonomic Cephalalgias	7. Arnold-Chiari Malformation
8. New Daily Persistent Headache	

Fig: 1

- New onset of headache over the age of 50 years.
- Progressively worsening headaches over time.
- A ''side-locked'' headache which is always localised to a single location.
- Headache associated with any abnormality on neurological examination.
- Excessive or projectile vomiting.
- Headache associated with fever.

The standard investigations for headache are: FBC, urea and electrolytes, blood sugar,thyroid function tests, serum prolactin, serum growth hormone and neuroimaging, either MRI Brain or CT Scan Brain.

Migraine

Migraine is a common recurrent headache disorder occurring in 10-12% of the population and is three time more common in women with a peak prevalence between the age of 20-50 years (fig2).

It is defined as a neurological disorder characterised by recurrent bouts of severe headache which is accompanied by autonomic and neurological symptoms. The diagnosis of migraine is clinical and based on a careful history and examination. The International Headache Society has developed diagnostic guidelines which are now universally accepted and have standardised the criteria to meet a diagnosis of migraine with and without aura (fig 3).

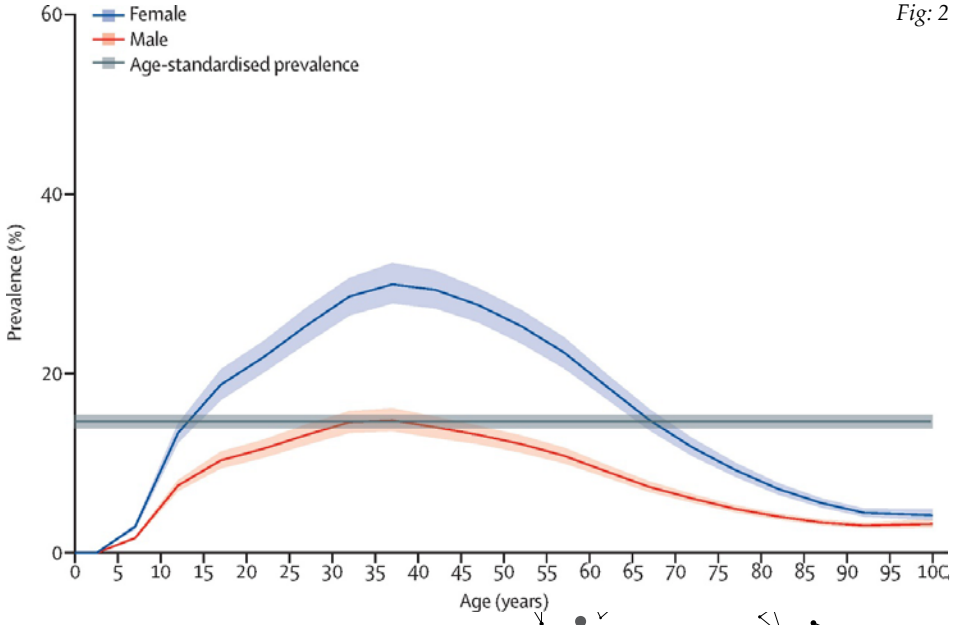


Fig: 2

Migraine Without Aura

A. At least 5 attacks fulfilling B-D

B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)

C. Headache has at least 2 of the following 4 characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe intensity
4. Aggravated by or causing avoidance of routine physical activity e.g (walking or climbing stairs).

D. During headache at least 1 of the following:
1. Nausea and or vomiting.
2. Photophobia and phonophobia.

E. Not better accounted for by another ICHD-3 diagnosis

Fig: 3

Patient's on average get 1-2 attacks per month with individuals typically having to retreat and lie down in a quiet dark room. Migraine is a leading cause of disability and greatly impacts on the individual's quality of life effecting her/his personal, social, familial and working lives. The lost productivity compromises promotion and advancement prospects in the workplace and examination results in students.

Migraine Aura occurs in 20-30% of migraine patients and usually precedes but can coincide with the headache. Patients can also experience migraine equivalents of migraine aura without headache. The aura is defined as a transient focal neurological symptom which lasts from 5-60 minutes and is completely reversible. The commonest aura symptom is visual and described as flashing lights, zig-zag lines, areas of blurred vision with an expanding scintillating scotoma. This is sometimes followed by sensory parasthesia of ''pins and needles'' or numbness, dysphasia and less commonly motor symptoms of muscular weakness and loss of power.

Chronic Migraine

Migraine is a progressive disorder in 10% of migraneurs which can lead to the development of Chronic Migraine. It is defined as a headache occurring on > 15 days per month in which on at least 8 days the attacks retain the characteristics of debilitating episode migraine attacks. It has peak prevalence in women in their 40's. Furthermore it is frequently complicated by Medication-Overuse due to the increasing reliance on simple analgesics, compound analgesics and triptans for pain relief.

Management of Migraine

The management of migraine is entering a transformational era with the arrival of new disease specific preventative therapies and the imminent approval of new acute therapies later this year. Choice of treatments are tailored to an individual's needs and optimised, by patients keeping a comprehensive headache diary. The local pharmacist is ideally placed in the community to have a pivotal role in migraine management. They have detailed knowledge of their customers and can advise on OTC medications, prescribed acute and preventative therapies, monitor side effects and identify patients who need GP or specialist referral.

Guiding principles in the management of migraine are:

- Keep a headache diary
- Identification and avoidance of trigger factors
- Evaluation of acute therapies
- Evaluation of preventative therapies
- Non-drug approaches

1. Headache Diary

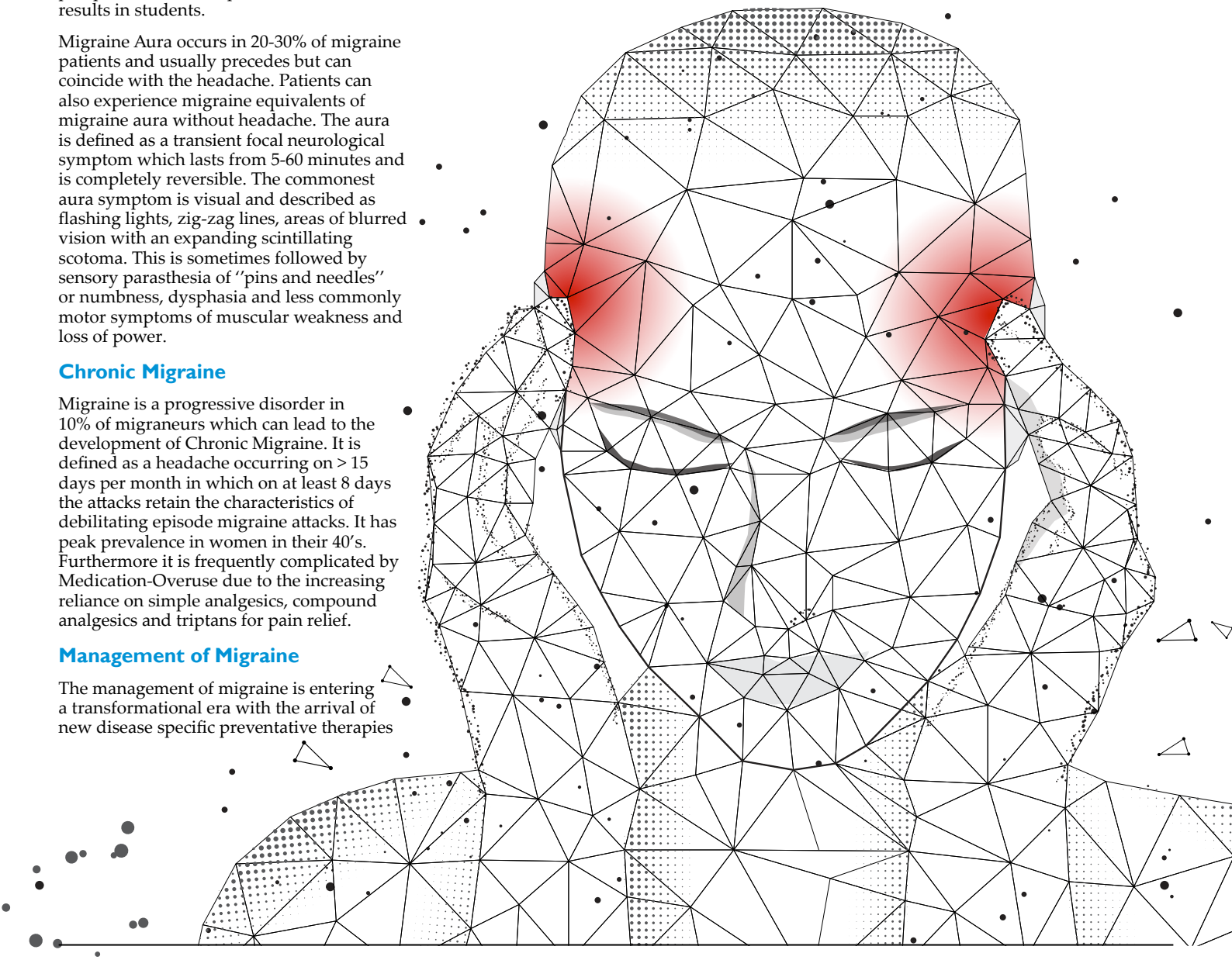
Headache diaries are the cornerstone of clinical practice enabling patient's headache details to be monitored. Accurate documentation of the frequency, severity, duration of attacks, identification of trigger factors, evaluation of acute and preventive therapy efficacy, and the accompanying disability, builds up a profile of each patient thereby optimising treatment choices on an individualised basis.

2. Trigger Factor

Trigger factors are identifiable in approximately 30% of migraneurs and include: dietary: cheese, chocolate, dairy products, processed foods, caffeine and alcohol. The menstrual cycle, generalised stress, missed meals, overtiredness, lack of sleep, exercise, dehydration, bright lights, sunlight and changing weather conditions are other important triggers. By mitigating against these triggers patients can avoid and reduce the frequency in which attacks occur.

3. Acute Therapies

The ideal acute therapy provides rapid and complete relief from headache and the associated symptoms within 2 hours, is free of side effects and is affordable and cheap. This is a challenging benchmark and in order to maximise efficacy patients need to take their acute therapy as early as possible after the onset of the headache. 1/3rd of migraine patients successfully manage their acute attacks with simple analgesics such as paracetamol, soluble aspirin and ibuprofen. Many, however, are non-responders to



these agents and they step up the analgesic ladder and self-medicate with compound analgesics such as paracetamol/codeine or ibuprofen/codeine preparations. There are dangers in this approach and patients need to limit their use of these medications to no more then twice weekly due to the risks of habituation, dependence and tolerance leading to Medication-Overuse-Headache. This precaution also applies to prescriptive compound narcotic analgesics and they should be avoided in the management of acute migraine attacks.

The triptans (5HT1B/1D) receptor agonists have dominated prescription medication for the acute attack for > 25 years (fig4).

Triptans: 5HT1B/1D receptor agonists:
1. Sumatriptan 50-100mg
2. Zolmitriptan 2.5mg
3. Eletriptan 40mg
4. Frovatriptan 2.5mg
5. Naratriptan 2.5mg
6. Almotriptan 12.5mg

Fig: 4

They are licenced for adults aged 18-65 years and are contraindicated in those with ischaemic heart disease, uncontrolled hypertension, previous stroke and structural brain lesions. 60-80% patients get relief from headache and their most bothersome symptoms within 4 hours. Side-effects include pins and needles, throat pain and non-cardiac chest pain. The triptans should also be limited to 10 days per month as their overuse is also a risk factor for medication-overuse-headache. Sumatriptan, the first of the triptans, is now available over the counter in pharmacies to patients with a confirmed diagnosis of migraine by their GP. The evolution of the triptans have established them as the standard bearer against which newer agents in clinical trials are measured against.

4.Preventative Therapies

The guidelines for the initiation of preventative therapies are evolving and should be considered in patients who experience:

- 4 or more headache days per month.
- Attacks which are prolonged and last for longer than 72 hours.
- Attacks which are non-responsive to acute therapies (e.g. triptans).
- Patients who cannot tolerate acute therapies due to side-effects.
- Patients who experienced pro-longed aura symptoms.

The goals and objectives of preventatives therapies is to reduce the frequency, severity and duration of attacks and enhance the efficacy of acute therapies.

Conventional preventative therapies are outlined in fig. 5.

Preventative Therapies:
1. Anti-hypertensive: B-blockers: propranolol, metoprolol, atenolol
2. Anti-convulsants: topiramate
3. Anti-depressants: amitriptyline, venlafaxine
4. Anti-hypertensive: candesartan
5. Flunarizine
6. Pizotifen
7. Onabotulinum Toxin injections

Fig: 5

Traditional preventative therapies are dominated by medications developed for other disorders and have serendipitously demonstrated a benefit in migraine prophylaxis. The efficacy of preventative therapies builds up over time and patients should be on a chosen agent for 3 months before its benefits are evaluated. The primary goal is to achieve at least a 50% reduction of attacks in patients with episodic migraine and a 30% reduction of headache days in patients with chronic migraine. Many patients discontinue their preventative within a few weeks due to side-effects and a perceived lack of efficacy.

The first disease specific migraine preventative therapies were approved in Ireland in late 2021. These agents are C.G.R.P. (calcitonin gene related peptide) monoclonal antibodies antagonists. (fig.6).

C.G.R.P. monoclonal antibodies	**Mode of Action**
1. Erenumab 70mg or 140mg S.C.	Receptor Antagonist
2. Fremanezumab 225mg S.C.	Ligand
3. Galcanezumab 120 mg S.C.	Ligand
4. Eptinezumab I.V.	Ligand

Fig: 6

Three of these agents (fremanezumab, galcanezumab and eptinezumab) are antagonists to the CGRP peptide (ligand) whilst erenumab is an antagonist at the CGRP receptor sites located on intracranial blood vessels and neurones. The monoclonal antibodies do not cross the blood brain barrier and their actions are mediated peripherally against the cgrp peptide and the peripheral neuronal receptors. They have a long half-life and are administered monthly (erenumab, fremanezumab) or 3 monthly (fremanezumab) by subcutaneous injection.

Erenumab and fremanezumab are licenced in Ireland for patients with Chronic Migraine (> 15 headache days per month), aged 18-65 years, who have failed to benefit, demonstrating a lack of efficacy for 3 conventional preventative therapies. Evidence of prior treatment failures, from the pharmacist, needs to be provided by patients in support of their application for these new treatments. The CGRP monoclonal antibody antagonists are exclusively prescribed within neurology departments on the high-tech hub.

To-date the efficacy of these medications is very encouraging and in the primary end point > 50% of patient achieve a >50% reduction in headache days. Many patients achieve a benefit within weeks and up to 25% are known as ''super-responders'' achieving a > 75% reduction in headache days. Patients also become less reliant on the need to use acute therapies such as the triptans or analgesics.

The CGRP monoclonal antibodies are well tolerated and the most commonly reported side effects are local reaction at injection sites, naso-pharyngitis, and constipation occurring in 3-4%. Blood pressure monitoring is also advised whilst on these medications.

Due to the widespread distribution of CGRP in the body long term safety data particularly in the cardiovascular and gastrointestinal systems is still being evaluated.

5.New and Emerging Treatments

The landscape for further new acute and preventative therapies is continuing to evolve and there are a number of agents already available in the USA and are awaiting approval in the EU. The most interesting of these are the small molecule CGRP antagonists, fig 7.

Small Molecule CGRP Antagonists
1. Rimegepant
2. Atogepant
3. Ubrogepant
4. Zavegepant

Fig: 7

Two of these agents, rimegepant and atogepant are potential ''game-changers'' in migraine management. They are licenced and prescribed in the USA to treat acute attacks and also as a preventative therapy to avoid future attacks. Patients can take up to 18 doses per month and the use of small molecule CGRP antagonists (gepants) is not a risk factor to developing medication-overuse-headaches. These end-points are being closely scrutinised in on-going trials and may well represent a significant step forwards in finding the ideal therapy which is a single therapy that provides acute relief and prevents future attacks.

Conclusions

The World Health Organisation has ranked migraine and other primary headache disorders as the second leading cause of years lived with disability in the world. Migraine continues to plague millions of people's lives. The management of migraine is rapidly changing and being transformed following the introduction of the CGRP monoclonal antibodies and the anticipated approval in the EU of the small molecule ''gepants''. International, peer reviewed, treatment guidelines are being updated incorporating these recent advances with the ultimate goals of improving the quality of life and reducing the disease burden of migraine on individuals.