Mechanisms and management of headache

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Headache is the commonest of human maladies, and many books have been devoted to the subject. In this article, the mechanisms of primary headache and its treatment will be considered. Most developments have been in primary headache, in particular migraine, so this will be the main focus. Recent reviews of migraine diagnosis and management are available. Diagnostic issues are beyond the scope of this review, though it is worth remarking that the codification of diagnostic criteria for all headache types, particularly migraine (Table 2), has been a useful step forward.

**Mechanisms of headache**

Understanding of headache has advanced considerably over the last decade. The severe primary headaches, migraine and cluster headache, have been studied extensively. In experimental animals, the detailed anatomy of the connections of the pain-producing intracranial extracerebral vessels and the dura mater has built on the classical human observations that it is these structures, not the brain, that are responsible for generating pain from within the head. Migraine is an episodic syndrome of headache with sensory sensitivity, such as to light, sound and head movement. The first of the migraine genes has been identified for familial hemiplegic migraine, in which about 60% of families have mutations in the gene for the \( \alpha \)-1 subunit of the neuronal P/Q voltage-gated calcium channel. This finding and the clinical features of migraine suggest that it might be part of the spectrum of disorders involving dysfunction of voltage-gated channels. Functional neuroimaging has suggested that brain stem regions in migraine, the dorsal mid-brain and dorsolateral pons, and, in cluster headache, the posterior hypothalamic grey matter site of the human circadian pacemaker cells of the suprachiasmatic nucleus, are good candidates for specific involvement in primary headache.

The pain of primary headache is now relatively well understood. The pain-producing innervation of the cranium projects through branches of the ophthalmic (first) division of the trigeminal nerve to the trigeminocervical complex. Serotonin (5-HT1B) receptors on the large extracerebral intracranial vessels can cause vasoconstriction, while there are 5-HT1D receptors on the peripheral branches of the trigeminal nerve and its central ramifications in the trigeminal nucleus. Activation of these receptors by agents such as the triptans cause vasoconstriction and neuronal inhibition which are thought to be the basis for aborting acute attacks of primary headache.

**Table 1. Common causes of headache (data from Ref 4).**

<table>
<thead>
<tr>
<th>Primary headache</th>
<th>Prevalence (%)</th>
<th>Secondary headache</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>migraine</td>
<td>16</td>
<td>systemic infection</td>
<td>63</td>
</tr>
<tr>
<td>tension-type</td>
<td>69</td>
<td>head injury</td>
<td>4</td>
</tr>
<tr>
<td>cluster headache</td>
<td>0.1</td>
<td>subarachnoid haemorrhage</td>
<td>&lt;1</td>
</tr>
<tr>
<td>idiopathic stabbing</td>
<td>2</td>
<td>vascular disorders</td>
<td>1</td>
</tr>
<tr>
<td>exertional</td>
<td>1</td>
<td>brain tumour</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**Table 2. Modified diagnostic criteria for migraine and cluster headache.**

**Migraine episodic attacks of headache lasting 4–72 hours with the following features:**

- two of:
  - unilateral
  - throbbing
  - aggravated by movement
  - moderate/severe intensity of pain

**Cluster headache: episodic attacks of pain lasting 15–180 min coming in daily bouts for weeks with the following features:**

- one of:
  - nausea/vomiting
  - photophobia and phonophobia
  - unilateral, often orbital or supraorbital
  - attack frequency of 1–8/day
  - associated with one or more of:
    - conjunctival injection
    - lacrimation
    - nasal congestion
    - rhinorrhea
    - ptosis
    - miosis
    - eyelid oedema
migraine and cluster headache. Moreover, the overlap of inputs from high cervical structures with trigeminal neurons in the most caudal part of the nucleus is likely to account for the common clinical reporting of neck pain in primary headache, even when there is little relevant structural neck disease, such as in young women (Fig 1).

Management of migraine

The management of migraine begins by explaining to the patient that migraine:
- is an inherited tendency to headache, and cannot be cured
- can be modified and controlled by lifestyle adjustment and the use of medicines
- is neither life-threatening nor associated with serious illness, except in women who smoke and are on oestrogenic oral contraceptives who are at increased risk for stroke — but migraine can, and often does, make life a misery
- management takes time and cooperation because information has to be collected, for example, from a headache diary.

Non-pharmacological management

The aim of non-pharmacological management of migraine is to help the patient identify situations that make the problem worse and to encourage their modification. It is important to explain to the patient that the tendency to suffer an attack probably varies because of some cycle changes in the brain which are not well understood. This is why avoiding some things on some days will prevent attacks and, perversely, enjoying them on other days produces no headache. The crucial piece of the puzzle is what the brain is doing – and this is the subject of intense study. Rather than make a long list of things to avoid, patients should first be encouraged to have regular habits and not exceed their limits. Regular sleep, exercise, meals, work habits, and some time for relaxation will be rewarding in terms of lessening headache frequency.

Acute attack therapies

Acute attack treatments for migraine can usefully be divided into:
- disease non-specific treatments, such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs)
- disease-specific treatments, such as ergot-related compounds and triptans (Table 3). It must be emphasised that most acute attack medications seem to have a propensity to aggravate headache frequency and induce a state of refractory daily or near-daily headache, ‘analgesic associated chronic daily headache’. Codeine-containing compound analgesics are a particular problem and require careful monitoring. Not all patients who stop taking regular analgesics will have a miracle cure of their headache, but almost all feel in some way better and are easier to treat with standard preventives (Table 4).

Approaches to treatment

Given the array of options to control an acute attack of migraine, how does one start? In the simplest approach to treatment described as *stepped care*, assuming there are no contraindications, all patients are given the simplest treatment such as aspirin plus an anti-emetic. This is an effective strategy proven by double-blind controlled clinical trials.
In an alternative strategy, known as **stratified care**, the physician determines (or stratifies) and initiates treatment based on the likelihood of response to levels of care. Lipton *et al*\(^1\) have proposed a migraine disability assessment scale (MIDAS). This scale, which is easy to use and freely available, is being tested to see whether it can be used to make treatment decisions. Until data are available from the ongoing studies, however, stepped care with clinical modification seems the most rational approach (Table 5).

**Disease non-specific treatments.** Simple treatments such as aspirin (900 mg) and paracetamol (1,000 mg) are cheap, they can be highly effective and usefully employed in many patients. The addition of domperidone (10 mg po) or metoclopramide (10 mg po) can be helpful, as can NSAIDs when tolerated. The success of the latter is often limited by inappropriate dosing, but naproxen (500–1,000 mg po or pr with an anti-emetic), ibuprofen (400–800 mg po) or tolfenamic acid (200 mg po) can be extremely effective. Tolfenamic acid has been shown in a double-blind placebo-controlled study\(^1\) to have comparable efficacy to sumatriptan 100 mg, which reinforces the general clinical view that NSAIDs can be useful in migraine.

**Disease-specific treatments.** When simple measures fail or more aggressive treatment is required, specific treatments must be used.

**Ergotamine** remains a useful anti-migraine compound, but its place as the first choice has slipped in recent years, a trend which is likely to continue. It should be strictly controlled because ergotamine overuse produces dreadful headache, in addition to many vascular problems. The **triptans** have revolutionised the life of many patients with migraine, and are clearly the most powerful option available to stop a migraine attack. They can be rationally applied by considering their pharmacological, physicochemical and pharmaco-kinetic features, as well as the available formulations\(^6\).

### Table 3. Oral acute migraine treatments.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Ergot derivatives:</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>900 mg</td>
<td>ergotamine</td>
<td>1–2 mg</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1,000 mg</td>
<td>sumatriptan 50 mg or 100 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>naratriptan 2.5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>rizatriptan 10 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>zolmitriptan 2.5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>eletriptan** 40 mg</td>
<td></td>
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</tbody>
</table>

### Table 4. Preventive treatments in migraine.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Selected side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizotifen</td>
<td>0.5–2 mg/day</td>
<td>weight gain, drowsiness</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40–120 mg bd</td>
<td>reduced energy, tiredness, postural symptoms</td>
</tr>
<tr>
<td>Tricyclics:</td>
<td>25–75 mg noce</td>
<td>drowsiness</td>
</tr>
<tr>
<td>amitriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dothiepin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>imipramine</td>
<td>25–75 mg</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** 1–1.5 mg/kg body weight is usually required for a response, but some patients are very sensitive and may need a total dose of only 10 mg.

<table>
<thead>
<tr>
<th>Valproate</th>
<th>400–500 mg bd</th>
<th>drowsiness, weight gain, tremor, hair loss, fetal abnormalities, haematological and liver abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methysergide</td>
<td>1–4 mg/day</td>
<td>drowsiness, leg cramps, hair loss, retroperitoneal fibrosis</td>
</tr>
</tbody>
</table>

**Note:** a one-month drug ‘holiday’ is required every 6 months.

* Often used with anti-emetic/prokinetics (eg domperidone 10 mg or metoclopramide 10 mg)

** Expected to be available in Europe in 1999.

NSAID = non-steroidal anti-inflammatory drug.

Commonly used preventives are listed, together with reasonable doses and common side effects. The [British National Formulary](http://www.bnf.org) should be consulted for detailed information.
Preventive treatments

The decision to start a patient on some form of preventive treatment requires input from both doctor and sufferer. From a medical viewpoint, the basis for considering it is a combination of acute attack frequency and attack tractability. Attacks unresponsive to acute attack medications are obvious candidates for prevention, while easily treated attacks may be less obvious. The other part of the equation relates to what is happening over time. If a patient diary shows a clear trend for increased frequency, it is better to start early with prevention rather than wait for the problem to become intractable. A simple rule for frequency might be the following:

- 1–2 headaches a month: there is usually no need to start a preventive treatment
- 3–4 headaches a month: it may be needed, but not necessarily
- 5 or more a month: prevention should definitely be discussed.

Options available for preventive treatment are included in Table 4.

Cluster headache

Cluster headache is a rare form of primary headache with a population frequency of 0.1%. It is perhaps the most painful condition that affects people, and should be managed if possible by a neurologist. Its core feature is periodicity, be it circadian or in terms of active and inactive bouts over weeks and months (Table 2). The typical cluster headache patient is male (male to female ratio 3:1), with 1–2 attacks of relatively short duration unilateral episodes of pain every day in bouts of 8–10 weeks a year, but who is usually perfectly well in between these bouts. Patients with cluster headache tend to move about during an attack, pacing, rocking or even rubbing their head for relief. The pain is usually retro-orbital, boring and very severe. It is associated with red or watering eyes, running or blocked nose, and eyelid droop on the same side as the pain. Cluster headache is likely to be a disorder involving central pacemaker regions of the posterior hypothalamus, and is related to a group of similar headaches, trigeminal-autonomic syndromes, which share central nervous system loci of dysfunction and many clinical features.

Management of cluster headache

Cluster headache is managed with acute attack treatments and preventive agents. The latter are usually required by all cluster headache patients at some time, while preventives can be almost life-saving for these patients, and are often needed to shorten the active periods.

Acute attack treatments

Cluster headache attacks often peak rapidly, and thus require a treatment with quick onset. Although not a new treatment, many patients with acute cluster headache respond well to oxygen inhalation. This should be given as 100% oxygen at 10–12 l/min for 15 min. It seems important to have a high flow and high oxygen content. Injectable sumatriptan has been a boon for many patients, with cluster headache; it is effective and rapid in onset, with no dose benefit over 6 mg and no evidence of tachyphylaxis. Sumatriptan is not effective when given pre-emptively, and as a placebo-controlled study is ongoing.

Preventive treatments

The options for preventive treatment in cluster headache depend on whether the patient has the episodic or chronic variety of the condition (Table 6). Most experts now favour verapamil as the first-line preventive treatment, though limited courses of oral corticosteroids or methysergide can be useful for some patients with the episodic variety and short bouts.
Verapamil has been suggested as a useful option for a decade and compares favourably with lithium. Clinical practice has clearly shown that higher doses need to be used than initially considered – certainly higher than those used in cardiological indications. Most patients start on doses as low as 40 mg twice daily, but doses up to 720 mg daily and higher are now employed. Side effects, such as constipation and leg swelling, can be a problem, but the issue of cardiovascular safety is more difficult. Verapamil can cause heart block by slowing conduction in the atrioventricular node, as demonstrated by prolongation of the A–H interval. Given that the PR interval on the ECG is made up of atrial conduction, A–H and His bundle conduction, it may be difficult to monitor subtle early effects as the dose of verapamil is increased. It needs to be studied in this group of patients, but for the moment it seems appropriate to do an ECG at baseline, and repeat it 1–2 weeks after a dose change, usually 80 mg increments, when doses exceed 240 mg/day.

Chronic daily headache

Perhaps no clinical issue in headache provides as much controversy, or as substantive a medical load, as that of daily headache. It is certainly not all simply tension-type headache (Table 7). Population-based estimates of daily headache demonstrate that 4.5–4.8% of the populations in Spain, the USA and the UK have daily or near daily headache (RB Lipton; personal communication). Daily headache may be primary or secondary, and it seems clinically useful to make this distinction when making management decisions. Population-based studies bear out clinical practice in that a large group of refractory daily headache patients overuse various over-the-counter preparations.

### Chronic daily headache and migraine

It is widely accepted that some of the primary headaches, tension-type headache, cluster headache and paroxysmal hemicrania, have chronic varieties, but this question is unresolved for migraine. Few headache authorities would argue that migraine can never be chronic in terms of frequency, but it is a vexed issue whether patients with frequent headache, some of which fulfills standard criteria for migraine and some for tension-type headache, have a single migrainous problem in biological terms.

According to the population-based surveys quoted above, about two-thirds of daily headache patients have chronic tension-type headache and about one-third satisfy the Silberstein-Lipton criteria for transformed migraine. The philosophy behind transformed migraine, a term coined by Mathew, is that some patients who inherit a migrainous biology end up with chronic headache. The typical patient will have daily headache of a dull, non-specific type, punctuated by more severe attacks which often, in isolation, fulfill standard criteria for migraine. This group is dominant in headache specialty clinics, about 90% of patients in referral headache clinics having transformed migraine, usually with analgesic overuse. They may have a biologically more difficult problem, which is the basis for their over-representation in referral centres. If it is accepted that all other forms of primary headache have chronic counterparts, particularly the quintessentially episodic primary headache, cluster headache, having frequent migraine is not such a difficult concept, and perhaps frequent migraine should simply be called chronic migraine, by analogy with the other primary headaches.

Treatment of frequent headache with migrainous features requires control of analgesic or ergotamine overuse and instigation of preventive treatments. It is exceptional for a patient with medication misuse to be successfully treated with preventives unless these medications are stopped. The most useful preventives are tricyclics, valproate and...
Headache may be considered as primary or secondary in terms of causality.

The most common severe primary headache is migraine, affecting 12% of the UK population.

On the basis of current understanding of the pathophysiology, both migraine and cluster headache may be regarded as neurovascular headaches, not simply as vascular headaches.

Non-pharmacological management of migraine consists mainly of lifestyle advice, so that sufferers can avoid situations in which attacks will be triggered.

Preventive treatments for migraine should usually be considered on the basis of attack frequency, particularly its trend to change with time, and tractability to acute care.

Acute care treatments for migraine can be divided into non-specific (general analgesics, eg aspirin, NSAIDs) and treatments specific to migraine (ergotamine, the triptans).

The triptans, sumatriptan, naratriptan, rizatriptan, zolmitriptan and eletriptan, potent 5HT1B/1D receptor agonists, are major advances in the treatment of acute migraine.

Chronic daily headache in association with analgesic overuse is probably the major avoidable cause of headache in the UK.

monoamine oxidase inhibitors. Comorbidity with depression is common in migraine, so appropriate management of depression is important. Hospital admission and treatment with a course of intravenous dihydromeglitamine can be an effective way to break the cycle of persistent headache.

Acknowledgments

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References

29. Hardebo JE, Dahlöf C. Sumatriptan nasal spray (20 mg/dose) in the acute
The concept of dementia has evolved over the last decade from one of progressive global intellectual deterioration to a syndrome of progressive impairment in memory and at least one other cognitive deficit (aphasia, apraxia, agnosia or disturbance in executive function), in the absence of another explanatory central nervous system disorder, depression or delirium (DSM–IV). However, even this concept is inadequate as researchers and clinicians become more aware of specific cognitive profiles of different dementia syndromes. For instance, in early Alzheimer’s disease (AD) there may be isolated memory impairment for several years before progression, and in the frontotemporal dementia (FTD) memory impairment may appear late in the disease. Accurate diagnosis is essential for patient advice and management. Early detection will become increasingly important with the advent of disease modifying treatments.

If a treatment slows progression of dementia, it should be administered at the earliest stage possible. This review summarises some recent developments, focusing on the common neurodegenerative dementias. The relative frequencies of the different causes of dementia change with the age of onset, are illustrated in Fig 1(a) and (b).

Alzheimer’s disease

AD is the commonest cause of dementia. The earliest deficits involve