

## HEADACHE

**(1) MIGRAINE**

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*This article is the first of a series on various types of headache*

**M**igraine is a common condition which is believed to affect between 15 and 18 per cent of women and six per cent of men.<sup>1,2</sup> This article considers both the diagnosis and management of migraine. During a migraine attack, the trigemino-vascular system is activated. The trigeminal nerve communicates with blood vessels causing vasodilation and pain. The important receptors are serotonergic, since blood vessels are driven by the 5-HT<sub>1B</sub> and the trigeminal nerve by the 5-HT<sub>1D</sub> subtypes at both ends.

**DIAGNOSIS**

In the late 1980s, the International Headache Society (IHS) formulated a classification for migraine (see Panel 1) which has helped us to determine correct patient groupings for migraine clinical trials. This classification was never intended to be applied to individual attacks but merely to identify people with migraine. If five attacks met the criteria, the patient was given the diagnostic label of "migraineur". It is important to realise that not all four symptoms have to be present and so it is quite possible for the patient to have a

mild headache which is bilateral and still have migraine.

Over recent years, clinicians have realised that it is also important to question patients with acute or intermittent headaches about their quality of life and ability to perform normal activities. High impact acute headache would tend to have a default diagnosis of migraine and the IHS classification is used to confirm this.

The main part of the classification is concerned with the headache phase of the attack. However, approximately 10 per cent of patients will have reversible sensory symptoms in the hour preceding the headache. These symptoms are known as auras and will often include visual changes such as zigzag lines or scotoma (holes in the vision) but a variety of other symptoms, such as word-salading (words being mixed up), dizziness and numbness may also occur. About 40 per cent of patients describe vaguer symptoms which can last substantially longer. In the day or two before an attack, prodromal symptoms, such as cravings, lethargy, etc, can be observed. From these two phases, useful warnings can be identified and patients who take simple treatments during such a warning may have success in heading off a migraine before it has really started.

The last phase of migraine, which is often ignored, is the post-drome. This occurs once the headache has subsided and usually involves the patient feeling washed out or hung-over. Occasionally, the patient may feel entirely the opposite, almost as if they are super-human. Even though relatively little can be done to alleviate these postdromal symptoms, the cost in terms of disruption to work, chores and social activities which can result from this phase should not be underestimated.

By paying attention to the degree of impact each phase has on a

patient, different management strategies may be developed. Headache specialists now often draw "impact curves" with patients to illustrate the shape of an individual's attacks.

**Differential diagnosis** It is important to remember that those patients whose management is unsuccessful may have been misdiagnosed and, therefore, be taking inappropriate treatment. Sinister symptoms are outside the scope of this article but in reality, patients, pharmacists and general practitioners all worry about the misdiagnosis of presenting symptoms of serious underlying disease. They should, however, be reassured that such presentations are extremely rare. The majority of headache sufferers who seek advice will have the common acute high impact headache of migraine or, chronic headache. The next article in this series will explain that it is important that chronic daily headache is not misdiagnosed as migraine.

**MANAGEMENT OF MIGRAINE**

It may be useful at this point to draw a picture of the average migraineur.<sup>4</sup> Most sufferers will have approximately one or two attacks a month, will be between the ages of 25 and 55 years and will rarely experience more than 40 attacks in a year.

Untreated, an average attack will last approximately one day. It must be stressed that it is important to include the patient in all decisions regarding migraine management because the patient needs to develop a specific strategy that works. This strategy usually includes the avoidance of trigger factors where possible, acute intervention for break-through attacks and the use of prophylactic agents in "high frequency" patients (more than four attacks per month).

Patients with less frequent but more prolonged attacks may warrant prophylactic treatment if their migraine is unresponsive to the full range of acute therapies.

**AVOIDING TRIGGER FACTORS**

It is believed that in patients with a susceptibility to migraine attacks various trigger factors (see Panel 2) will come together on a particular day to tip the patient into the acute symptoms described above. Once identified, many risk factors, especially foods, are easily avoided. Others, such as weather changes or menstrual cycles, are more difficult to avoid, but appreciation of their importance can be put to

**PANEL 1: DIAGNOSTIC POINTERS FOR MIGRAINE<sup>3</sup>**

- 1 Headache is at least two of the following: unilateral; pulsating; moderate to severe intensity; aggravated by routine activities
- 1 Accompanying symptoms may include: photophobia; phonophobia; nausea with or without vomiting
- 1 Attacks last from 4 to 72 hours
- 1 Patients are usually symptom-free between attacks

**PANEL 2: TRIGGER FACTORS FOR MIGRAINE****Hormonal changes**

Hormone replacement  
Menstruation  
Oral contraceptive therapy  
Pregnancy

Artificial sweeteners  
Caffeine  
Chocolate  
Cultured dairy products  
Fermented/pickled foods  
Fruits

**Environmental factors**

Bright/flashing lights  
Emotion (eg, anger)  
Missed meals (hypoglycaemia)  
Smoke  
Strong odour (eg, perfume)  
Too much/little sleep  
Weather changes

Monosodium glutamate  
Nitrates (eg, in cured meats)  
Sugar  
Sulphites  
Vegetables  
Yeast

**Exercise or exertion**

Eye strain  
Head injury  
Irregular/no exercise

**Foods/ingredients**

Alcohol

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good use.

#### ACUTE TREATMENT

Assessment of the acute response to drug interventions has become more awkward because of the diversity of end points now used in clinical trials.<sup>5,6</sup> Treatments fall into two broad categories: first analgesics and analgesic combinations; and, secondly, migraine-specific therapies, such as the triptans, and ergotamine.

**Analgesics and analgesic combinations** Most patients will have tried taking analgesics before consulting a health care professional. However, they may not have taken an appropriate dose of a drug, or taken it at the right time. Because of the worries about gastric stasis, to achieve reasonable blood levels, larger than usual doses of analgesics are suggested (I advise 900mg of aspirin, 1.5g of paracetamol or 600mg of ibuprofen to be taken). If possible, these should be taken before the headache phase develops. The timing of the dose is paramount in achieving the best possible outcome.

There is little evidence from clinical trials across large populations that combination drugs with caffeine and codeine are more effective than simple analgesics. However, individual patients will experiment with different products. As long as they achieve the goal of being back to normal within a couple of hours with OTC therapy and the frequency of headaches does not increase, I have no major objection to this approach. However, pharmacists should be aware that patients using significant amounts of analgesics, particularly those containing codeine, may be developing, or indeed have, chronic daily headache. These patients would be best referred to their GP.

The addition of a gastric motility agent, such as metoclopramide or domperidone, is of particular benefit to those patients in whom vomiting is a major part of their migraine. Increasing gastric motility also allows better absorption and efficacy of the analgesic. In clinical trials, soluble aspirin 900mg with metoclopramide 10mg tended to give headache relief figures in the region of one third to one half of patients at two hours. A migraine-specific product, Migramax, contains both metoclopramide and lysine acetylsalicylate. The lysine group confers additional solubility and, therefore, more rapid absorption of the aspirin; aspirin is in contact with the gastric mucosa for a shorter time, potentially giving fewer gastric side effects and enhanced efficacy.

Another drug with a specific migraine indication is tolfenamic acid (Clotam Rapid) which is a non-steroidal anti-inflammatory drug. A published placebo-controlled, randomised trial has shown tolfenamic acid to be equivalent to sumatriptan. However, in the trial, the success rates were above those normally expected from sumatriptan 100mg at a two hour interval. It would, therefore, be useful to have other studies to confirm these results.

**Isometheptene** Isometheptene (Midrid) is available both OTC and on prescription. There is little clinical trial evidence to support its use, but it is a popular drug, particularly in the United States.

**Triptans** The introduction of the 5-HT<sub>1</sub> agonists (triptans) has increased treatment options in migraine and provided an opportunity not only to reappraise management strategies but also to deliver more effective care. Triptans appear to work by stimulation of 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors. In the UK, there are six licensed triptans; sumatriptan (Imigran), zolmitriptan (Zomig), naratriptan (Naramig), rizatriptan (Maxalt), almotriptan (Almogran) and eletriptan (Relpax). All these drugs are used in clinical practice but the mainstay is sumatriptan. One further triptan (frovatriptan) may be launched during the next 12 months.

For patients who do not gain control with more general approaches, the triptans have proved to be a life-changing therapeutic option, although only a minority of those who could possibly benefit have been prescribed them.

Sumatriptan was launched approximately a decade ago and there is now substantial clinical experience of this agent. As well as tablet form, sumatriptan is available in subcutaneous and intranasal formulations to avoid the upper GI tract. These formulations act faster than tablets and are attractive for patients who have early vomiting as a major feature of their migraine.

Zolmitriptan was the second triptan to be launched. It was orig-

inally thought that it had activity at three 5-HT<sub>1</sub> sites, and was therefore expected to penetrate the trigeminal nucleus better than sumatriptan. However, it remains unclear whether this confers additional benefits. Zolmitriptan is currently available as tablets and a recently launched melt formulation. With the latter, the patient places the lozenge on the tongue and it dissolves in the saliva over a few seconds. The solution is then swallowed and absorbed from the stomach. The orange flavour seems to be well tolerated and rarely causes any taste disturbance. A major advantage is that the patient is able to take the treatment earlier in the attack (since no glass of water is required) and thus has a better chance of success. Zolmitriptan nasal spray is also in the latter stages of its development programme.

Naratriptan is given at a dose of 2.5mg. Its summary of product characteristics states that side effect rates are similar to those of placebo. In studies, a disadvantage was that, at two hours, some patients found it to be less effective than the other triptans. In those who find the drug effective, an advantage is a reduction in recurrence rate (recurrence being defined as headache successfully relieved but returning within 24 hours). Recurrence occurs about one-third of the time with the other triptans and about one-fifth of the time with naratriptan. In summary, it would appear that naratriptan has advantages for those patients who have recurrence or adverse events and this leads some practitioners to favour using this drug first-line, then moving to the other triptans if it is ineffective.

Rizatriptan was launched in 1998. It has a small molecule, which allows rapid absorption and quick access to action areas. It was also designed to have little action at other receptors, particularly 5-HT<sub>1A</sub>. This may be of benefit in the early phase of treatment since there may be less nausea caused by 5-HT<sub>1A</sub> stimulation. Tablets are available in 5mg and 10mg and there is also a 10mg melt version.

Almotriptan was launched in early 2000. It is available as a 12.5mg tablet and, like naratriptan, appears to result in reduced adverse events and recurrence rates, while still being effective for most patients.

Eletriptan will be launched early this year. It will be available as a tablet and the initial dose suggested is 40mg, although, if this proves insufficient, the dose may be increased to 80mg. The clinical trial data show this drug to be as effective as others in the family. There may be some requirement for dose adjustment because potential interactions can occur with drugs which have cytochrome P3A4 inhibitor action. These include macrolide antibiotics and some antifungals.

All the triptans have a similar range of unwanted effects. The most common are tiredness, dizziness, nausea, neck and shoulder stiffness and a sensation of heaviness or pressure in various part of the body, including the chest and throat. All drugs in the class have been extensively investigated and evidence, including ECG monitoring, suggests that the chest and throat symptoms are not necessarily of cardiac origin. Although the mechanism is yet to be determined, causes such as oesophageal spasm have been postulated. In practical terms, it is usually best to warn the patient that these side effects may occur but to reassure them that true cardiac symptoms are rare. The triptans are contraindicated in patients with known ischaemic heart disease or uncontrolled hypertension and they are not recommended in patients over the age of 65.

**Ergotamine** The use of ergotamine has been almost completely superseded by the triptans because of its potential to cause acute side effects, such as nausea, abdominal pains and cramps, and also because of its relatively low relief rate, particularly in the oral formulation.

Patients currently using ergotamine on an infrequent basis who find it efficacious and without side effects would appear to be using the drug optimally, and would not necessarily require a change in therapy. The most worrying aspect would be the possibility of an increasing use of ergotamine leading to ergotism, a form of chronic daily headache. In this circumstance, the patient should be referred for further GP assessment.

**Dihydroergotamine** Dihydroergotamine is superior to ergotamine but inferior to the triptans. Its side effect profile is reduced in comparison to ergotamine. Having been withdrawn from the UK last

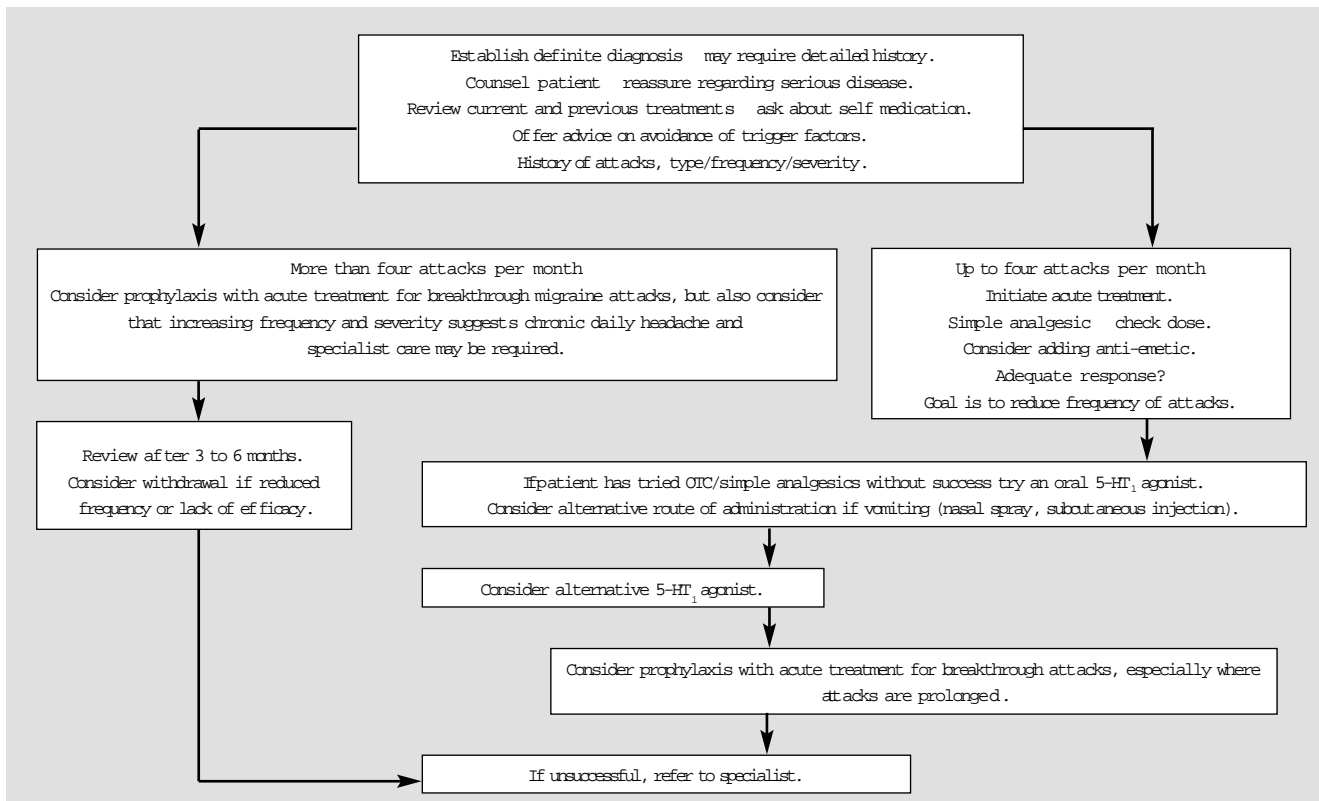


Figure 1: A migraine management strategy

year, it is only used by specialists in cases of triptan failure.

#### PROPHYLACTIC THERAPIES

Drugs to reduce the frequency of migraine have been used for decades and not always with good foundation. The mode of action of these drugs is poorly understood but it is thought that antagonism at 5-HT<sub>2</sub> receptors may be important. In general, drugs are thought to be successful if there is a 50 per cent reduction in the rate of attacks in 50 per cent of patients. During the last decade, with the advent of the high efficacy triptans, we have seen less emphasis being placed on prescription prophylactic agents. The most commonly used licensed drugs in the UK are beta-blockers and 5-HT<sub>2</sub> antagonists. The general trend in prophylaxis is that, because the prescription agents have relatively low efficacy and a reasonable chance of causing side effects, compliance becomes a major issue. Because of this, it is my opinion that it is best to start with modest doses and gradually titrate up if necessary.

**Beta-blockers** This class of drugs is the most commonly used worldwide. Beta-blockers are contraindicated in patients with conditions such as asthma and peripheral vascular disease. Propranolol, atenolol, metoprolol and timolol are all used, although propranolol is the most commonly prescribed in the UK. My own approach is to start with a low dose (10mg *bd*), building up gradually. Inderal LA (160mg) or Half Inderal LA (80mg) are commonly used but a larger daily dose does confer the problem of additional side effects. One analysis of propranolol reported that, on average, there was a 44 per cent reduction in the frequency, duration and intensity of attacks.

**Pizotifen** Pizotifen (Sanomigran) has antihistaminic and 5-HT<sub>2</sub> receptor blocking activity and, in adults, the reduction in frequency of attacks is less than that of beta-blockers. Possible side effects are weight gain and sedation.

**Methysergide** Methysergide (Deseril) is an effective prophylactic agent but, because it carries the serious side effects of fibrotic conditions such as retroperitoneal fibrosis (fibrous material that can affect the ureters, and therefore, urinary flow), it is usually reserved for patients who have failed to respond to alternative prophylactics.

**Other prescribed prophylactic agents** Tricyclic antidepressants, selective serotonin reuptake inhibitors and sodium valproate, have

all been shown to have some efficacy in migraine prophylaxis.

**OTC prophylactic agents** Because of the relatively low efficacy and tolerability issues with the prescription prophylactics, patients often prefer to try OTC options first. Products such as vitamin B<sub>2</sub> (400mg *od*), magnesium (200mg *od*), feverfew and even aspirin (75mg *od*) are all options for prophylaxis. When using prophylactic agents, it is always useful to explain to patients that they should only change one treatment at a time. In this way, they can reduce the possibility of confusion over which drugs are effective.

#### CONCLUSION

The management of migraine initially requires an accurate diagnosis, especially to exclude chronic daily headache. Once the migraineur is correctly identified, an appropriate strategy needs to be developed.

In the general population, soluble oral analgesics, with or without an anti-emetic, may be all that is required. More specific migraine therapies, such as the triptans, are available for those in whom this approach fails. It should be remembered that, during patients' lives, the expression of their migraine may vary and the intervention required may need to be reassessed and adjusted. Patients may have a variety of migraine types in the short term and this can require a range of treatments to achieve optimal control. The aim of a good management strategy (see Figure 1) should be to enable patients to be in control of their migraine rather than have it control them.

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