# Migraine headaches: A brief overview

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## Abstract

This article aims to provide a concise, high-level overview of the classification, management and treatment of migraine. Migraine is a common, debilitating neurological disorder that is characterised by the presence of severe headaches, which may last anything from a few hours to a few days (4–72 hours). Thus, the condition is characterised by episodes of severe migraine headache, frequently accompanied by nausea and vomiting. These headaches may be unilateral or bilateral and patients may also experience a range of associated features. Acute attacks require rapid, abortive treatment and the rate of recurrence needs to be reduced and managed through the use of effective prophylactic measures.

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## Introduction

According to the International Headache Society, a migraine is a headache that lasts for 4–72 hours and presents with at least two of the following symptoms: unilateral localisation, moderate to severe pain intensity, aggravation by movement, and a pulsating feeling. The headache is also usually accompanied by nausea, vomiting, photophobia (sensitivity to light) and phonophobia (sensitivity to sound).[1] Migraine headaches are usually classified according to two major subtypes, namely migraine with an aura, and migraine without an aura.[2] Migraine is considered to be chronic when it occurs for a minimum duration of four hours per day, and lasts for more than 15 days per month, within a three month period.[3] Chronic migraine is frequently associated with the so-called medication-overuse-headache.[4]

A migraine headache is usually preceded by a premonitory phase that lasts for hours before the headache begins. This phase is characterised by fatigue, mood changes and gastrointestinal problems, which could persist throughout the entire migraine attack. One in five 'migraineurs' (i.e. people who suffer from migraine) also experience an aura, which consists of visual, sensory or motor disturbances. The aura phase is followed by actual headache and this, in turn, is followed by a recovery phase, or postdrome (also referred to as a 'migraine-hangover'), characterised by fatigue and continued sensory disturbances.[1,5]

## Pathophysiology

Migraine headaches have a controversial pathophysiology. The most widely acceptable pathophysiological process involves the activation and sensitisation of the trigemino-vascular system (TVS).[6] When the TVS is activated, the signal travels through the trigeminal ganglion to the neurons in the trigemino-cervical complex, with calcitonin gene-related peptide (CGRP) as the main neurotransmitter.[7] CGRP is a potent vasodilator, produced in the central and peripheral neurons, that has been implicated in the transmission of pain signals and is released during severe migraine attacks.[8]

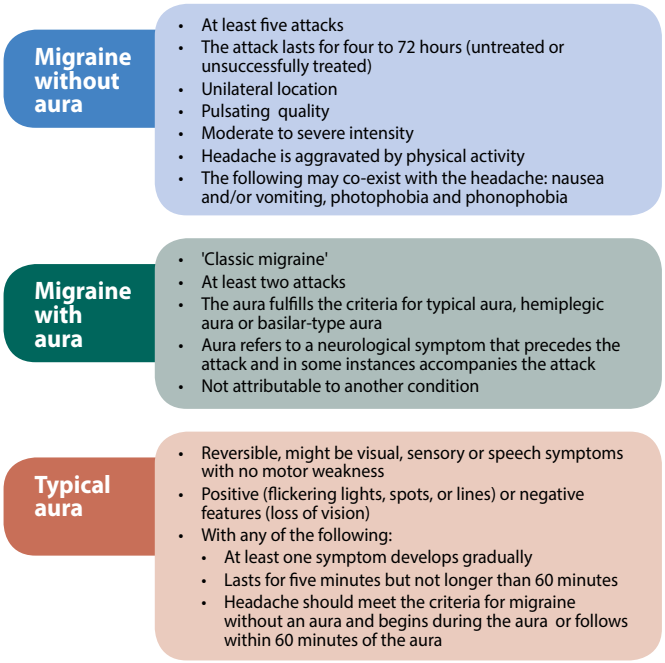


**Figure 1.** Subtype classifications of migraine (International Headache Society)

## Classification

Migraine is usually classified as having two major subtypes, namely migraine with an aura, and migraine without an aura. Additional subtype classifications are depicted in Figure 1.

## Diagnosis

The diagnosis of migraine is made based on the clinical presentation or symptoms of the patient, and by excluding other causes of frequent headaches.[9] In many cases the pain experienced during migraine attacks occurs on one side or one half of the head (i.e. unilaterally).[10] The pain is described as severe and is accompanied by nausea and/or vomiting, hypersensitivity to light, sound and odour.[7]

According to Carol-Artal (2014), chronic migraine diagnosis relies on the International Classification of Headache Disorders (ICHD-3) beta criteria because there are no biological markers for chronic migraine.

**Table I.** International Classification of Headache Disorders diagnostic criteria for migraine (adapted from Weatherall, 2015)

| |
|---|
| 1. At least five attacks fulfilling criteria 2–4 |
| 2. Headache attacks lasting 4–72 hours |
| 3. Headache has at least two of the following four characteristics:<br>a. Unilateral location<br>b. Pulsating quality<br>c. Moderate or severe pain intensity<br>d. Aggravation by or causing avoidance of routine physical activity |
| 4. During headache at least one of the following:<br>a. Nausea and/or vomiting<br>b. Photophobia and phonophobia |
| 5. Not better accounted for by another ICHD-3 diagnosis |

## Pharmacological management

### *Migraine prevention*

Migraine attacks can range from moderate to severe pain and may be preceded by other symptoms. The migraines can change from being episodic to being chronic. Although episodic migraine can remain unchanged for years, there is also the likelihood that they could remit or develop into a situation whereby they may be classified as chronic, with an increasing severity and frequency of headaches per month. When the headaches do become chronic, it would be highly advisable to look at the migraineur in question and individualise preventative migraine therapy. According to Diener et al (2015), these drugs will, on average, reduce migraine frequency by 50% in about 40–45% of patients; however, compliance and adherence are poor because of their many adverse events.

Studies have provided support for the use of a number of drugs for the prevention and treatment of migraine, even though many of the drugs used for prophylaxis of migraine attacks are prescribed off-label. Drug classes for migraine prevention are described below.

### *β-blockers*

The following beta-blockers have proven efficacy in this setting: atenolol, metoprolol, nadolol, propranolol and timolol.[2] Use of these drugs should be carefully monitored in patients who exhibit undesirable adverse effects and switched to a different class, such as the antiepileptics (e.g. valproic acid).

### *Antiepileptics*

Several antiepileptics have shown increasing potential in migraine prevention. Treatment options include carbamazepine, valproate, gabapentin, topiramate and lamotrigine.[2] In this class, topiramate is one of the most effective therapy options to consider in patients with chronic migraine.

### *Other*

Calcium-channel blockers (verapamil), angiotensin II-receptor antagonist inhibitors (candesartan), antidepressants (amitriptyline and venlafaxine).[2]

### *Botulinum toxin A*

Onabotulinum toxin A is classified as a neurotoxin, which is primarily a product of the anaerobic bacterium, *Clostridium botulinum*. The toxin appears to exert its mechanism of action by inhibiting the release of nociceptive mediators involved in the pathogenesis of migraine. These include substance P, CGRP and glutamate; it inhibits these nociceptive mediators from the peripheral termination of primary afferents.[4] In the two randomised clinical trials that the drug has undergone it was evident from the data collected that onabotulinumtoxin A is a safe, well-tolerated, and effective prophylactic treatment in patients suffering from chronic migraine.[3] Even though this drug is not yet registered in South Africa, it shows potential and could be one of the mainstay therapies for treating chronic migraines.

### *Classes and examples of chronic migraine prophylactic agents*

**Table II.** The classes and examples of drugs that are used in the prevention of migraines in South Africa according to Shellack and Shellack (2013)

| Class | Examples |
|---|---|
| Beta-blockers | Atenolol<br>Metoprolol<br>Nadolol<br>Propranolol<br>Timolol |
| Antiepileptics | Carbamazepine<br>Valproate<br>Gabapentin<br>Topiramate<br>Lamotrigine |
| Calcium-channel blockers | Verapamil<br>Candesartan |
| Angiotensin II receptor antagonist inhibitors | Candesartan |
| Antidepressants | Amitriptyline<br>Venlafaxine |

## Managing acute attacks

Weatherall (2015) mentions that acute migraine attacks should be treated early when the pain is still mild. According to Roceau, Antochi and Bajenaru (2015), current guidelines recommend non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and paracetamol for the treatment of acute mild to moderate migraine attacks. Many of the drugs used for the treatment of acute migraine attacks are also used for treating chronic migraine.[9]

Ergot alkaloids, such as ergotamine, are 5-HT-receptor agonists and also bind to α-adrenoceptors and dopamine receptors. Their use has been reduced since the arrival and introduction of the triptans.[4] Their use has also been declining due to their unwanted side-effects, inconvenience and a high likelihood for causing medication-overuse headaches.[2]

Sumatriptan was specifically formulated for the treatment of acute migraine attacks. It has a high specificity for the serotonin receptors 5-$HT_{1B}$ and 5-$HT_{1D}$. This mechanism of action produces cerebral vasoconstriction, secondary to their inhibition of calcitonin gene-related peptide (CGRP) and inflammatory peptide release.[2] The triptans are most effective when they are taken when the pain is mild to moderate.[8] There are a few more triptans that have been introduced for use in South Africa, including zolmitriptan, naratriptan, rizatriptan and elitriptan.[2]

The concomitant use of other agents that increase serotonin levels, such as the SSRIs and the serotonin-noradrenaline reuptake inhibitors (SNRIs), should be avoided due to the danger of developing serotonin syndrome. The triptans should also be avoided in patients with a history of ischaemic heart disease, cerebrovascular disease and uncontrolled hypertension.[11,12]

A novel, highly-selective 5-HT1F-receptor agonist with a seemingly good cardiovascular safety profile, namely lasmiditan, is currently in clinical development. Two CGRP antagonists have also shown promise during clinical development, olcegepant and telcagepant. The latter has, however, been discontinued due to safety concerns.[13,14]

**Table III.** NSAIDs used for acute migraine treatment (adapted from Weatherall 2015)

| NSAIDs | Dosage |
|---|---|
| Paracetamol | 1 g |
| Aspirin | 900–1200 mg |
| Ibuprofen | 400–800 mg |
| Naproxen | 250–500 mg |

**Table IV.** Triptans used for acute migraine treatment (adapted from Weatherall 2015)

| Triptan drugs | Dosage |
|---|---|
| Sumatriptan | 50–100 mg orally, 10–20 mg nasal, 6 mg subcutaneously |
| Almotriptan | 12.5 mg |
| Eletriptan | 40–80 mg |
| Frovatriptan | 2.5 mg |
| Naratriptan | 2.5–5 mg |
| Rizatriptan | 5–10 mg, s/l melt |
| Zolmitriptan | 5–10 mg orally, s/l melt, 5 mg nasal |

## Conclusion

Migraine headaches are commonly encountered in the clinical practice setting. Patients suffering from migraine have to endure an often-debilitating neurological disorder, with frequent attacks of severe headache that require acute, abortive treatment. The recurrence of these episodes may also be markedly decreased through the use of effective preventive measures, including the use of prophylactic medication. The pharmacist may play a vital role in the effective management of migraine through the promotion of a better understanding of the correct and effective use of migraine treatment options, as well as the reduction and management of associated risk factors and behaviours.

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