

# Migraine

## What is migraine?

Migraine is a severe form of headache which can last from a few hours to 72 hours or longer. Symptoms are very variable, but five stages are recognised:

- the *prodrome*, when there may be mood variations and changes in gut activity;
- the *aura* - a short-lived period of visual disturbances such as changing patterns of flickering lights;
- severe *headache*, aggravated by light and sound, that may be accompanied by nausea or vomiting;
- *resolution*, as the headache declines and deep sleep may occur;
- the *postdrome*, when the patient feels fatigued and lethargic.

A wide range of factors can precipitate an attack, such as bright and flickering and fluorescent lights, TV and movie viewing, excessive noise, certain foods, menstruation, disturbed sleep pattern, and smoking. Stress and/or underlying depression are also important trigger factors.

Approximately one-fifth of migraine sufferers experience aura, the warning associated with migraine, prior to the headache pain. Visual disturbances such as flashing lights and blind spots begin from twenty minutes to one hour before the actual onset of migraine. There have been many theories proposed to provide a mechanism for migraine, mostly involving some aspect of blood flow or neurological patterns in the brain.

Aura was once thought to be caused by constriction of small arteries supplying specific areas of the brain. Meanwhile, it is clear that aura is due to transient changes in the activity of specific nerve cells. These nerve cells trigger the trigeminal nerve to release chemicals that irritate and cause swelling of blood vessels on the surface of the brain. These vessels send pain signals to the brainstem, an area that processes pain information.

The pain of migraine is typically felt around the eye or temple area. Once the attack is full-blown, many people will be sensitive to anything touching their head. Activities such as combing their hair or shaving may be painful or unpleasant.

## Who does migraine affect?

Migraine headaches are thought to affect about eight per cent of the European population, with twice as many women affected as men. This means that some 40 million European citizens suffer from various forms of migraine. The vascular headache is most commonly experienced between the ages of 15 and 55, and 70-80 per cent of sufferers have a family history of migraine.

Genetic epidemiological twin studies have demonstrated a significant heritability for migraine, with more than 60 per cent of liability to migraine coming from addi-

**Migraine is a severe form of headache. It makes life a misery for millions of people. The pharmaceutical industry has developed many products to treat it. Increased understanding of migraine could lead to other effective treatments. Future advances could further relieve the misery and increase the quality of life in patients suffering from migraine.**



tive genetic factors. However, although family and twin studies show that there is a genetic component, no genes predisposing to common forms of the disease have been identified.

#### **Present treatments:**

Many products are available for migraine, some for prevention (prophylaxis) and others to treat an ongoing attack. *Prophylactic* agents include beta blockers, serotonin (5HT)-antagonists (partly with antihistaminic effects), and a central alpha-agonist. Though useful, some of these have side effects.

Therapy for an acute attack most often involves analgesics for mild to moderate attacks, or a non-specific 5HT receptor agonist for more severe attacks, perhaps combined with an anti-emetic for feelings of nausea. However, in the last decade, five selective 5HT<sub>1</sub> receptor agonists, known as 'triptans', have been introduced and have quickly taken a leading position in migraine therapy.

The first of these was originally given by injection, but is now available in oral and nasal spray forms as well. Other triptans are now available, partly also in non-tablet forms that dissolve in the mouth without water. The triptans are thought to act by contracting dilated blood vessels in the brain, but may also constrict the coronary arteries and are therefore not suitable for people with hypertension, coronary heart disease or kidney or liver impairment.

There is still a huge unmet need in migraine prophylaxis. Migraine presents a big problem amongst neurology out-patients. The WHO, in its chart of comparative disability, places a day with migraine at the same severity as a day with quadriplegia. Current standard treatment relies on acute therapy, which is taken at the first sign of the disease to reduce the severity and duration, but these treatments become less effective with long-term use.

#### **What's in the development pipeline?**

Further triptans are in clinical development with a longer duration of action. Further highly selective triptans are being tested in clinical trials. Studies are also in progress to extend the indications of some currently approved triptans and to find new formulations such as intranasal sprays. New medicines in development mainly act in different ways from triptans.

Several research groups are conducting trials in the prevention of migraine with medicines which have already been indicated for other uses, such as molecules for the treatment of insomnia, schizophrenia and mania in bipolar disorder. Investigators are studying a melatonin receptor agonist with both high affinity for melatonin MT<sub>1</sub> and MT<sub>2</sub> receptors and selectivity over the MT<sub>3</sub> receptor.

Nitric oxide (NO) may be involved in migraine headaches, and a benzopyran derivative that inhibits nitric oxide release is currently in clinical trial. Furthermore, it has been found that anti-epileptic medicine may be efficacious for the prophylaxis of migraine. Another research project is exploring the feasibility of prophylaxis with a glutamate receptor antagonist.

In the past 25 years dopamine research has shown that dopamine plays a significant role in the pathogenesis of the disease. The literature indicates that migraineurs are hypersensitive to dopamine agonists with respect to some of the premonitory symptoms such as nausea and yawning. Genes of the dopamine system are also candidates for involvement in migraine. Therefore, scientists are trying to find out whether functional genetic variation in the dopamine transporter acts as a risk factor for migraine. There is also research ongoing on non-specific dopamine D<sub>2</sub> receptor antagonists to demonstrate their clinical efficacy in migraine.

Currently, treatments are classified as preventive or acute-attack therapies, although it is expected that this distinction will become blurred over time. A gap-junction blocker which acts by inhibiting the abnormalities of brain function thought to underlie the development of migraine attacks, an inducible nitric oxide synthetase (NOS) inhibitor and *botulinum* toxin A are all being investigated in clinical trials as preventive therapies. Calcitonin gene-related peptide receptor (C GRP) antagonists, vanilloid TRPV1 receptor antagonists and NOS inhibitors are all being investigated in clinical trials for acute migraine.

C GRP is a vasoactive peptide that contributes to the neurogenic inflammation seen in migraine. C GRP itself has been shown to trigger migraine-like headache and levels of this peptide in the cranial circulation are increased during a migraine attack. These findings point to the potential utility of C GRP receptor antagonists as therapeutics. Indeed, clinical proof-of-concept in the acute treatment of migraine has already been demonstrated with intravenous C GRP receptor antagonists. Meanwhile, oral forms of C GRP receptor antagonists are in early clinical development.

### **The longer-term future:**

Although the therapeutic options for migraine are becoming more abundant, understanding of the mechanisms involved in a migraine attack is still limited, and it seems likely that approaches will continue to be discovered to meet continuing clinical needs in this common disorder.



### **DISCLAIMER**

EFPIA has made all reasonable efforts to include accurate and up-to-date information in this PDF, but cannot guarantee completeness or accuracy of the information. You must consult your doctor, or other qualified healthcare professional on any specific problem or matter covered by the information in this PDF. The "Medicines for Mankind" publications are made available on condition that no part of the publications (including photographs) may be reproduced or abstracted without prior agreement with the European Federation of Pharmaceutical Industries and Associations (EFPIA). Under no circumstance can any of the material included in this PDF be used in promotional material and/or campaigns.

Editing Board: Dr. Robert Geursen (Chief Editor), Peter Heer, Bill Kirkness, Philippe Loewenstein, Steve Mees, Dr. Jean-Marie Muschart, Marie-Claire Pickaert (Coordinator).

Photocredits: ABPI, Allergan, AstraZeneca, EFPIA/Lander Loeckx, Damian Foundation, Galderma, Hilaire Pletinckx, Roche, sanofi-aventis; Design & Production: Megaluna

Last update: June 2008