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## REVIEW ARTICLE

# UPDATE IN DIAGNOSIS AND TREATMENT OF MIGRAINES

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**ABSTRACT**

**Background:** Headache disorders are among the most common pain disorders of the nervous system. Half to three quarters of the adults aged 18–65 years in the world have had headache in the last year and among those individuals, more than 10% have reported migraine.
**Aim:** To explore the updates of migraine diagnosis and treatment.
**Methods:** Systemic review of PubMed filter finds publications to support keywords of the current study. **Findings:** A psychological evaluation is usually not a routine diagnostic method in headache diagnosis. However, it is recommended for patients who suffer from a stress factor triggering their headaches. Blood chemistry and urine analysis including tests for several new compounds targeting 5-hydroxytryptamine, neuropeptide, and other receptors are under examination. The changes in treating acute attacks of migraine have produced better understanding and classification of the pharmacology of 5-hydroxytryptamine and provide impetus for improving the classification of headache. CT scans are also used in diagnosis, if CT is normal, then the indication for lumbar puncture and MRI. Migraine therapy ranges from the use of simple analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen to triptans, antiemetics, or the less commonly used dihydroergotamine. Abortive treatments are usually more effective if they are given early in the course of the headache; a large single dose tends to work better than repetitive small doses.
**Conclusion:** Migraine is a common, chronic, incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, new diagnostics approaches and treatment modalities were declared.



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## INTRODUCTION

Pain, according to the International Association for the Study of Pain, is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (1). Nociceptors are high-threshold sensory receptors of the peripheral somatosensory nervous system that are capable of transducing and encoding noxious stimuli (2). Pain transmission is a consequence of complex peripheral and central operations. These processes can be modulated at different levels of the nervous system via different pathways (3). Headache disorders are among the most common pain disorders of the nervous system. Headache is a painful and disabling feature of a small number of primary headache disorders (occurring for no obvious reason, not the result of any other underlying disease or process) namely migraine, tension-type headache and cluster headache (4). Headache can also be caused by or occur secondarily to a long list of other conditions, for example medication overuse headache or inflammation of intracranial tissues (4,5). According to the World Health Organization (WHO), it has been estimated that prevalence among adults of current headache disorder (symptomatic at least once within the last year) is 47%. Half to three quarters of the adults aged 18–65 years in the world have had headache in the last year and among those individuals, more than 10% have reported migraine. Headache on 15 or more days every month affects 1.7–4% of the world's adult population. Despite regional variations, headache disorders are a worldwide problem, affecting people of all ages, races, income levels and geographicalareas (6). Although less common than tension type headache migraine affects more than 10% of the world's population, causes substantially more individual morbidity, and creates a significant socioeconomic burden on the individual and society. Migraine prevalence in women far exceeds that of men in adulthood, with female to male ratios of 2.8:1, peaking at 3.3:1 between age 40 and 45 years (6,7). The female predominance is maintained in the postmenopausal age group, albeit slightly less at 2:1. Prior to puberty, migraine prevalence is higher in boys than in girls. Because of migraine impact on everyday life, the current study

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aimed to assess the pathophysiological mechanisms and the clinical relevance of migraine headache, new diagnostic methods, and treatment (6,8,9). The current study aimed to explore the updates of migraine diagnosis and treatment.

**Anatomy of the nociceptive system in the cranial region**

According to the Headache Classification Subcommittee of the International Headache Society, migraine is considered a neurovascular disorder that is characterized by a severe, debilitating and throbbing unilateral headache, and can be associated with nausea, vomiting, photophobia, phonophobia and diarrhea (10). Most of the intracranial tissues does not contain nociceptors. However, intracranial blood vessels: in the dura mater including major sets of vessels such as the middle meningeal artery, or blood vessels of the circle of Willis at the base of the brain are supplied with sensory nerves and receptors that respond to any thermal or mechanical stimuli (11). An understanding of the sensory innervation of pain sensitive intracranial tissues is essential in order to understand the pathophysiology of intracranial pain that occurs in migraine.

**Nociceptors of the peripheral tissues**

Nociceptors respond to noxious stimuli that can produce tissue damage. Mechanical, chemical, or thermal nociceptive stimulation will recruit peripheral nociceptors that conduct the nociceptive signal towards the central nervous system. Thermal or mechanical nociceptors are free nerve endings of finely myelinated A-delta afferent fibers and respond to extreme temperature and mechanical stimuli such as sharp, pricking pain sensation. Polymodal nociceptors are free nerve endings of unmyelinated C-fibers and respond to high-intensity mechanical or chemical stimuli and hot or cold temperature (12). In the head region the trigeminal nerve is the primary source of nociceptive neurons. Sensory terminals of the trigeminal nerve innervate both extra and intracranial tissues. The sensory innervation is provided by all the three branches of the trigeminal nerve: by the ophthalmic-, maxillary- and mandibular branches. Although in the pain sensitive intracranial structure dura mater encephalialso thicker, myelinated A-beta nerve fibres have been identified, pain was the only sensation that could be induced by applying different stimuli to the exposed dura mater (13).

**Primary sensory neuron of the nociceptive pathway**

Primary sensory neurons are pseudounipolar cells. In the somatic sensory system their cell bodies are localised in the dorsal root ganglia, in the trigeminal system in the trigeminal ganglia (Gasserian ganglia) that occupies a cavity (Meckel's cave) in the dura mater, covering the trigeminal impression near the apex of the petrous part of the temporal bone (14). Nociceptors release their transmitter substances upon stimulation. Many of the neurons contain the excitatory glutamate. Significant populations of sensory nerves contain also vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), substance P(SP) and neurokinin A (NKA). Most of these peptidergic nerve fibers are closely associated with blood vessels in the pain sensitive intracranial structures (e.g. dura materencephali)(15,16). Previous studies have shown that a significant number of meningeal sensory nerves are chemosensitive; a type of sensory ganglion cells that is morphologically, neurochemically and functionally distinctand which expresses the transient receptor potential vanilloid 1 (TRPV1) receptor(19). Activation of TRPV1 receptors on these sensory neurons is implicated in the release of the vasoactive neuropeptide content of sensory nerves which may play a significant role in the local regulatory mechanisms of the innervated tissue(17). The chemosensitive primary sensory neurons are small-diameter neurons with thinly myelinated A-delta or unmyelinated C-fibres. The TRPV1 receptor is a member of the family of transient receptor potential ion channels(18). TRPV1 receptor is also known as the capsaicin receptor. It is a protein encoded by the TRPV1-gene and it has six transmembrane domains and a short, pore-forming hydrophobic stretch between the fifth and sixth domains. The receptor is activated by a wide variety of exogenous and endogenous physical- and chemical stimuli (low pH, heat above 43°C, capsaicin, resiniferatoxin and the so-called endovanilloids(19,20,21).

Chemosensitive primary afferent neurons have a dual function. On one hand, they transmit nociceptive impulses towards the central nervous system and, on the other hand, by the release of different neuropeptides from their peripheral nerve endings they induce local effector responses. Activation of the TRPV1 receptors of chemosensitive neurons initiates the release of vasoactive peptides, CGRP, SP and NKA from the peripheral nerve terminals(20,22).The neuropeptide CGRP is formed in the alternative splicing of the calcitonin/CGRP-gene located on chromosome 11. CGRP functions as a potent vasodilator and transmitter in nociception. It acts on a G-protein coupled receptor, calcitonin receptor-like receptor (CALCRL), when linked with a protein called receptor activity-modifying protein (RAMP1) which produces the CGRP-receptor (22,23). SP and NKA are neuropeptides belonging to the group of tachykinins responsible for neurotransmission and neuromodulation of inflammation and nociception(24). They increase the permeability of postcapillaryvenules in the affected tissue. Apart from their involvement in the initiation and maintenance of the neurogenic inflammation, CGRP and SP are also implicated in the degranulation and activation of mast cells leading to the release of histamine(25). This causes additional vasodilation through the activation of H1- and H2-receptors of arterial blood vessels(26). Nociceptor endings can be also sensitized in the inflamed tissue by inflammatory mediators. Sensitized nociceptors may respond to stimulus intensity that was previously not noxious or painful(27,28).

**Second order neurons in the nociceptive pathway**

As the nociceptive endings are activated in the peripheral tissue by noxious stimuli, and the transmitter substances are released, a transmission of nociception takes place through the myelinated and unmyelinated fibres towards the spinal cord and the trigeminal subnucleuscaudalis(29). Nociceptors of the somatosensory system form synapsis in the spinal cord with specific second order nociceptive neurons. Their cell bodies are located in the Rexed laminae I and II. These neurons are activated exclusively by mechanical or thermal nociceptive stimuli. The axons of these specific nociceptive neurons combine to form the spinothalamic tract(29). The second type of neurons is known as non-specific neurons, and their cell bodies are located in Rexed lamina V of the spinal cord. These neurons respond to nociceptive stimuli preferentially but not exclusively. They are known as wide-dynamic range neurons, because they can be activated by nociceptive and non-nociceptive mechanical stimuli as well (29,30). The trigeminal nerve consisting of the central processes of trigeminal primary

afferents enter the brain stem at the pontine level and projects to a sequence of sensory nuclei called the trigeminal brain stem nuclear complex (TBNC). The TBNC is composed of the principal sensory nucleus (Vp) and the spinal trigeminal nucleus (Vsp).It has long been recognized that part of the Vsp is primarily responsible for processing nociceptive and temperature information from the face and head, whereas the Vp is involved in processing tactile information. Nociceptive regions of Vsp has a very similar histological layering to Rexed laminae in the spinal cord, where lamina I corresponds to the marginal layer and lamina II to the substantia gelatinosa (22,30).

**Ascending trigeminal pathway**

The second order spinal trigeminal afferent axons decussate and form the ventral trigeminal lemniscus contralateral to their cells of origin. They ascend in the ventral trigeminal lemniscus as crossed second order spinal trigeminal afferents. They travel with afferents that leave the ventral trigeminal lemniscus as trigeminoreticularfibers, which terminate in the brain stem reticular formation (30). They travel also with afferents that leave the ventral trigeminal lemniscus as trigeminomes encephalicfibers, which terminate near the midbrain periaqueductal gray. They terminate in the ventral posteromedial nucleus (VPM) and in the intralaminar nuclei of the thalamus (Figure 1)(31).

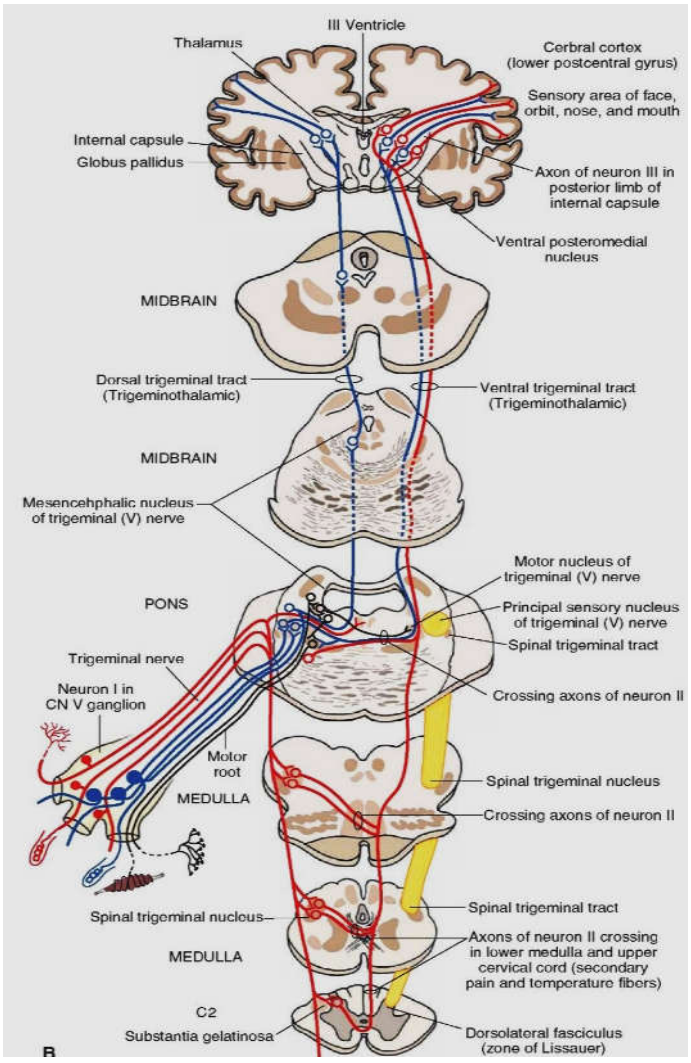


**Figure 1. Trigeminal pathway**

**Thalamic nuclei processing trigeminal information**

Multiple thalamic nuclei process information in the pathway. The VPM processes sharp pricking pain. The intralaminar nuclei process other poorly localized sensations of dull, burning pain, deep, aching pain, temperature and crude touch(32).

**Cortical areas involved in processing of nociceptive information**

The spinal trigeminal pathway terminates in multiple cortical areas. The third order VPM axons end in the primary somatosensory cortex, which provides for accurate localization in the face area of the source of the sharp, pricking pain. The intralaminar nuclei axons terminate in the cingulate gyrus and insula of the cerebral cortex, which provide for poorly localized sensations of dull and aching pain, temperature and crude touch(33).

**Pathophysiology of the trigeminal nociceptive system**

**Peripheral sensitization of primary sensory neurons**

Peripheral sensitization is an acute, chemical-induced form of functional plasticity of neurons, which converts high-threshold nociceptors into low-threshold sensory neurons. This form of sensitization occurs when the nerve terminals (e.g. meningeal nociceptors) of the neurons of the trigeminal ganglion are soaked with inflammatory mediators (prostaglandin E2, bradykinin, serotonin and cytokines) along the vasculature of the cerebral dura mater. Peripheral sensitization in migraine attacks is explained clinically by intracranial hypersensitivity (the headache worsens during coughing or physical activity) and by a throbbing element in the pain of migraine (sensitized nociceptors become hyperresponsive to the otherwise innocuous and unperceived rhythmic fluctuation in intracranial pressure produced by normal arterial pulsation) (34).

**Central sensitization of the nociceptive pathway**

The essence of central sensitization is that the second-order neurons in the trigeminocervical complex become hyperexcitable. The altered behavior of the second-order neurons is based on the increased glutamate sensitivity of the NMDA receptors and the neuronal nitric oxide synthase activity stimulated by nitric oxide. This process is explained clinically by face and scalp allodynia and by neck stiffness (extracranial tenderness), symptoms occurring sometimes parallel with headache attacks (35).

**Cortical spreading depression as correlate of migraine aura**

About a third of migraine patients complain of transient focal aura symptoms beginning from minutes to hours before headache, or occurring during either the headache phase or in its absence. Description of migraine with aura from the year 1870 onwards has reported a slow, gradual progression of aura symptoms (36). In 1941, Lashley (37) suggested that aura symptoms reflect a cortical process progressing with a speed of 3 mm/min across the primary visual cortex.Cortical spreading depression (CSD) was first described by Aristides Leao in 1944(38). Studying experimental epilepsy for his PhD thesis(39), Leao came across a depression of electroencephalographic (EEG) activity moving through the

rabbit cortex at a rate of 3–6 mm/min after electrical or mechanical stimulations. The negative wave was sometimes preceded by a small, brief positivity, and always followed by a positive overshoot of 3–5 min. CSD is a slowly propagating wave of neuronal and glial depolarization lasting a few minutes that can develop within the cerebral cortex or other brain areas after electrical, mechanical or chemical depolarizing stimulations. CSD is considered as the neurophysiological correlate of migraine aura(40). It is characterized by massive increases in both extracellular K+and glutamate, as well as rises in intracellular Na+and Ca2+. These ionic shifts produce slow direct current potential shifts that can be recorded extracellularly. Moreover, CSD is associated with changes in cortical parenchymal blood flow. CSD has been shown to be a common therapeutic target for currently prescribed migraine prophylactic drugs(41). Additionally, CGRP antagonists have been recently reported to inhibit CSD, suggesting the contribution of CGRP receptor activation to the initiation and maintenance of CSD not only at the classic vascular sites, but also at a central neuronal level(40,42,43).

leading to pain and vasodilation as illustrated in (Figure 2) (45). Evidence from animal experiments shows that the brain stem is involved in the generation of migraine attacks. During the attacks, increased blood flow was found in the cerebral hemispheres in cingulate, auditory and visual association cortices and in the brain stem. However, only the brain stem activation persisted after the injection of sumatriptanthat induced complete relief from headache and phono- and photophobia. These findings supported the idea that the pathogenesis of migraine is related to an imbalance in activity between brain stem nuclei regulating antinociception and vascular control (46). According to the neural theory, hyperexcitability in the nervous system may lead to activation of the sympathetic system and inflammatory changes in the peripheral tissue(47).

**Vascular theory**

According to vascular theory, vascular disturbance leads to migraine attacks through activation of the trigeminal sensory system. This theory has been established by Wolff in the

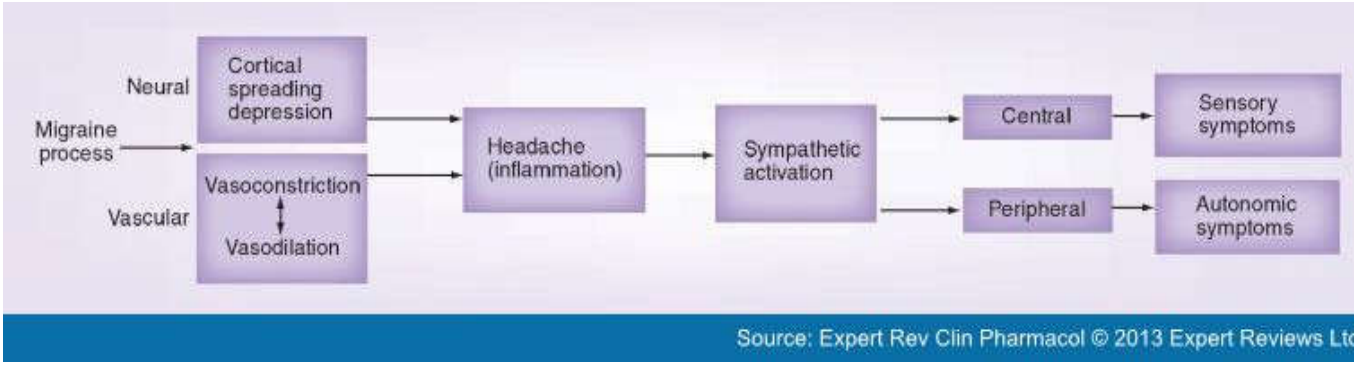


**Figure 2. An overview of the path mechanisms of migraine headache**

**Pathophysiology of migraine**

According to the International Headache Society's International Classification of Headache Disorders, migraine is classified into two major subtypes(44):

Migraine with aura (MA) accounts for 20% of the migraine cases, it is unilateral and is associated with prodromal aura which precedes by 10-30 minutes of neurological symptoms. The premonitory phase is usually associated with an increase in emotional sensitivity, difficulty in reading and speaking and sensitivity of the sensory system. The most characteristic features of the migraine aura are the visual symptoms (blurred vision, sparkle or flashes), confusion, vertigo and loss of consciousness which all can be reversed. Migraine without aura (MO) which accounts for 80% of the migraine cases, starts with the premonitory phase and many patients suffer vague symptoms preceding the attack.The attack can last 4 to 72 hours. The frequency of the attacks can be variable.Many patients are hypersensitive to sensory stimuli during headache attacks.

The pathophysiology of migraine is still not completely clear. However, aura phase is characterized by the cortical spreading depression that is accompanied by vasoconstriction, followed by vasodilation with local edema formation in the affected tissue. It was suggested that in migraine patients the spreading of the cortical depression will stimulate the nerve cells and release several endogenous substances that cause inflammation

1940s and it is believed that attacks are initiated by vasoconstriction of the intracranial blood vessels and cause reduction of blood flow, and this reduction may initiate the aura phase.

As a compensatory mechanism vasodilation of the blood vessels occurs as a result of inflammatory reaction in the tissue. Eventually this leads to triggering migraine headaches. The stimulation of the trigeminal sensory nerves that are found around the dilated intracranial blood vessels leads to development of pain(47,48).

**Neural theory**

This theory states that migraine is an episode of neurological disorder with paroxysmal symptoms. This attack is triggered by hyperexcitability of the cortical or brain stem neurons and the transition to CSD (49). Nowadays the so called "neurovascular" mechanism as the pathophysiological mechanism in the background of migraine is discussed. It assumes both neural and vascular changes leading to complex activation of the ascending trigeminal nociceptive pathway and changes in intracranial blood flow (49,50).

**Thephases of a migraine attack**

Migraine attack is an extraordinary complex brain event that takes place over hours to two-threedays. It starts gradually and

the individual passes from one phase to the other.33Itis convenient to describe the phases of a migraine attack in 4 phases (51):

1. The premonitory phase
2. Aura phase (in migraine with aura)
3. Headache phase
4. Postdrome phase

**The premonitory phase**

The first symptoms of an attack are premonitory that occur up to hours before aura and headache (52). A better understanding of this phase gives also an important window of opportunity for the acute therapy of headache patients. The most commonly reported symptoms preceding headache are fatigue, irritability, difficulty with concentrating, mood swings, yawning, neck stiffness, photophobia and nausea. Other symptoms includechanges in appetite, food craving, bloatedness, and changes in facial expression. Some of these symptoms appear and dissipate before the headache phase, whereas another may build up in intensity leading up to the headache, occur during the headache phase and persist well beyond the resolution of the pain. Several of these symptoms that have been described in the premonitory phase also occur in the postdrome phase, which raises several questions regarding the nature of the trigger of migraines. While bright light, loud sounds, strong smells are identified as migraine triggers,patients usually have a baseline difference in sensory sensitivity that could make them susceptible to these triggers (51,52,53).Current hypotheses regarding the premonitory symptoms have been involved in the study of the neurotransmitter dopamine (54).One supporting evidence includesthe observation that exogenously administrated dopamine receptor agonist produces some of the symptoms that are experienced by migraine patients in the premonitory phase like yawning, nausea, drowsiness and lightheadedness. Administration of dopamine receptor antagonist which reverses some of the symptoms and prevents the occurrence of subsequent headache, showed greater efficacy when it was given (up to 12 hours) before the forthcoming headache (55).But, the dopaminergic mechanism in the premonitory phase is only one component of a complex neurochemical cascade (56).Another hypothesis regarding the premonitory phase of the migraine is the role of the hypothalamus. There are widespread changes in the brain excitability that occur preceding a headache. The symptoms involve changes in mood, appetite and energy. Positron emission tomography shows an increase in the blood flow to the hypothalamus during the premonitory phase of a migraine attack (57). These specific hypothalamic mechanisms and findings represent a good target for therapy that could be administered before headaches take place. For example, there are specific hypothalamic peptides that may represent a new therapeutic target in migraine known as orexin, which have shown a relationship between sleep quality and migraine (58). Orexin regulates the sleep-awake pattern in humans and recent clinical studies have shown promisingresults in orexin antagonist restoring sleep architecture, in which sleep is considered to be an important factor for alleviating pain associated with migraine (57-60).

**The aura phase**

Migraine aura is a distinctive phase of headache. Studies on animals have shown that CSD activates nociceptive mechanisms. The majority of patients have reported headache, photophobia and phonophobia within the same 15-minutetime frame they have begun to experience the aura symptoms and this suggests that the pain and the other symptoms in the migraine aura may run in parallel, occurringat the same time rather than a direct stream consequence of the aura (61). A study based on single-photon emission computed tomography (CT), PET and magnetic resonance tomography (MRI), demonstrated dramatic changes in blood flow of both hemispheres during the aura phase. It also highlighted significant changes in the metabolism during the migraine aura phase in which both increased and decreased perfusion occurs. However, a CT and MRI study has shown that during the onset of the aura the hypoperfusionoccurs first, followed by hyperperfusion during the aura phase (62).

**The headache phase**

It is considered to be the most critical phase of the migraine attack, not only affecting the head, but the entire body. The attack can range from mild to severe, occurring at any time of the day. It is usually unilateral which can be shifted from one side to the other. If the migraine persists for approximately 72 hours, then it is called “status migrainosus” and may require medical attention. The pain getsgenerally worse by doing any kind of physical activity (63).

**The most common symptomsof the headache phase are (64):**

1. Unilateral throbbing headache
2. Nausea and vomiting
3. Photophobia, phonophobia
4. Neck pain
5. Diarrhea and constipation
6. Dizzinessand vertigo
7. Depression and anxiety

There have been a few imaging studies focusing on the vascular changes that occur during migraine attacks. Scientist Schoonman and his colleagues (65), could not find any significant dilation in the middle meningeal artery during migraine attack. Contrary to this, scientistsAsghar *et al*. (66) have found a noticeable dilation in both middle meningeal artery and middle cerebral artery when using CGRP for inducing the symptoms. Administration ofsumatriptan resulted a less painful headache as well as contraction of middle meningeal artery. Novasoconstriction could be observed in the middle cerebral artery. This latter finding makes it difficult to ascertain if the dilation of the blood vessels plays any role as a cause of pain or is a pathophysiologicalmechanismoccurring parallel with headache.Sensory hypersensitivity in migraine patients can be due to the inflammatory reaction of the trigeminal nerve, which causes pain around the eye, sinuses and the jaw. Furthermore, photophobia, phonophobiaand allodynia are considered to be symptoms generated by the activation of central nociceptive mechanisms (67).

**The postdrome phase**

After headache attack the majority of patients have following symptoms (68):

- Tiredness and weakness.
- Cognitive difficulties and mood swings.

- Residual head pain and lightheadedness.
- Gastrointestinal upset.

Some patients may think these symptoms are the adverse effects of the acute medication, but it is actually part of the headache attack (69).

**Risk factors of migraine**

Migraine is considered as a chronic recurrent disorder that might progress in some patients. There are risk factors which may provide a base for aggressive intervention which are divided into non-remediable and remediable categories (70,71) (Table 1).

**Table 1. Risk factors of migraine**

| Non-remediable | Remediable |
|---|---|
| Age | High frequency of attacks |
| Low education status | Medication overuse |
| Low socioeconomic status | Caffeine addiction |
| Head injury | Obesity |
| | Snoring |
| | Stressful life events |

The remediable risk factors are consideredessential for intervention to change the natural progression of the migraine and so preventing it from reaching a chronic stage (72).

**High frequency of attacks**

The prevalence of chronic migraine is higher in first degree relatives of individuals with chronic migraine. One of the most important factors for progression of headache or migraine from being episodic into chronic type is the number of headache days at baseline or who experienced threeor more headaches per month(73).

**Medication overuse**

Symptomatic medication overuse is considered as poor prognosis for migraine. There have been many studies investigating the relationship between chronic use of medication and chronic daily headache(74). For instance:

**Barbiturates:** chronic daily use up to 5 days can lead to migraine progression, and is more pronounced in females.

**Triptans:** they will induce migraine progression in individuals with a high frequency of migraine baseline about 10-14 days per month.

**Opiates:** exposure to high dose of opiates for about 8 days per monthcan progress the migraine, and is more common in men.
Antiinflammatories: are not considered as overuse in those cases when they are taken less than 10 days long.

**Caffeine addiction**

It plays a role in transforming the episodic headache into a chronic type. Sudden withdrawal of caffeine consumption in individuals who suffer from chronic migraine rebound headaches can be induced(75). It is important to note that caffeine is found not only in coffee but also in tea, soft drinks and some medication.

**Obesity**

The relationship between headache and obesity are complex and not very well understood. Obesity is known for its proinflammatory, prothrombotic state and the increase in the amount of adipose tissue and macrophages. The latter two also participate in the inflammatory process by releasing cytokines, interleukin 6 and tissue necrosis factor-α (TNF-α) also C-reactive protein(76).Plasma CGRP concentration has been foundincreased in obese patients especially in females. Individuals with body mass index (BMI) higher than 30 have five times greater risk developing migraine than people with a normal BMI.Peoplewith a BMI rangeof 25-29 have a threefold risk(77).

**Sleep apnea and snoring**

There have been many studies on the relationship between snoring, breathing disorders, sleep disorders and progression of headache. Breathing disorders are strongly associated with cluster type headaches. A cross-sectional study of more than 3000 Danish men, indicates that snoring is associated with at least one type of headache and this study was independent of weight, age, hypertension and other sleep disturbances (78).
Since snoring is considered an independent risk factor for headache, lifestyle changes should be considered forthose who snore andare obese. It is recommended for obese individualsto lose weight and quit smoking, and for those who are addicted to alcohol to reduce their alcoholconsumption. As for the pharmacological point of view, if the patient is suffering from nasal congestion, should be treated with nasal decongestion or steroid spray. In obstructive sleep apnea, the best treatment option is continuous positive airway pressure. In addition, Mandibular advancement devices hold the lower jaw and tongue forward, making a space to breathe and prevent snoring(79,80).

**Psychiatric disease and stressful life events**

There have been few cross-sectional studies to assess why patients who suffer from chronic migraine are more likely to have depression and anxiety symptoms. According to a recent study, chronic migraine is more common in women with major depression disorder(81). All patients with migraine should be screened for depression and their intervention should be targeted toward non-pharmacological and pharmacological techniques. A non-pharmacological approach is via cognitive-behavioral therapy focusing on relaxation techniques, also raising awareness in patientsto therole of thoughts generated by stress and resulting headaches(82).

**Diagnosis of headaches**

**Differential diagnosis of migraine**

Headache is considered as one of the most common symptoms in neurology practice. The differential diagnosis of this highly prevalent symptom is vast. There are over 300 different headache types and aetiologies(83). In 2004, the International Headache Society formulated the headache classification with diagnostic criteria for a broad range of headache disorders. These criteria are based on an international consensus of experts and have been endorsed by the World Health Organisation and incorporated into the International Classification of Diseases(84,85).

- Established a uniform terminology and consistent diagnostic criteria.
- Facilitated epidemiologic studies and multinational clinical trials.
- Provided the basis for current research and treatment guidelines.

In order to establish the type of headache a careful examination and the taking of medical history should be done(86). The following criteria help to distinguish between migraine and other types of primary headaches:

**Tension type headache**

**Special symptoms of tension type headache include:**

- Pressure or tightness around both sides of the head or neck
- Mild to moderate pain which is steady and not throbbing pain
- The pain does not worsen by any activity
- Over the course of the headache the pain can either increase or decrease
- There might be muscle pain of the head, neck and shoulders

Patients with this type of headache usually go through a stressful event before the headache takes place. Unlike migraine, tension type headache usually has no symptoms such as nausea and vomiting or sensitivity to light or sound, although some patients can have both tension and migraine headache symptoms (87,88).

**Cluster headache**

Defined as severe, debilitating headaches that occur weekly or monthly, can be followed by a headache free period. Men are more commonly affected than women (89).

Symptoms of cluster headaches are (90):

- It starts quickly without any warning.
- It is characterized as deep, excruciating and explosive in intensity.
- The pain begins around the eyeball and the temple.
- Miosis, lacrimation, nasal congestion and forehead sweating.

This type of headache can occur at any age, and is usually associated with a family background (91).

**Differential diagnosis of aura**

Although it is considered a benign and reversible phenomenon, there are a few neurological diseases that may mimic the migraine aura. In elderly people aura can be seen without headache. Patients with vascular disease such as, transient cerebral ischemia (TIA) can exhibit late onset, short duration focal symptoms and negative visual symptoms rather than positive visual symptoms which can be seen in migraine. These patients require further investigation for vascular insult. Patients who have focal epilepsy, particularly in the occipital lobe can exhibit visual hallucination, which can be negative (scotoma, hemianopia) or positive (phosphenes, sparks or flashes), or change in size (macrosopsia, micropsia) or shape (metamorphopsia) (Table 2) (92).

**Table 2. Comparison between migraine and TIA**

| Migraine | TIA |
|---|---|
| Positive visual symptoms | Visual loss |
| Gradual onset | Abrupt |
| Sequential progression | Occurs simultaneously |
| Repetitive attack | |
| Duration of one to 3 hours | Duration is less than 15 minutes |
| Headache phase follows 50% of patients | Headache uncommon |

**Further diseases that may cause a problem in differential diagnosis:**

- Demyelinating disease.
- Carotid artery dissection.
- Venous sinus thrombosis.
- Vasculitis.
- Simple partial seizure.
- Tumor.
- Human Immune Deficiency virus (HIV).

**Table 3. Characteristics of common headache syndromes**

| Symptom | Migraine headache | Tension headache | Cluster headache |
|---|---|---|---|
| Location | Unilateral in 60-70% of patients, occurs on both sides of the forehead or all over the head in 30% of cases | Bilateral meaning involves both sides of the head. | Almost always unilateral, usually begins around the eye or temple. |
| Characteristics | Gradual in onset, builds up over time, pulsating moderate to severe intensity, aggravated by routine physical activity | Pressure or tightness which waxes and wanes. | Pain begins quickly, reaches a crescendo within minutes, is deep, continuous, excruciating and explosive in intensity. |
| Activity | Prefers to rest in a dark, quiet room | May remain active or may need to rest | Remains active |
| Duration | 4-72 hours | Variable | 30 min to 3 hours |
| Associated symptoms | Nausea, vomiting, photophobia, phonophobia, may have an aura phase, but can involve other senses or cause speech or motor problems | None | Tearing and redness of the eye on the same side of the headache, runny nose, pallor, sweating, drooping eye, rarely with neurological deficit. |

**Other types of headaches that may cause differential diagnostic problem**

**Sinus headache:** sinus infection may cause recurrent headaches, but usually it is uncommon. However, those patients may have migraine type headaches. Sinus headaches usually last for several days and do not cause any nausea or vomiting as is the case of migraine (93).

**Post-traumatic headache:** this usually starts one to two days after a head injury. Most people report a generalised dull, aching, constant discomfort that worsens intermittently, vertigo, light-headedness, difficulty in concentrating, problems with memory and irritability (94). The headache may last up to weeks or even months after the trauma (Table 3) (95).

The clinician's diagnosis is basedon the patient's description of the headache andthe examination. Most patients usually do not require X-rays or imaging tests. A CT scan or MRI may be recommended in some circumstances, in the case, for example, of unusual symptoms, or if there areany danger signs or any abnormalities during the examination (96).

**Other possibilities for imaging studies include (97):**

- A headache that is steadily worsening despite treatment.
- Sudden changes in the pattern of the headache.
- Signs and symptoms that suggest that another medical condition may be causing the symptoms.

**Worrisome headache and red flags (98):**

- Systemic symptoms of patients (fever, weight loss) or secondary headache risk factor (HIV, systemic cancer).
- Neurological symptoms or abnormal signs (confusion, impaired alertness, or consciousness).
- Onset: sudden, abrupt or split-seconds.
- Elder patients: new onset and progressive headache. Especially in middle age (giant cell arteritis).
- Previous headache history or headache progression: first headache or different characteristics (change in frequency of the attack, severity or clinical features).

If any sort of activity elicits these features, it is considered as a part of new headache evaluation because their presence may signify an underlying pathological condition that requires further evaluation and imaging studies and it is obligatory to rule out any secondary causes of headache(99, 100). The presence of any systemic symptoms may suggest an infection or systemic inflammatory disorder. In this case laboratory tests can help in the diagnosis of secondary headache (101).The mode of the onset is an important feature, patients with an abrupt or sudden headache require assessment to exclude subarachnoid hemorrhage, arterial dissection or increased intracranial pressure(102). Any progression of headache in a middle-aged patient that changes the pattern should be investigated. A neurological test focuses on excluding any disease of the brain(103). A psychological evaluation is usually not a routine diagnostic method in headache diagnosis. However, it is recommended for patients who suffer from a stress factor triggering their headaches(104).

**Laboratory Investigations and Imaging**

Blood chemistry and urine analysis: Although it is not routinely needed in the evaluation of headaches, it can help in case of suspicion of secondary headache disorder, for example, thyroid function, diabetes, temporal arteritis, viral encephalitis, bacterial meningitis and occasionally when medication is prescribed to the patient then laboratory tests may be necessary (105).

**CT scans:** It is recommended to excludeother conditions, also for the progression of the headache(106).

MRI: To produce the best clear image of the brain without the use of X-rays. MRI is recommended if the patient is suffering from daily or chronic headaches and if the CT scan does not show definitive results or evaluation of certain parts of the brain. The American Academy of Neurology has concluded that CT and MRI are unlikely to significantly increase the diagnostic field, especially in the case of recurrent migraine.This applies to patients whose headache fits a broad definition of recurrent headache with no change of pattern, history of seizure or focal neurological sign(107).

**EEG:** Electroencephalographyis not a standard procedure but can be performed if the clinician suspects seizures, atypical migraine aura or residual focal defects or encephalopathy. According to the American Academy of Neurology it has advanced a rational series of guidelines based upon the available evidence, and has concluded that EEG lacks both sensitivity and specificity and therefore, it is not considered a useful routine in the evaluation of patients with headache(108).

**Lumbar puncture:** If CT is normal, then the indication for lumbar puncture are (109):

- The first unusual headache
- Thunder-scalp headache with negative CT scan
- Sub-acute progressive headache
- Headache associated with fever, confusion, meningitis or seizure
- High or low cerebrospinal fluid pressure suspected (even if papilledema is absent)

There is no formal guideline on the use of the lumbar puncture as a diagnostic test. However, it is critical in a number of conditions and contraindicated in others, such as, with meningoencephalitis or subarachnoid hemorrhage(110,111). Patients who exhibit first headache or thunder-scalp headache should always consider having an acute neurology event, even though many migraines can occur in this manner. If the CT scan is negative a lumbar puncture can be performed in this event. Patients with subacute progressive type of headache, lumbar puncture is recommended to rule out fungal and Lyme disease, inflammation (vasculitis), or neoplasms (carcinomatous leptomeningeal disease)(112).

**The indicationof magnetic resonance and conventional angiography(112,113):**

- Aneurysm (>5mm)
- Arteriovenous malformation
- Arterial dissection
- Venous thrombosis
- Acute subarachnoid hemorrhage
- Vasculitis

Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) are non-invasive methods for visualising the circulation of the craniocerebral region, and useful as a screening procedure for suspected aneurysm or any of the other indications listed above. Otherwise, there is no reason to perform the angiography in patients with headache who have normal neurological examination and normal brain MRI(112).

**Treatment and prevention of migraine**

In order to have an effective management plan there are certain points that need to be addressed(114,115):

- To establishdoctor patient relationship
- To educate the patient about the nature and mechanism of the illness which will encourage the patient to actively participate in the management program.
- To have a treatment plan:
- Know the mechanism of the disorder
- Strategies for identifying and avoiding triggers
- Behavioral management strategies:
- Regular sleep, exercise, meals
- Stress management, biofeedback
- Cognitive behavioral therapy
- Pharmacological management plan:
- Acute therapy
- Preventive therapy

**Strategies for migraine therapy**

A number of medications are available to treat migraine, the choice depends on the severity and frequency of headaches (116-120).

Acute treatment which is initiated during the attack to relieve the pain and to stop the progression of the attack:

a. Nonspecific
   i. Non-steroidal anti-inflammatory drugs (NSAIDs)
   ii. Opioids
   iii. Neuroleptics
   iv. Analgesics
   v. Corticosteroids
b. Specific
   i. Ergotamine/dihydroergotamine
   ii. Triptans
2. The principle of acute treatment:
3. To treat the headache as early as possible in the attack to reduce the intensity and duration of pain.
4. Use correct dose and formulation, especially in patients with nausea and vomiting.
5. The acute therapy is only restricted to 2 or 3 days to avoid the rebound.
6. For patients receiving preventive therapy, provide acute agents to treat breakthrough attacks.
7. If treatment fails, conduct a thorough follow-up investigation to determine the reason for failure.
8. There are three classes of drugs, according to the severity of migraine (121):
9. Mild to moderate
10. Moderate to severe
11. Migraine prophylaxis

In the symptomatic treatment of mild to moderate migraine, nonspecific medication such as NSAIDs are considered to be pain relieversthat are not specific to migraine, and the combination of both analgesics and NSAIDs are usually used to treat mild to moderate acute migraine. Aspirin and acetaminophen have shown some effective results in reducing the pain in some patients. Over the counter analgesics can be used in the management of migraine including ibuprofen and acetaminophen/aspirin/caffeine combination. These agents inhibit lipoxygenase and cyclooxygenase enzymes that produce prostaglandin, which sensitizes nociceptors leading to migraine (121,122). Opioids and barbiturates are not approved therapies because they can be addictive. Nevertheless, barbiturates combined with aspirin are indicated for the treatment of tension type headaches(123).Metocloramide drug is used to treat nausea and vomiting, which are common symptoms of migraine type headaches(124).

**Triptans as the management of migraine**

Triptans are selective serotonin (5-HT1B, 1D) receptor agonists. Triptans are thought to work in three main ways(125):

- Causing peripheral inhibition of CGRP and SP release from the trigeminal nociceptive afferents.
- Modulating the second order neuron centrally in the trigeminal pathway.
- Vasoconstriction of the intracerebral blood vessels.

Alteration of serotonin metabolism has been reported to trigger symptoms of a neurogenic inflammation. Serotonin receptor can be stimulated by triptans so it canreduce vascular reactions induced by the release of sensory neuropeptides from primary sensory neurons(126). Sumatriptanwas first introducedin therapy in Europe in 1991 and helped millions of people who suffered acute attacks of migraine. To this day clinicianspreferthese drugs over all kinds of triptans because of its quick relief of symptoms and because it can be administered parentally, orally and also intranasally(127,128). In the 1960s, Kimball and colleagues(129), intravenously infused serotonin that was successful in alleviating the pain of migraine. In England, a decade later a team of researchers aimed to find a serotonin receptor type that benefits from serotonin administration and they discovered the now known 5-HT1B receptor, which is located in the cranial and not in the peripheral blood vessels. After the discovery of this receptor their objective was to find the drug to produce selective vasoconstriction of cranial vessels after they have been distended and inflamed in migraine. Sumatriptan was the end result of their work, once it is administered parenterally it showed a dramatic effect and was well tolerated in most patients(130). However, during an extensive study serotonin receptor were also found in the coronary arteries, thus, it is contraindicated to administer the drug to people with cardiovascular disease(131). Scientific controversy still remains about triptansand whetherit actually constricts the cranial vessels that are distended and inflamed or whether it inhibits the trigeminal afferent neurons and therefore blocks the pain signaling transmission. In the early 1990s, molecular biology data showed that triptans haveaffinity also to another subtypeof serotonin receptor known as 5-HT1D.This receptor is located in neurons, but in the cranial vascular smooth muscles they are absent(132). Triptans are effective drugs, theyusually relieve painwithin two hours. All different types of the drug can be administered by several different routes; these includeeven subcutaneous injection. Oral tablets and nasal sprays, other types of administration are being considered such as patches(133,134).

Other types of serotonin receptor agonistsused in migraine therapy(135,136,137):

- Zolmitriptan is the secondtriptan drug available in the US, and is more lipophilic than sumatriptan, absorbed 50% more rapidly, has a longer half-life, has an active metabolic rate and achieves pain-free results within 1 to 2 hours.
- Rizatriptan is designed to be fast acting, and achieve pain free results within two hours, also patients prefer

this drug because of the high consistency of efficacy due to the faster relief.

- Naratriptan is the third triptan drug available for treating acute migraine, and is different from the first drug sumatriptaninthat it has a longer half-life, itis more lipophilic and has a higher bioavailability, unfortunately it is less effective and has a slow onset of action, so as a result it takes longer than 2 hours to have effect.
- Almotriptanisthe new drug which is rapidly absorbed, with a longer half-life and higher bioavailability, known also for its low probability of drug to drug interaction, and has lower adverse events. It is metabolised in three ways:
  1. Monoamine-mediated oxidative deamination
  2. Cytochrome P450 3A4-mediated oxidation
  3. Flavin mono-oxygenase.
- Frovatriptan has the longest half-life among all triptan drugs, about 26 hours, and lessdrug to drug interaction, is also metabolised by both liver and kidney where its excretion also takes place. Frovatriptan needs more than 2 hours to relieve the pain, thus, making it similar to naratriptan in its characteristic of slow action. However, this drug has shown to be beneficial in treating menstruation related migraine, as prophylaxis starting 2 days before the onset of the menstrual bleeding.

**Ergotalkaloids: dihydroergotamine (DHE)**

They were the first anti-migraine drugs available, DHE is one of the ergotamine analogues and can be administered as a nasal spray or by injection, rectal suppositories or sublingual tablets. The ergot alkaloidsare considered to be non-specific serotonin receptor agonists and vasoconstrictors. Their pharmacological effect is direct stimulation of the cerebral vascular smooth muscles, its precise mechanism is still not clear, it is probably the interaction with the serotonin receptors(138).The indication is only restricted for patients suffering moderate to severe migraine. This drug taken in combination with caffeine, is less effective than triptan for acute migraine and not used for chronic daily management of vascular headache. These days'ergotamine is less used owing to triptan availability. Although, ergotamine may still be used in the case of status migrainosus (type of headache that tends to cause more than just pain, it is considered as a medical emergency, the pain could last up to 72 hours or even more). Ergotamine are contraindicated in peripheral vascular diseases, hypertension, impaired hepatic or renal function and pregnancy because of the teratogenic effect. It may cause uterine contraction, fetal distress, gastrointestinal atresia and miscarriage. Also about 10% of patients have nausea and vomiting symptoms as a side effect of the drug(139,140).

**Migraine prophylaxis (preventive therapy)**

Physicians consider administering prophylactic drugs if the patient is having intermittent migraine headaches (more than 15 days a month). Patients should receive prophylaxis(141, 142):

- If the migraine attacks disrupt their life
- When the frequency of the attack increases and makes the patient use acute treatment more often so in this case, puttingthem under the risk of medication overuse.
- Should be considered in patients with greater than three moderate to severe headache days per month, also for patients with greater than 8 headache days a month.

Prophylactic therapy is considered to be effective when the frequency of headache is reduced by 50% or even more, and when the intensity and duration is reduced (142).

**Principles of management(143):**

- Always start treating with a low dose and gradually increase over a period of time
- Continue using the drug for at least 2 to 3 months at therapeutic dose before deciding the effectiveness
- Warning the patients about the adverse effects
- Establish a management plan

We know five approved preventive medications for migraine (144):

- Propranolol
- Timolol
- Divalproex sodium
- Topiramate

In case of any contraindication of one of these drugs, there are various categories of preventive medication (144,145,146):

- β-blockers: these are effective for migraine prevention, the common side effects are lethargy, hypotension and sleep disorder, it is contraindicated in asthma patients, bradycardia and congestive heart failure. Most common drugs are: propranolol, atenolo and timolol.
- Calcium channel antagonists: are verapamil, flunarizine, nimodipine and nifedipine. Constipation is considered one of the most common side effects of the drugs.
- Antidepressants:it is much more useful in patients with co-existing depression and tension type headaches, because the use of antidepressants to treat migraine alone may make it worse. The four major types of antidepressants are:
- Monoamine oxidase inhibitor (MAOI)
- Selective serotonin re-uptake inhibitors (SSRI)
- Serotonin norepinephrine re-uptake inhibitors (SNRI)
- Tricyclic antidepressants (TCA)
- Anticonvulsants (membrane stabilizer): they are frequently used and the most common drugs are sodium valporate, topiramate. It is contraindicated during pregnancy because of the possibility of neural tube defects. Topiramate should not be taken by patients with kidney stones.
- Nonsteroidal anti-inflammatory drugs: these should be carefully taken as they may cause medication overuse.
- Miscellaneous preventive treatment: Botox (botulinum toxin type-A) injection can be helpful for migraine patients.
- Herbal, vitamins, minerals, riboflavin, butterbur and coenzyme Q10, although all have low side effects.

**Migraine during pregnancy and lactation**

It is best to avoid drugs during this period if possible, first trying the non-pharmacological approach such as, diet, and hydration, avoid triggering factors, and have regular meals and modify lifestyle. It is safe for pregnant women to take magnesium as prophylaxis for migraineand beta blockers (147,148).

**Conclusion**

Migraine is a common, chronic, incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, new diagnostics approaches and treatment modalities were declared. A psychological evaluation is usually not a routine diagnostic method in headache diagnosis. However, it is recommended for patients who suffer from a stress factor triggering their headaches. Blood chemistry and urine analysis including tests for several new compounds targeting 5-hydroxytryptamine, neuropeptide, and other receptors are under examination. The changes in treating acute attacks of migraine have produced better understanding and classification of the pharmacology of 5-hydroxytryptamine and provide impetus for improving the classification of headache. CT scans are also used in diagnosis, if CT is normal, then the indication for lumbar puncture and MRI. Migraine therapy ranges from the use of simple analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen to triptans, antiemetics, or the less commonly used dihydroergotamine. Abortive treatments are usually more effective if they are given early in the course of the headache; a large single dose tends to work better than repetitive small doses.

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