

# **National Consensus on Diagnosis and Treatment of Primary Types of Headaches**

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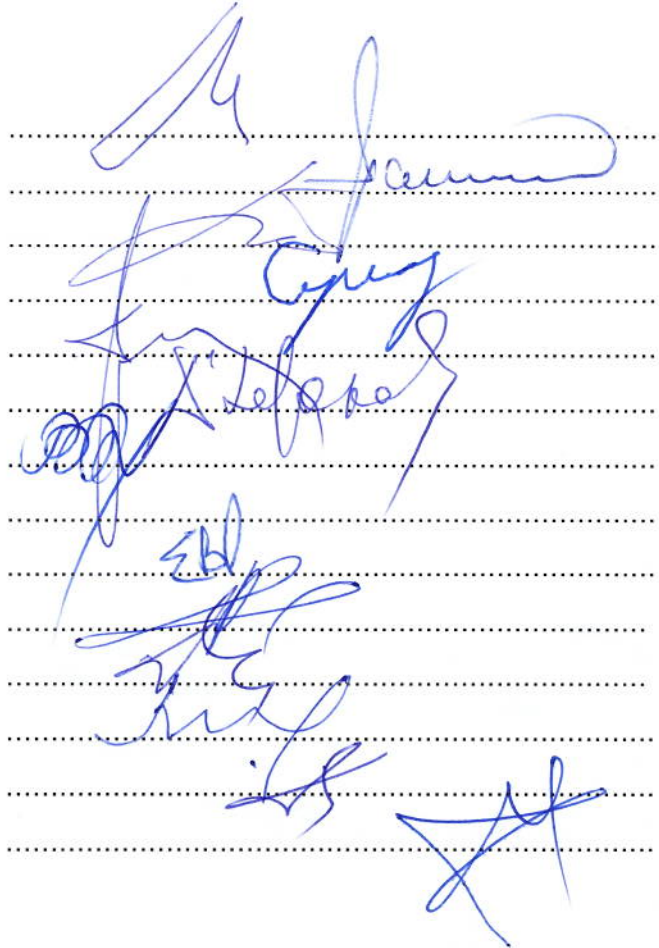
At the initiative of the Bulgarian Headache and Pain Society

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## National Consensus on Diagnosis and Treatment of Primary Types of Headache

Today, 11.04.2023, we, the undersigned experts, have reached a consensus on the diagnosis and treatment of the primary types of headaches:

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The image shows a series of horizontal dotted lines, each corresponding to a name in the list to the left. Blue ink signatures are written across these lines. The signatures are highly stylized and cursive. The first signature is at the top, followed by several others that are more densely packed. The final signature is a large, distinct star-like shape at the bottom right.

Headache is the most common complaint that patients report during their visits to various medical specialists. In many cases it is a symptom of a neurological, mental or somatic disease. In the third edition of the International Classification of Headaches (Cephalalgia, 2018), primary and secondary headaches caused by other diseases are differentiated, and in these cases the treatment is directed to the underlying disease.

**Primary headaches** include migraine, tension headache, and trigeminal autonomic cephalalgia. Primary headaches include a group of other primary headaches that are clinically heterogeneous, occurring less frequently and for which there hasn't been enough research. These include primary cough headache, exercise headache, associated with sexual activity headache, the thunderclap headache, cold-stimulus headache, also external -pressure headache, stabbing, nummular, hypnic headache and new daily persistent headache.

**Secondary headaches** include examples that are attributed to: trauma or head and neck damage, cranial and/or cervical vascular disease, non-vascular intracranial damage, administration of a substance or its withdrawal, infection, homeostasis disorder. Headache or facial pain attributed to disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial and cervical structures, mental illnesses, painful cranial nerve lesions and other facial pains and other headaches.

**Epidemiological** studies show that about 51% of the population (56% of women and 39% of men) suffers from primary headache, with patients often having two or more different types of headache. The prevalence of migraine in the male population is about 6%, and in the female population it is 3 times higher and reaches 18%. On average, the disease rate is 10-14%. Cluster headache is rare and can be found in 0.07 to 0.4% of the population, and it is 4-6 times more common in males. Episodic tension-type headache occurs in 80% of the population. Chronic headache occurs less frequently in 40% of people. The tension headache is slightly more common in women than in men, at a ratio of 1.16:1.

**The pathophysiological mechanisms** of the onset, modulation, and duration are the same for all types of headache. They are associated with depolarization and activation of nociceptive neurons of the cranial nerves (trigeminus, vagus, glossopharyngeus) or the upper cervical spinal cord roots. The activation is caused by a mechanical, chemical or inflammatory stimulation of nociceptors. After the occurrence of the nociceptive affection, there is no difference according to the stimulus that causes it.

**The diagnosis** is based on a detailed description of the headache using the International Headache Society (IHS) criteria of 2018. Before the final diagnosis and initiation of the treatment is done, the patient should present a headache diary. In it, for a

period of at least a month, they should have marked the days with a headache, the duration and intensity of the pain (weak, moderate, strong) and the hours of the day with the strongest headache.

A thorough **case history** with a description of the characteristics of the headache is most important for the diagnosis, especially in patients with more than one type of headache:

- Does the patient have headache for the first time? Primary headaches are old and show the same characteristic over time. The biggest challenge is making the diagnosis in patients with headaches that have started last month. The new headache may have been present from before, but now it could have changed its characteristics. Changes only in the frequency and strength of an old headache does not make it a new one.
- How old was the patient when it started (what is its duration)? The duration of the headache directs to a chronic or malignant disease. Acute headache, especially in the presence of neurological symptoms, requires urgent and in-depth clarification.
- Under what circumstances has it started?
- At what time of day does it begin?
- How long does it last?
- Its relation to the menstrual cycle, puberty, pregnancy and menopause.
- Frequency.
- Localization of pain.
- The characteristics of pain.
- Accompanying symptoms
- What medications has the patient taken, in what doses and what was their effect?

**Diagnostic methods** or tests specific to diagnosing are not available. The disease is diagnosed by strict compliance with the criteria presented for the various headaches. Paraclinical examinations help to rule out secondary headaches.

- **Laboratory tests** include full blood count, ESR (to exclude temporal arteritis over 45 years of age), biochemistry and urine testing. When tested, antinuclear antibodies, thyroid hormones, prolactin and serology are examined.
- **Neuro-imaging brain studies** are conducted after consulting with a neurologist and in a suspicion of secondary headache.
  - *X-ray* is performed in case of a suspicion of a cervical pathology or pathology of the temporomandibular joint in patients with a tension type headache. X-ray data on cervical spondylosis are rarely a cause of headache.
  - *Computer tomography* (CT) is conducted in case of a suspicion of space-occupying lesion in the brain, such as an abscess, hydrocephalus, cerebral

edema, stroke, or hemorrhage. CT cannot detect brain aneurysms, but they rarely cause headaches before rupturing. The indications for CT are the presence of associated neurologic signs or symptoms, a recent headache and a change in the character of a headache that occurred a long time ago.

- Magnetic Resonance Imaging (MRI) allows an earlier visualization of pathology of the brain. It is indicated in patients with a suspicion for a space-occupying lesion in the posterior cranial fossa (not visualized well with CT) and the spinal cord, as well as a demyelinating process. MRT angiography is indicated for the identification of small aneurysms and cerebral vasculitis.

- **Ultrasound methods** for the examination of the nervous system (non-doppler, doppler and duplex) are applied in case of a suspicion of secondary headache. The patient is referred to this examination by a neurologist.
- **Neurophysiological examinations** (EEG, evoked potentials, TMS) show altered cortical excitability, during a headache attack and also between the attacks, when there is no headache. These non-specific changes, as well as the abnormalities in the EEG, found in approximately 20% of patients, are of no diagnostic value. Neurophysiological examinations may have diagnostic value to exclude secondary headaches. The judgment is conducted by a neurologist.
- **Biopsy** of the temporal artery is performed in cases of suspected temporal arteritis.
- **Lumbar puncture** is necessary in case of suspicion of increased intracranial pressure, granulomatous inflammation such as sarcoidosis, meningeal malignant involvement, Lyme disease, cryptococcal infection and tuberculosis.
- **An ophthalmological examination** is required in case of suspicion of acute glaucoma and for possible correction of the refraction.

**The working capacity** in 15% of the patients during a headache attack is reduced and they are absent from work. Patients with migraine cannot work on an average of 2-6 days a month. The tension type of headache impacts the working capacity less than migraine, where the headache attacks are severe. However, there is also a big social significance of the tension type of headache, as it occurs more often.

In a large percentage of the cases, patients are self-medicating, mostly with analgesic drugs, which may lead to developing a new type of headache or a significant worsening of their pre-existing headache. On the other hand, one-third of the patients either have never visited a doctor or discontinued visits very soon because of the insufficient effect of the treatment. Physicians themselves do not always have the necessary knowledge and experience to diagnose and adequately treat these types of headaches, and often patients

are unnecessarily sent to the hospital for diagnosing by conducting a number of unnecessary tests and examinations that add more cost.

**Differential diagnosis** of the headaches involves primarily differentiating primary from secondary headaches. To differentiate secondary headaches, the so-called 'red flags' are of immense importance: an acute headache that is unusually severe or worsens within 24 hours, headaches starting at the age of 50+, progressive development, change in the pattern of an existing headache, self-provoking or suddenly triggered by physical effort, fever, general or neurological symptoms. The presence of 'red flags' requires the use of diagnostic methods for the differentiation of the underlying disease.

Secondly, a differential diagnosis is made between the various primary headaches.

# Migraine

## Definition

- Migraine is an idiopathic chronic disease characterized by attacks of recurrent headache lasting 4-72 hours. Typically, it is presented with one-sided localization, pulsating pain, moderate or severe in intensity, augmented by routine daily activity and accompanied by nausea, vomiting, photophobia and phonophobia.

**Pathophysiology** is associated with increased cerebral excitability due to abnormalities in calcium membrane channels and secondary vascular changes. Particularly important is the initial activation of the trigeminovascular system by a wave of depolarization (neuronal and glial hyper-excitement) in the cerebral cortex that causes the aura. Distributed coronary depolarization (depression) causes changes also in the brain blood flow, oligemia occurs, lasting from 2 to 6 hours, following the velocity and direction of the wave. Local release of neuropeptides (substance P, neurokinin A and calcitonin gen-related peptide - CGRP) results in vasodilation and aseptic neurogenic inflammation of the dural and meningeal blood vessels. Vascular changes mainly affect small blood vessels and are epiphenomenon caused secondary by the neurogenic mechanisms. Expansion and aseptic inflammation of the dural vessels is under serotonergic control. 5-HT<sub>1B/1D</sub> receptor agonists suppress the release of neuropeptides and discontinue vasodilatation, sterile inflammation and headache.

**Classification** includes basically two types of migraine - without aura and with aura. It is also subdivided into episodic and chronic. When the attacks are more than 15 per month (at least 8 of them typical migraine) for more than 3 months, there is a chronic migraine. There are also different *variations*. The variations of migraine with aura are: typical aura with migraine headache, typical aura without headache, migraine with brainstem aura, hemiplegic migraine and retinal migraine. Periodic syndromes in childhood, migraine precursors include: recurrent gastrointestinal disorders (cyclic vomiting, abdominal migraine), benign paroxysmal vertigo and benign paroxysmal torticollis in childhood. Migraine complications include status migrainosus (a migraine attack lasting over 72 hours), persistent aura without cerebral infarction, migrainous infarction, and migraine aura-triggered seizures. In 10% of women, migraine occurs primarily during the menstrual cycle and is typically without aura. These attacks are of longer duration and are accompanied by marked nausea. *Menstrual migraine* is defined as attacks that occur only 2 days before menstruation until the third day of the menstrual cycle. A diagnosis can be made based on history of a headache in two of three menstrual cycles. It can be defined as menstrual

migraine without aura, menstrual migraine with aura or menstrual associated migraine (headache occurs also outside the menstrual cycle) with and without aura.

The **clinically** complete migraine attack occurs in four phases: prodromes, aura, headache and accompanying symptoms, postdromes.

Prodromes are observed in 60-90% of patients, hours or 1-2 days before the attack, more often in migraine without aura. The most common symptoms are anxiety (46%), neck stiffness, phonophobia (42%), photophobia, irritability (42%), yawning, (30%), mood disorders (depression or euphoria) and appetite, insatiable desire for chocolate consumption, fatigue, drowsiness, nausea, blurred vision, yawning, paleness and other autonomic symptoms.

*Aura* is a complex of focal neurological symptoms that precede and rarely accompany the headache. It is observed in 15-20% of patients, but even these patients have aura before some of the attacks. The most common (in 90%) is the visual aura. Next in terms of frequency are sensory disturbances, expressed in pins and needles, which spread unilaterally in the body, face and tongue. Less often, speech impairment (aphasia) occurs. In each patient, during different attacks, all three types of aura can occur, both individually and sequentially. Symptoms of a brainstem aura may also occur that if associated with muscle weakness, the disease is defined as a hemiplegic migraine that has different genetic and pathophysiological characteristics.

*The headache* is usually frontotemporal, unilateral. Only in 15% of patients the pain is always on the same side. The severity of the pain is different in each attack and in the various patients. *Allodynia* appears in advanced stages of the attack in 80% of patients. It is due to the central sensitization of the trigeminovascular neurons in the spinal trigeminal nuclei. Cranial autonomic symptoms can also be added.

*Postdromes* occur in 80% of patients and last from several hours to 2 days. The most common manifestations are asthenia, tightness of the neck, fatigue, somnolence and difficulty in concentrating.

*Trigger factors* are those external factors that cause a migraine attack in 65-95% of patients within 48 hours of occurrence. They may not cause a direct attack but increase their monthly number. Several trigger factors have been identified: stress, mental tension, anxiety, depression, hormonal factors (menstruation, ovulation, anovulatory medications), change in lifestyle (sleep, eating), weather changes, switching to other time zones, sensory stimuli (light, noise, odors), diet, alcohol (especially champagne, white and red wines, beer), medications (nitroglycerine, reserpine, estrogens) and physical exhaustion. Longer sleep is the cause of migraine at the weekend. In some patients the role of trigger factors plays



certain foods such as chocolate, mature cheeses, citrus fruits, canned meats, food containing nitrites, aspartame, monosodium glutamate (Chinese food) and fried foods. Less often trigger foods can be tomatoes, onions, garlic, kiwi, nuts, oysters, mussels and crabs.

**Chronic migraine** is a migraine with very frequent attacks. Transformation of the episodic into chronic migraine is also associated with the natural course of the disease and the presence of risk factors. After multiple migraine attacks with aura, definitive brain lesions are found in the deep white brain matter or brain strokes. The number of seizures has increased for many years and chronic migraines are progressively reached in women around the age of 40. The nature of the migraine attack changes over time - the headache decreases in intensity, the accompanying symptoms become weaker and occur less frequently. A daily headache is developed that consists of a long-term background (tension-type or headache due to drug abuse), which is overloaded with migraine headaches. In most patients, the headache intensifies at the end of the day.

**Medication-overuse headache** develops in patients who have abused for years with headache medications. The overuse of analgesics alters the activity of serotonin receptors and increases the predisposition to headaches.

**The diagnosis** is given on recurrence of relatively unilateral seizures. Everyone may experience a migraine attack during their lives, but this does not mean that there is a migraine.

In order to be diagnosed as '**migraine without aura**', the following criteria should be met:

1. At least 5 attacks meeting the criteria 2 to 4.
2. Headache attacks, lasting 4-72 hours (untreated or without treatment effect).
3. Headache should meet at least 2 of the following criteria:
  - Unilateral location
  - Pulsating quality
  - Moderate or severe pain intensity
  - Aggravation by routine physical activity
4. During the headache, at least one of the following symptoms is present:
  - Nausea and/or vomiting
  - Photophobia or phonophobia
5. Symptoms cannot be better explained with another type of headache.

If less than 5 attacks occur, probable migraine is diagnosed.

**For children** of the age by 18 years old the same criteria are used, and the duration of the headache is from 2 to 72 hours and it is often bilateral and frontotemporal.

In order to be diagnosed as '**migraine with aura**', the following criteria should be met:

1. At least 2 attacks meeting the criteria 2 and 3.
2. The occurrence of one or more Fully reversible symptoms of aura:
  - visual
  - sensory
  - speech or language related
  - motor
  - brainstem
  - retinal
3. Presence of at least 3 of 6 features:
  - At least one of the symptoms of the aura spread gradually within 5 minutes or more
  - two or more aura symptoms occur in succession
  - each individual aura symptom lasts 5 – 60 minutes
  - at least one symptom of the aura is unilateral
  - at least one symptom of the aura is positive
  - aura is accompanied or followed by a headache within 60 minutes
4. Symptoms cannot be better explained with another type of headache.

The typical aura manifests itself with visual, sensory and speech-related symptoms, with no motor, brainstem, and retinal symptoms. A typical aura can also occur without headaches. When it first occurs at the age of 40+, the symptoms are mostly negative (hemianopsia) when the aura is prolonged or very short, should be differentiated from transient ischemic attacks. The motor symptoms of the aura can last up to 72 hours. Aphasia is always considered as a one-sided symptom, but the dysarthria may be unilateral or bilateral. Pins and needles are positive aura symptoms.

The same criteria apply to children under the age of 18.

The diagnosis of **migraine with brainstem aura** (old term basilar migraine) is given to patients meeting the migraine with aura criteria, who also meet the following two criteria:

1. Presence of at least two fully reversible stem symptoms: - dysarthria, - vertigo, - tinnitus, - hypacusis, - diplopia, - ataxia not associated with sensory deficit, - decreased level of consciousness (Glasgow coma scale <13).
2. Lack of motor and retinal symptoms

**Hemiplegic migraine** is diagnosed in patients with migraine with aura that meets the following criteria:

1. Fully reversible muscle weakness
2. Fully reversible visual, sensory and/or speech/language symptoms

There are several forms of hemiplegic migraine: familial hemiplegic type 1, 2, 3 or associated with other loci and sporadic hemiplegic form.

In the presence of at least one first- or second-degree relative with migraine aura, including motor weakness, the diagnosis of familial hemiplegic migraine is made, and in the absence of relatives with such symptoms - sporadic hemiplegic migraine.

**Retinal migraine** (previous name ophthalmic) is diagnosed in migraine patients with aura that meets the following two criteria:

1. Fully reversible, monocular, positive and/or negative visual phenomena (e.g. scintillations, scotomata or blindness) confirmed during an attack by either or both of the following:

- clinical visual field examination
- the patient's drawing of a monocular field defect

2. At least two of the following:

- Symptoms are spreading gradually over  $\geq 5$  minutes
- Symptoms last 5-60 minutes
- Accompanied, or followed within 60 minutes, by headache

3. Symptoms cannot be better explained with another type of headache and amaurosis fugax is excluded.

The diagnosis of **menstrual migraine without aura** is made when attacks occur in 2 out of three menstrual cycles meeting the criteria for migraine without aura, occurring from 2 days before menstruation to the third day of the menstrual cycle. The patients do not have attacks outside the menstrual cycle and do not get aura.

The diagnosis of **menstrual-related migraine without aura** is made in patients who meet the criteria for menstrual migraine but have attacks outside of the menstrual cycle.

The diagnosis of **menstrual migraine with aura** is made when attacks meet the criteria for migraine with aura and menstrual migraine.

**Menstrual-related migraine with aura** meets criteria for migraine with aura and menstrual-related migraine.

**Chronic migraine** is diagnosed when the following criteria are met:

1. Headache (similar to migraine or tension) occurring for  $\geq 15$  days in the month for at least 3 months and meeting criteria 2 and 3.

2. Occurring in a patient who has had at least 8 attacks meeting criteria for migraine with or without aura

3. On  $\geq 8$  days/month for  $>3$  months, meeting any of the following criteria:

- For migraine without aura
- For migraine with aura
- Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

4. Symptoms cannot be better explained with another type of headache

■ **General practitioner (GP) should:**

- refer the patient for diagnosis and treatment to a neurologist

■ **The neurologist should:**

■ determine whether there is migraine with or without aura, using the diagnostic criteria

■ refine the diagnosis, performing, if necessary, the relevant paraclinical examinations and consultations with other specialists.

■ Refer the patient to an office or clinic for the treatment of pain when one of the relatively rare forms of migraine is suspected, such as: typical aura without headache, migraine with brainstem aura, hemiplegic migraine and retinal migraine and periodic syndromes in childhood that may precede or be associated with migraine

■ Inpatient treatment is required for migraine complications, including migraine status, persistent aura without cerebral infarction, migraine cerebral infarction and migraine-triggered epileptic seizures.

**Diagnostic methods** include the diagnostic criteria for diagnosis.

■ A pharmacological test can be performed with one tablet of nitroglycerin, resulting in migraine-like headache (without aura) if migraine is present in patients. The diagnostic value of the pharmacological test is low.

**Differential diagnosis** is made with other primary and secondary headaches.

**1. Differential diagnosis in cases with other types of primary headache**

a/ **tension-type headache** – double-sided, very often in the back of the head, clamping or pressing, weak or moderate, not aggravated by routine daily activity and is with a longer duration. It should not be forgotten that migraine can be combined with a tension-type headache in the same patient.

b **cluster headache** – unilateral (one-sided), most often orbital, piercing, extremely severe, and lasting 15-180 minutes. It is men who mostly suffer and attacks occur mainly at night. There are accompanying symptoms that are not found in other types of primary headache. The migraine headache may change from one side to the other during the various attacks, while the cluster one remains on the same side during each period.

c/ **chronic paroxysmal hemicranias** - its symptoms resemble cluster headaches, but the attacks are shorter and occur mostly in women.

## 2. Differential diagnosis in cases with different types of secondary headache

a/ headache in cases of **subarachnoid hemorrhage** - occurs suddenly in physical effort, it is in the back of the head and there are symptoms of meningeal irritation.

b/ **cerebral vein and sinus thrombosis** headache - diffuse, tantalizing, progressively increasing intensity, and evidence of focal neurological symptoms.

c/ **transient ischemic attacks** begin after the age of 50, unlike migraine. They develop rapidly, only negative motor symptoms occur, continue under 10 minutes, and there is no evidence of heredity.

d/ headache in cases of **brain tumors** - occurs gradually, progressively intensifies, especially during the night and early morning hours, and soon general brain and focal neurological symptoms are added.

e/ headache in cases of **acute glaucoma** - acute night headache, orbital and retroorbital, which most commonly occurs in older people with hypermetropia. The affected globe of the eye is rigid in palpation, the ipsilateral pupil is dilated, the cornea is not clear.

f/ **Temporal (giant cell) arteritis** occurs with headache accompanied by increased scalp sensitivity, jaw pain when chewing, visual disturbances and low-grade fever. In 26% of the patients there are visual ischemic complications and in 15% - blindness. It is necessary to measure ESR and hematocrit and to perform a biopsy of the temporal artery.

These are just some of the diseases that can cause difficulty in diagnosing migraine. It should not be forgotten that any neurological, mental and somatic disease can begin with a headache or it may occur later on.

- **The neurologist** should refer the patient to an office or clinic for the treatment of pain in case of:
- establishing an anamnestic and clinical evidence of secondary headache or a change in the characteristics of an already established migraine.
- Data for migraine headache transformation into chronic and medication overuse headache.

■ **The neurologist** in office or clinic for the treatment of pain should refine the diagnosis by performing, if necessary, relevant paraclinical examinations or consultations with other specialists, in the light of the changes that have occurred or the background data collected from the case history, clinical examination, and paraclinical evidence of secondary headache.

■ In cases of chronic migraine and medication overuse, the neurologist should conduct hospital detoxication by providing adequate treatment for the migraine attacks that have occurred.

## **Treatment**

### ***1. Treatment of Migraine Attacks (Abortive Treatment of Migraine Attacks)***

Symptomatic treatment aims to reduce the severity and duration of headache attacks, accompanying symptoms, excessive use of analgesics, and prevent chronic disease. Treatment can be done through two different tactics - stepped or stratified. In a step approach, the headache attacks are initially treated with nonspecific medications and, if they are not efficient, switch to treatment with specific medications. In the stratified approach, the drug is selected according to the severity of the attack - mild attacks are treated with non-specific medications, and the severe ones - with specific. Stratified treatment approach is preferred because it considers the different needs of the patient in the various types of attacks. It is necessary to provide efficient symptomatic treatment for severe headache attacks, following strict monitoring of the frequency of drug use. In mild and moderate attacks, alternative drugs with fewer side effects are needed. Treatment of attack is not desirable to be applied for more than two days a week because of the danger of occurrence of headache caused by drug overuse.

**The criteria** for separate abortive treatment are:

- headache attacks are to 2-3 per month
- treatment is efficient and does not harm other systems in the body

#### **1. Non-specific medications for treatment of mild and moderate attacks**

They are used to treat mild migraine attacks, in patients who have contraindications for the use of triptans and in triptans abusing patients during the withdrawal period. They should not be used for more than 15 days a month, regardless of the daily dose.

a/ Paracetamol – 1 g at the onset of the attack is less effective.

*b/ non-steroidal anti-inflammatory drugs (NSAIDs)* inhibit prostaglandin synthesis and affect the transmission of pain impulses in the trigeminal vascular system. It should not be used for more than 10-14 days a month. The ones applied most often are:

- Diclofenac at a dose of 50 - 100 mg per attack
- Ibuprofen at a dose of 400 – 800 mg per attack
- Naproxen at a dose of 500 – 1000 mg per attack

*c/ antiemetics* - during an attack the absorption of oral drugs is reduced because of delayed gastric emptying, even in the absence of nausea and vomiting. This requires the administration of antiemetics half an hour before taking specific or non-specific medications. Alternatively, parenteral formulations of the drugs can be used.

- metoclopramide 10 mg per attack. For children, a 0,1 mg/kg single dose, a maximum daily dose of 0,5 mg/kg.
- domperidone 20 mg per attack

*d/ Corticosteroids* are used to treat prolonged and refractory to treatment attacks, primarily with a migraine status.

- prednisone at a daily dose of 40-60 mg daily orally for 3 to 5 days
- dexamethasone 8-16 mg intramuscularly.

Analgesics (opioid and non-opioid) and analgesic combinations **are not recommended** for the treatment of migraine attacks because of the risk of overuse and transformation of the headache.

In **pediatric age** ibuprofen (10 mg/kg) and paracetamol (15 mg/kg, up to 1 g) are used. Aspirin is effective but should not be used under 15 years of age due to the danger of Reye's syndrome.

**2. The specific medications for treatment of moderate and severe attacks** include the selective serotonin agonists and CGRP receptor antagonists.

**Selective serotonin agonists (triptans)** inhibit dural neurogenic inflammation, directly affect the excitability of the cells in the trigeminal nuclei in the brain stem by stimulating 5-HT<sub>1B/1D</sub> receptors and causing vasoconstriction of the meningeal, dural, cerebral and pial vessels. They also differ in the dosage form (oral, parenteral), time to reach maximum plasma concentrations, half-life, bioavailability, duration of effect and time required for effect to be reached, speed of onset of action (speed of reaching maximum plasma concentration during attacks  $T_{max}$ ), second-hour headache response (patients without pain), pain-free period, 24-hour reoccurrence of the pain, long-term headache

response, repeatability of the effect, compatibility, adverse reactions and safety and drug interactions. In general, they are divided into two groups

*The first group of triptans* has a rapid start but shorter action (half-life of 2-4 hours) and includes:

- eletriptan tablets 20, 40 and 80 mg - one of the most efficient and fast-acting triptans, with a longer duration of effect that brings it closer to the long-acting triptan group. The single dose is usually 40 mg, the maximum dose for 24 hours is 80 mg.

- frovatriptan tablets 2,5 mg – one of the most efficient and fast-acting triptans, with a longer duration of effect that brings it closer to the long-acting triptan group. The single dose is usually 2,5 mg, the maximum dose for 24 hours is 5 mg.

- rizatriptan tablets 5 and 10 mg - characterized by a very good absorption, not affected by gastric stasis during an attack. One of the fastest and most efficient triptans that affects the pain in the first 2 hours in most patients. In approximately 30% of patients, the pain resumes after 2 hours, requiring re-administration of the drug. The single dose is 10 mg, the maximum dose for 24 hours is 30 mg.

- zolmitriptan tablets 2.5 and 5 mg - drug action starts slower than rizatriptan, its bioavailability is the smallest compared to other triptans. It has the most pronounced cardiac and noncardiac (nausea, dizziness, sleepiness, asthenia, etc.) adverse effects compared to other triptans, which limits its application. The single dose is 2.5 mg, the maximum dose for 24 hours is 5 mg.

- sumatriptan tablets 25, 50 and 100 mg. The single dose is 50-100 mg, the maximum dose for 24 hours is 200 mg. It has low oral bioavailability, does not cross the blood-brain barrier, causes vasoconstriction of the coronary and cerebral arteries, anxiety, chest pain, paresthesia.

*The second group of triptans* with a slow start but longer action includes:

- naratriptan (2.5 mg) - the action of the drug starts slower and its maximum efficacy is reached at the fourth hour post-dosing but provides at least a 24-hour period of pain response and is therefore preferred to patients with a recurrent headache. It has a long plasma half-life (6 hours) and high oral bioavailability, which explains its long-term therapeutic effect and fewer cases of recurrent headache. The single dose is 2.5 mg, the maximum dose for 24 hours is 5 mg.

The choice of triptan depends on the patient's response. In any case, fast-acting medications are preferred, but in some patients the headache returns at the second hour after triptan administration, requiring a second dose. In these cases, triptan with a slow start but longer duration may be preferred. If after the second dose the headache occurs again,



NSAIDs are administered. Patients whose headache is recurrent in any attack after use of triptan can use both triptan and NSAIDs at the onset of the attack.

Taking triptans leads to the occurrence of 'triptan symptoms' - tingling, insensitivity, warmth, weight and tightness in different parts of the body, including in the chest. The thoracic symptoms are due to changes in the motility of the esophagus, skeletal muscle effects, central sensitization of the pain pathways, and changes in pulmonary vascularization. They mimic angina attacks but no changes in coronary blood supply have been established. However, all triptans are contraindicated in patients with cardiovascular and marked cerebrovascular disease, severe, uncontrolled arterial hypertension, peripheral and cerebral vasculopathy, Raynaud's syndrome, prolonged or unspecified aura, migraine with a stem aura and hemiplegic migraine. They are also contraindicated in patients under 18 or over 65. They are also contraindicated for concomitant administration with serotonin reuptake inhibitors due to the risk of serotonin syndrome. They are contraindicated for administration with MAO-A inhibitors such as moclobemide because they are metabolized by the MAO-A enzyme. If taken together with cimetidine, oral contraceptives, ciprofloxacin, erythromycin, clarithromycin, ritonavir, indinavir or propranolol, their serum levels increase, which increases the side effects. Taking naratriptan by smokers leads to increasing of its plasma concentrations.

These medications should not be used more than 10 days a month to avoid the risk of medication-induced headaches. They are taken immediately after the onset of the headache before it gets stronger. When the headache occurs again within 48 hours, the drug may be repeated, but not earlier than 2 hours after the first dose. NSAIDs can also be used additionally.

**CGRP receptor antagonists**, small molecule inhibitors of CGRP (gepants) are effective in treating migraine attack. They act by binding to CGRP receptors and influencing CGRP-induced neurogenic inflammation and vasodilation and trigeminovascular nociceptive activation. Antagonism of CGRP receptors on mast cells, satellite glial cells and astrocytes prevents CGRP-induced neuroinflammation. Gepants suppress CGRP-induced vasodilation without causing vasoconstriction, making them a preferred alternative in patients with contraindications to triptan therapy. Considering that 30-40% of patients do not respond to treatment with triptans, the development of this group of drugs gives hope for effective treatment of migraine attacks. Gepants are recommended for the treatment of a migraine attack in the absence of an adequate effect from the application of two or more different triptans. Frequent intake of gepants does not lead to headache due to drug abuse.

*Rimegepant* is a CGRP receptor antagonist that affects pain and associated symptoms up to 2 hours after taking the medication and with a duration of effect of 24-48 hours. It is administered in a dose of 75 mg perorally during an attack. Side effects include dizziness, nausea and urinary infections.

**In pediatric age** the following drugs can be used: sumatriptan nasal spray for children and adolescents (10 mg for weight less than 40 kg and 20 mg for weight over 40 kg), zolmitriptan nasal spray (2.5-10 mg) for the age of 12+, rizatriptan tablet for children at the age of 6+ and adolescents (5 mg for body weight between 20 and 40 kg and 10 mg for weight over 40 kg), almotriptan for adolescents aged 12+ (6.25-12.5 mg) and eletriptan 40 mg.

**During pregnancy**, paracetamol may be used during the first trimester and NSAIDs during the second and third trimesters. Domperidone may be administered; it is not desirable to administer triptans.

*Ergotamine alkaloids* (ergotamine tartarate 2 mg orally) **should not be used** as recommended by the European Medicines Agency in 2013 because the risk outweighs the benefits of their application. They cause generalized vasoconstriction due to their effects on different types of serotonin, alpha-adrenergic and dopaminergic receptors. Exceptionally, they can only be used in patients who have used them for a long time, have no vascular contraindications and frequent attacks and the medications have proved efficacy.

- ergotamine tartarate at a dose of 2 mg orally at the onset of the attack

### **3. Neuromodulation methods for treatment of migraine attacks:**

- Single-pulse transcranial magnetic stimulation (e. TMS) is administered occipitally by the patient in a migraine attack with aura, during aura, or at the onset of the headache.
- Non-invasive vagus nerve stimulation (NIVS). The portable device (gammaCore) is placed on the neck (the cervical branch of the n. vagus). There are 2 consecutive (one left and one right) 2-minute stimulations at the onset of the pain. If necessary, the session may be repeated after 20 minutes and after 2 hours.
- Supraorbital/supratrochlear transcutaneous stimulation (Cefaly) is administered at the onset of a headache attack. It is made by a portable stimulator with the form of a diadem/rhombus that is positioned on the forehead. It is a low-frequency stimulation targeting the upper branches of n. trigeminus.

- Taking ergotamine at a dose of 2 mg daily for more than 3 months may cause medication headaches and other complications.
- The neurologist should perform ambulatory or hospital detoxication by providing adequate treatment for the migraine attacks that have occurred.

- The treatment of migraine attacks is performed by a neurologist according to the strength and duration of the attacks.
- For **mild** and moderately severe attacks, non-specific medications are administered.
- For moderately severe and **severe** attacks, specific medications are administered.
- *Drugs of first choice* are the selective serotonin agonists. In case of insufficient effect, non-specific medications can be added.
- *Drugs of second choice* are CGRP receptor antagonists. They are used in the absence of effect from three different selective serotonin agonists. In case of insufficient effect, neuromodulating methods are additionally applied to treat an attack.
- If there is no effect on attacks, the patient is referred for consultation in a specialized office or clinic for treatment of pain.

- In cases of headaches that are not affected within 72 hours, in cases of severe attacks with overdosage of drugs, or those are totally inefficient or other, threatening syndromes occur, patients are referred for emergency hospitalization.

**Status migrainosus** is one of the complications of migraine. The headache is severe and lasts for over 72 hours without remission regardless of treatment. There are nausea, vomiting, diarrheas that lead to dehydration and electrolyte disturbances. Sleep and eating are also affected. During status migrainosus the patient can develop a cerebral infarction.

Treatment requires hospitalization for 2 to 4 days, appropriate medication, metabolic control, emotional support, rest and sleep. The first step is rehydration of the patient and administering metoclopramide 10 mg intravenously (for 1 minute). Administer dexamethasone 4 mg intravenously or prednisone 80-100 mg daily. Sumatriptan (6 mg s.c.) or naratriptan is to be administered if the patient has not overused these medications. If ergotamines have been administered, one should wait at least 24 hours before administering other drugs. Prophylactic medications are administered concomitantly with symptomatic medications to avoid recurrence of the headache, which is a serious problem. Administration of sodium valproate intravenously (500 mg/hr. or 750-1000 mg daily) is effective in 70% of patients. The serum concentration should be kept below 100 µg/ml.

- Migraine status is an urgent condition. Establishing a migraine status, the neurologist should immediately hospitalize the patient into a neurological ward. Rehydration is performed there, parenterally incorporating corticosteroids and antiemetics, and the vital functions are monitored.

The treatment of **menstrual migraine** is carried out during the headache attack and as short-term prophylaxis around the menstrual cycle. In the event of headache, the same medications as with migraine - NSAIDs (naproxen 2 times of 550 mg a day) and triptans are used. Sumatriptan 100 mg and rizatriptan 10 mg are efficient, while zolmitriptan and naratriptan are not.

**Hemiplegic migraine** is treated with NSAIDs and aspirin. Specific remedies for treating the attacks are not applied because the symptoms are due to vasoconstriction and the risk of cerebral infarction is high.

**Migraine with brainstem aura** is treated with NSAIDs and aspirin. No specific agents are used to treat the attacks as well as in the cases of hemiplegic migraine.

**Chronic migraine** is difficult to treat. Most patients have had drug overuse for years, so the first step in treatment is withdrawal and detoxification. You need to minimize or withdraw for 1-2 months all abortive medications. The patient only remains on prophylactic treatment. Two strategies are used to withdraw the medication used - a sudden or gradual withdrawal after the inclusion of terminator drugs. Sudden withdrawal results in serious symptoms associated with cessation of drug overuse - increased headache, nausea, vomiting, agitation, restlessness, anxiety, sleep and mood disorders, arterial hypotension, tachycardia, rarely epileptic seizures and hallucinations. The duration of these symptoms is from 3 to 8 weeks. To reduce the severity of them, it is advisable to initiate prophylactic treatment 4 weeks in advance. Because of the risk of epileptic seizures and delirium, barbiturates, opioids and benzodiazepines are gradually reduced over several days and not abruptly withdrawn.

The patient is hospitalized for rehydration, choice of prophylactic treatment, cessation of the cycle of severe pain and training. In case of vomiting, infusions of antiemetics (domperidone, metoclopramide 10 mg, children 0,1 mg/kg to a maximum daily dose of 0,5 mg/kg) are also used. Repeated applications of neuroleptics intramuscularly (haloperidol 5 mg, droperidol 1-2,5 mg or chlorpromazine 10-50 mg) may also be used. Oral atypical neuroleptic olanzapine can be administered orally at a daily dose of 5-10 mg. When

neuroleptics are administered, care should be taken to prolong the QT interval in the ECG examination.

All co-morbid somatic and mental illnesses and factors associated with exacerbation of headaches should be identified. Individual programs, including non-pharmacological (physiotherapy, rehabilitation, relaxation, biofeedback, behavioral and psychotherapy), and pharmacological methods are being developed.

In some cases, it is necessary in the first days to administer single doses of medication to treat the attack with very severe headaches. These drugs are called 'terminator' or 'transient' because they are applied until the pathophysiological cycle of chronic headache is broken. Naratriptan 2.5 mg twice daily or sumatriptan 25 mg 3 times daily for 10 days are efficient. Combination treatment of  $\beta$  blocker and antiepileptic can be used. Very effective is the administration of corticosteroids (prednisone 100 mg for one day), followed by decreasing doses of 20 mg per day for 1-14 days. Amitriptyline 25 mg, NSAIDs (naproxen 500 mg/d), gabapentin 2400 mg/d, topiramate 50-100 mg/d, valproate orally (750 mg/d) or intravenous (up to 500-1000 mg/d) can be used. If a patient has abused opioids, clonidine 0.1-0.2 mg administered three times a day is efficient. Administration of  $\alpha$  adrenergic agonist tizanidine is efficient as adjunctive therapy. Particularly suitable is the administration of botulinum toxin.

Once the acute phase passes, behavioral therapy is initiated. Prophylactic treatment should be continued, considering that prophylactic medications that have not previously been efficient become efficient after discontinuation of drug abuse. The first year after treatment is risky - 40% of patients are again beginning to abuse medication. Abuse is more common in patients with headache than with migraine and in patients using analgesics compared to triptans.

## ***2. Prophylactic Treatment of Migraine Attacks***

It aims to reduce the frequency and severity of the attacks and the risk of progression of the disease. It is considered disease-modifying treatment because the frequency of the attacks and the abuse of pain-relieving drugs are risk factors for the progression of the disease.

Migraine patients are subdivided into three groups according to the need for prophylactic treatment: patients who must perform it, who may have it, and those who do not need such treatment.

All patients with more than 3 attacks monthly or more than 1 severe attack **are indicated** for prophylactic treatment. These are about 40% of patients with migraine. Patients with no effect of symptomatic treatment are also indicated.

It is **imperative** to undergo prophylactic treatment for patients with 6 or more attacks monthly or with 4 or more moderate or 3 or more severe attacks.

Patients with 4-5 mild or 3 moderate or 2 severe attacks **may** be treated prophylactically.

The principles of prophylactic treatment require that an individual regimen be developed, selecting the appropriate drug for each patient and providing symptomatic treatment for occurring attacks. If the treatment is inefficient for 8 weeks, it should be stopped a drug from another group should be administered. Prevention is considered efficient if it reduces the frequency of the attacks by 50% after at least 3 months of administration. In some difficult cases it is necessary to combine medications from different groups. Prophylactic treatment, when it is efficient enough, is administered for 12 months, after which the dose should be reduced and a 'medication break' be given, with providing of symptomatic treatment. If the attacks become more frequent, which occurs in 50% of patients, prophylaxis should be continued for a further year.

The patient should receive information about the disease, so that they could to play an active role in his/her treatment. They should try to determine the trigger factors, the number and severity of the attacks, and their response to medication.

It is necessary to take measures for certain diseases (arterial hypertension, obesity, iron deficiency anemia) and to avoid medications (vasodilators, hormonal estrogen-progesterone drugs) that aggravate the disease. The use of oral contraceptives and smoking increases the risk of stroke that is increased in migraine patients.

**1. Lifestyle changed** - Lifestyle changes that include regular sleep and eating, avoiding stress and fatigue (physical and mental), weight reduction, physical activity, avoiding noisy, windy, clogged, cold or hot and highlighted places, strong odors and altitude changes are recommended. It is necessary to avoid factors that the patient has noticed that provoke headache attacks. Some patients are sensitive to certain foods (cheese, chocolate, citrus, etc.) and alcohol, which should be excluded from the diet. A restriction diet should only be maintained if the patient has established with certainty that certain foods and drinks are aggravating the disease.

## **2. Antiepileptic medications**

- Topiramate 100 mg daily is the most effective anticonvulsant.
- Sodium valproate 600-1500 mg daily

- Gabapentin 900 to 1800 mg daily
- Pregabalin 300-600 mg daily

### 3. Medications related to noradrenaline and serotonin.

- *Tricyclic antidepressants*
  - amitriptyline 25 – 75 mg in the evening

- *Serotonin and noradrenaline reuptake inhibitors*

- duloxetine 30 – 60 mg daily
- venlafaxine 75 - 150 mg daily
- mirtazapine 30 - 60 mg daily

■ Antidepressants suppressing serotonin reuptake (SSRI) are inefficient and cause headache as a side effect.

### 4. Non-selective beta ( $\beta$ 1 and $\beta$ 2) adrenergic blockers.

- propranolol 80-320 mg daily
- metoprolol – 200 mg daily
- atenolol – 40-100 mg daily
- timolol – 20 mg daily
- nadolol – 80-240 mg daily

### 5. Non-selective calcium channel blockers

- flunarizine 10 mg in the evening
- verapamil 240-480 mg daily
- amlodipine 5-10 mg daily

**6. Monoclonal antibodies** (MAB's) bind to the calcitonin gene-related peptide (CGRP) or the CGRP receptor. MAB's are recommended in patients with chronic migraine (CM) who failed 2 different classes prophylactic treatments either due to lack of efficacy, comorbidities or occurrence of adverse reactions. In patients with CM it is recommendable not to stop their current oral preventive treatment when initiating treatment with monoclonal antibodies. Withdrawal from the oral prophylactic treatment should be considered at later stage, when efficacy of monoclonal antibodies is established.

- erenumab 70-140 mg s.c. monthly dose. Targeting the CGRP receptors
- fremanezumab 225 mg s.c. monthly dose or 675 mg s.c. every 3 months. Targeting the CGRP peptide
- galcanezumab 120 mg s.c. monthly dose. Targeting the CGRP peptide

**7. Botulinum toxin** is administered as a second-line prophylaxis in patients with chronic migraine. OnabotulinumtoxinA (Botox) 155-195 U is applied every 3 months.

**8. Gepants** are used for migraine prophylaxis after failure of prophylaxis with at least two other classes of medication.

*Rimegepant* 75 mg taken every other day orally reduced the number of migraine headache days by 50%. The effect occurs already at the end of the first month after starting the treatment.

**9. Neuromodulation methods** with a possible prophylactic effect are divided into non-invasive and invasive (occipital nerve stimulation and stimulation of the sphenopalatine ganglion). Invasive methods are of predominantly experimental significance and are not available in the country. Non-invasive methods are:

- supraorbital/supratrochlear transcutaneous stimulation (Cefaly). It is administered by a portable stimulator with the form of a diadem/rhombus that is positioned on the forehead. It is used in patients with episodic migraine with or without aura. It is a low-frequency stimulation targeting the upper branches of n. trigeminus. It is used once daily for 20 minutes for prophylaxis.
- transcranial direct current stimulation (tDCS). Reduces the frequency of migraine attacks after 15-minute sessions administered twice weekly at the back of the head (occipital cortex). Because of the significantly smaller size of the device, it is superior to the HF-rTMS.
- high frequency repetitive transcranial magnetic stimulation (HF-rTMS). Applied over the primary motor area (M1) in 12 sessions every other day, as a prophylactic treatment for episodic and chronic migraines it reduces the frequency of the attacks.
- single pulse transcranial magnetic stimulation (s.p. TMC). It is applied through a portable device for prophylactic treatment. The device is placed in the area of the occipital cortex by applying 2 pulses over a 30-second interval.
- non-invasive vagus nerve stimulation (niVNS). It is applied by a portable stimulator on the cervical branch (on one and/or on both sides) of n. vagus as a prophylactic treatment for chronic migraine.

With **children**, prophylaxis can be performed with flunarizine 5 mg/d), amitriptyline (1 mg/kg/day), topiramate (2 mg/kg/day), valproate (10-40 mg/kg/day), gabapentin 20 mg/kg/day) and levetiracetam at a dose of 20-40 mg/kg/day. For children over 7 years of age, propranolol may be administered 1-2 mg/kg/day, up to 40-50 mg twice daily.

Prophylactic treatment should not be given **during pregnancy**. Most women (60-70%) with migraine have an improvement during pregnancy.



**Mini-prophylaxis** in patients with menstrual migraine is applied around the menstrual cycle.

*Estrogens* are used for perimenstrual prophylaxis of menstrual migraine attacks when the menstrual cycle is regular and the time of its onset is known. They are contraindicated in migraine with aura, in women with estrogen-dependent tumors and venous thromboembolism.

- Estradiol 1,5 mg gel daily, 3 days before the expected menstruation, for 7 days in total.

- Estrogen 100 µg transdermal patches 3 days before menstruation until the 5<sup>th</sup> day of menstruation.

*NSAIDs* are administered 1 week before and 1 week after the menstrual cycle.

- naproxen sodium 1100 mg daily.

*Triptans* are taken 2 days before and 3 days after the cycle.

- sumatriptan 25 mg 3 times a day.

- naratriptan 1 mg twice a day.

### ***Hemiplegic migraine***

- verapamil 120 mg 3 times a day

### ***Migraine with a brainstem aura***

- flunarizine 10 mg daily

- verapamil

- antiepileptic drugs

Prophylaxis is obligatory with ***retinal migraine***

- calcium channel blockers

- anticonvulsants

- magnesium 400 mg twice daily

- riboflavin 400 mg daily

- The decision to include one or another drug for the prophylactic treatment of migraine is made by a neurologist. The treatment lasts for at least 12 months, and in the second month its effectiveness is evaluated and decision is made whether to continue with the same drug or to include another one. In some difficult cases, two or more drugs can be combined.

- Drugs of **first choice** for prevention are antiepileptics, tricyclics and antidepressants related to norepinephrine and serotonin, non-selective beta-adrenergic blockers and non-selective calcium channel blockers. Topiramate 100 mg daily is most effective.
- Drugs of **second choice** are monoclonal antibodies directed against CGRP and botulinum toxin. They are used in patients with chronic migraine and in patients with episodic migraine unresponsive to first-line medications.
- Third choice medication is Rimegepant 75 mg taken every other day. It is given after failure of prophylaxis with at least two other classes of second-line drugs. In case of insufficient effect, neuromodulating methods are additionally applied.

- The neurologist should examine the patient with migraine twice a year and in any case of deterioration. The patient should be monitored for:
  - effect of the applied abortive treatment
  - effect of the applied prophylactic treatment
  - symptoms of overdose of the therapy
  - worsening of the symptoms due to insufficient dose
  - secondary chronification
- In case of insufficient effect of the prophylactic treatment at an optimal dose, the patient is referred for consultation in a cabinet or clinic for the treatment of pain.
- Such consultation is urgently required in the presence of symptoms of overdose of therapy.
- No therapy is allowed to be prescribed without a personal examination of the patient.

## Tension-type Headache

### Definition

- Tension-type headache is characterized by episodes of headache, lasting from minutes to days, clamping or compressive, bilateral, mild or moderate in intensity, not enhanced by routine daily activity and accompanied by photo and/or phonophobia.

**Pathophysiology** is mainly associated with contraction of pericranial muscles and increased pain sensitivity. Long-term muscle tension leads to relative ischemia of the contracted muscle due to compression of the small blood vessels and further intensification of the headache due to the formation of metabolites (bradykinin, serotonin, prostaglandins, lactic acid) and pain augmentation. Increased nociceptive afferentation from the muscles enters the stem trigeminal nuclear complex, which is the main relay of sensory information. Recurrent headache episodes reduce the threshold for subsequent episodes by changes in myofascial tissues. Secondly, it decreases the activity of the antinociceptive systems and, as a last resort, activates the stem nociceptive neurons, which increase the pain. Thus, the episodic headache becomes chronic and the disturbances in the central mechanisms of pain begin to prevail. The descending supraspinal modulation is disturbed. The palpatory sensitivity in muscles is due to a reduced pain threshold and central sensitization.

It is **classified** as an episodic and chronic tension-type headache. The episodic one in turn may be rare (infrequent) and frequent. The headache may or may not be associated with pericranial sensitivity.

**Clinically**, in 90% of patients it is going on with mild to moderate permanent headache. The headache is bilateral, especially in women, with 20% to 55% of patients being unilateral. The pain is pulsating (in 65%) or pressing. The duration of each headache attack is very different (on average 12 hours), unlike the migraine attack. Typical is the localization of pain in different muscles at each attack, as well as the varying intensity of pain. Remissions between the attacks may be long-lasting in contrast to migraine. About 10% of patients wake up at night (between 1 and 4 am) because of the pain. In some cases, the headache is the strongest at the end of the day in connection with the growing stress during the work day.

**Diagnosis** is based on clinical criteria.

#### **Diagnostic criteria for Infrequent episodic tension-type headache:**

1. At least 10 episodes of headache occurring <once a month (<12 days/year) and fulfilling criteria 2-4.
2. Headache lasting from 30 minutes to 7 days.

3. Availability of at least two of the following characteristics:

- Bilateral location
- Pressing or tightening (non-pulsating) quality of the pain
- Mild or moderate intensity
- Not aggravated by routine physical activity such as walking or climbing stairs

4. Availability of both of the following conditions:

- Lack of nausea or vomiting
- Lack of photophobia and phonophobia at the same time, but only one of the two symptoms may be present.

5. Symptoms cannot be better explained by another type of headache

Criteria for diagnosing with **frequent episodic tension-type headache** are the same, but require more than 14 days with headaches monthly or 12 to 180 days per year for >3 months.

**Episodic tension-type headache (infrequent or frequent) associated with pericranial tenderness** should meet the criteria for episodic tension-type headache and increased tenderness of pericranial muscles to manual palpation. In the case of **the headache not being associated with pericranial tenderness**, this is not established.

#### **Diagnostic criteria for chronic tension-type headache:**

1. Headache occurring on  $\geq 15$  days/month ( $\geq 180$  days/year) for >3 months, fulfilling criteria 2-4.

2. Lasting hours to days, or unremitting

3. Availability of at least two of the following 4 characteristics of the pain:

- Bilateral location
- Pressing or tightening (non-pulsating)
- Mild or moderate intensity
- Not aggravated by routine physical activity such as walking or climbing stairs

4. Availability of both of the following conditions:

- Lack of photophobia, phonophobia or mild nausea at the same time, but only one of the two symptoms may be present.
- Lack of neither moderate or severe nausea nor vomiting

5. Symptoms cannot be better explained by another type of headache

Both episodic and chronic type of headache may or may not be associated with pericranial tenderness detected by manual palpation.

- **General practitioner (GP) should:**
- refer the patient for diagnosis and treatment to a neurologist

- **The neurologist should:**
- determine whether there is a tension-type of headache using the diagnostic criteria;
- by manual palpation of the pericranial muscles, determine the form of the headache;
- determine the total number of days with headaches monthly and annually;
- should refine the diagnosis by conducting relevant paraclinical examinations or consultations with other specialists if necessary.

**Diagnostic methods** include manual palpation of the pericranial muscles. Tension-type headache requires different examinations and consultations more often than other types of primary headache because it is more difficult to differentiate from secondary headaches.

- Palpation of the pericranial muscles (m. frontalis, m. temporalis, m. trapezius, mm., pterygoideus lateralis and medialis, m. masseter, m. sternocleidomastoideus) to search for palpable soreness that confirms the diagnosis. Often there is an increased sensitivity and tension of the paravertebral muscles in the neck and back. The binding sites of the muscles should also be palpated. The palpation is performed symmetrically and systematically with small rotational movements of the second and third finger of the hand. In palpation, attention is paid not only to palpatory soreness, but also to increased tonus and altered muscle consistency, as well as to their symmetry. There are palpatory soreness and altered muscle tonus also in the periods without headaches. Sore little knots are often found in the muscles. Palpatory tenderness outside the attack is most pronounced in patients with chronic headache.

- A useful diagnostic method can be the intake of alcohol, which suppresses the tension-type headache, but enhances migraine.

**Differential diagnosis**, as with all types of headache, involves firstly differentiating primary from secondary headache.

*Secondary headache*, similar to the tension-type one, can be due to head trauma, cerebrovascular disease, non-vascular intracranial disturbance, substance intake and their withdrawal, non-brain infections, metabolic disorders, skull, neck, eyes, ears, sinuses, teeth, mouth, or other facial or skull structures damages. Of the secondary headaches, usually a differential diagnosis is necessary with headaches in vascular diseases of the nervous

system and space occupying lesions. Cervicogenic headache and temporal arteritis (more frequent after the age of 50) and dysfunction of the temporomandibular joint should be differentiated.

Differential diagnosis with *migraine* without aura is based on the shorter duration and periodicity of migraine attacks. In the migraine attack, the strength of the headache increases rapidly, whereas in the tension-type headache pain grows slowly. In migraine attacks, localization of pain is usually stereotypical, whereas the tension-type headache at each attack can engage different muscle groups.

The tension-type of headache occurs during stress or in anticipation of unpleasant events, while the migraine attack develops after stress. Physical activity does not increase the tension-type headache, but enhances migraine. Patients with tension-type headache usually do not discontinue their activity during the headache, unlike migraine patients who seek to seclude in a quiet and dark room and not move. Nausea and photophobia are more pronounced in migraine headaches, and vomiting is usually not observed in the tension-type headache. Differential diagnosis is more difficult in transformed (chronic) migraine, where the case-history data of typical migraine attacks at an earlier age has to be relied on.

Differential diagnosis with *cluster headache* is not difficult as this headache that affects men more often is very strong, local, occurring each day and several times a day and is accompanied by autonomic symptoms. Patients are agitated during an attack.

■ **The neurologist** should refer the patient to a to an office or clinic for the treatment of pain in case of anamnestic and clinical evidence of secondary headache or a change in the characteristics of an already established tension-type headache.

■ **The neurologist** in office or clinic for the treatment of pain should refine the diagnosis by performing, if necessary, relevant paraclinical studies or consultations with other specialists in the light of the changes or the data of secondary headache from the medical history and clinical examination of secondary headache.

## Treatment

### **1. Non-pharmacological treatment**

■ **Psychological treatment** - includes various forms of individual and group psychotherapy, behavioral therapy and hypnosis. Its application is appropriate in cases of anxiety data.

■ **Physiological treatment**

- Progressive muscle relaxation
- EMG biofeedback from frontal and temporal muscles.
- Acupuncture, acupressure, auto acupressure in the neck area immediately below the occipital bone to the top of processus mastoideus.
- Massage
- Cryotherapy
- Transcutaneous electro-neuro stimulation

## **2. Pharmacological treatment**

### *Episodic tension-type headache*

Not every headache attack is strong enough to require treatment. Analgesics do not affect headaches and analgesic combinations lead to medication overuse headache. Non-steroidal anti-inflammatory drugs are used, most often:

- Paracetamol 1 g a day once only
- Aspirin 1000 mg daily
- Ibuprofen 400 to 800 mg daily
- Naproxen 500 – 1000 mg daily

**With children** NSAIDs may be used (paracetamol, ibuprofen).

*Chronic tension-type headache.* Therapy is administered for 1 year, with subsequent dose reductions over the next 3 months.

- **Tricyclic antidepressants** - most likely to affect the headache
  - amitriptyline 25 to 75 mg in the evening.
- **Antidepressants that affect the reuptake of serotonin and noradrenaline**
  - duloxetine 30-60 mg daily
  - venlafaxine 75 – 150 mg daily
  - mirtazapine 30 mg daily

■ **Antidepressants suppressing serotonin reuptake** are inefficient and cause headache as a side effect.

**During pregnancy**, paracetamol may be used during the first trimester and NSAIDs during the second and third trimesters.

- The treatment of episodic and chronic tension-type headaches is performed by a neurologist after excluding any other condition that can present with a similar clinical picture.
- No therapy prescription is allowed without a personal examination of the patient.

■ If not affected by classical medication, the patient is referred for consultation in a specialized cabinet or clinic for the treatment of pain. Such consultation is urgently required in the presence of symptoms of overdose of therapy.

■ The neurologist should monitor the patient with a tension-type headache twice a year and in any case of worsening. The patient should be monitored for:

- Effect of treatment
- Developing dependence on a given drug
- Evidence of overdoses



## Trigeminal autonomic cephalalgias

This group of diseases share the clinical features of unilateral headache and, usually, prominent cranial parasympathetic autonomic features, which are lateralized and ipsilateral to the headache. Rarely, a typical migraine aura can also be added.

### 1. Cluster headache

#### Definition

- Manifests with attacks of severe, strictly unilateral pain in the orbital, supraorbital and/or temporal area or in any combination of these areas lasting from 15 to 180 minutes and occurring from 1 to 8 times a day. The pain is accompanied by ipsilateral manifestations of the autonomic nervous system (conjunctival injection, lacrimation, nasal congestion, rhinorrhea, sweating of the forehead or face, myosis, ptosis and eyelid edema) and agitation and restlessness.
- Attacks occur in series, lasting for weeks or months (cluster periods), separated by periods of remission for months or years, which is where the headache name comes from. About 15% of patients have chronic symptoms, without remissions.

**Pathophysiology** is associated with activation of the trigeminovascular system and unilateral hyperactivity of the trigeminal nerve nucleus. Autonomous changes are due to the paroxysmal activity of trigeminal sympathetic and parasympathetic nuclei due to activation of the trigeminovascular system. The increased activity of the trigeminal system may be due to reduced suppressive activity of the periaqueductal gray nucleus and nucleus raphe magnus, or to impaired control of the limbic system on the endogenous pain control system. The circadian rhythm of the headache is associated with the involvement of the supraiasmal nucleus and adaptation changes in the hypothalamic functions.

**Classification** includes mainly episodic and chronic (15%) headache. Chronic headaches may occur de novo or of the episodic type. In some patients, chronic headache may become episodic.

**Clinically**, the episodic headache occurs primarily in young men aged between 20 and 40. It occurs in periods of 2 weeks to 3 months, separated by long headache-free periods (months to years). During the period, attacks occur from one to several times (4 on average) a day, often (in 54%) at night the patient wakes up with pain. During each period of attacks, the pain is always on the same side, but it can change the side (in 14%) during the different periods. Triggering factors provoke an attack only during the period. These include alcoholic beverages, histamine, stress and vasodilators such as nitroglycerin.

Chronic cluster headache is identical to episodic with regard to attacks, but the periods between the attacks are no longer than 2 weeks and daily attacks prevail.

**Diagnosis** of a cluster headache requires it to fulfill the following **criteria**:

1. At least five attacks fulfilling criteria 2-4.
2. Severe or very severe unilateral pain in the orbital, supraorbital and/or temporal area, lasting 15-180 minutes when untreated.
3. Fulfills either or both of the following criteria:
  - availability of at least one of the symptoms, ipsilateral to the headache
    - Conjunctival injection and/or lacrimation
    - Nasal congestion and/or rhinorrhea
    - Eyelid edema
    - Forehead and facial sweating
    - Miosis and/or ptosis
  - A sense of restlessness or agitation
4. The attack frequency is between one every other day and 8 per day.
5. Symptoms cannot be better explained by another type of headache.

**Episodic headache** should fulfill the criteria for a cluster headache but have at least 2 cluster periods lasting from 7 to 365 days and separated by pain-free remission periods of more than 3 months.

**Chronic headache** must fulfill the criteria for a cluster headache, but have headache attacks occurring for more than 1 year without remission, or with remission periods lasting less than 3 months.

**Diagnostic methods** include diagnostic criteria and pharmacological tests. Administration of nitroglycerine, histamine or alcohol during a cluster period causes a typical attack and can be used as a diagnostic test.

1. Nitroglycerin 1 mg administered sublingually is the most effective triggering factor that causes a typical attack after about 30-50 minutes. One should keep in mind that after 3-10 minutes of taking the medicine, some healthy people may also experience a bilateral pulsing headache. The test is considered positive if the headache that is provoked has the same characteristic as the usual headache. Before the test, the patient should lie for at least 15 minutes. In order to trigger an attack, it is necessary that the patient has not had a spontaneous attack within the last 8 hours and has not taken any vasoconstriction medication for the last 18 hours. It is also necessary that they have not undergone a prophylactic treatment.

2. Subcutaneous administration of 0.3 mg of histamine causes bilateral pulsating headache after 1.5 minutes for about 5-10 minutes in all people, and 20-40 minutes later, a typical attack is triggered.

3. **Alcohol** in small amounts is an effective trigger in about 50% of patients, causing an attack after 30-50 minutes.

4. The use of other diagnostic methods is of value except when a differential diagnosis with secondary headaches is required.

**Differential diagnosis** with other primary headaches is not difficult because attacks and remissions of cluster headache are very typical.

### 1. Differential diagnosis with other types of primary headache

■ **migraine without aura** - there is a lesser frequency of attacks and they are of a longer duration. Night migraine attacks appear to occur late at night, usually at dawn. There are nausea and vomiting, local neurological symptoms occur rarely.

■ **chronic paroxysmal hemicrania** is very well influenced by indomethacin. Attacks of chronic paroxysmal hemicrania are more common and shorter, associated with less general anxiety and are predominantly diurnal.

### 2. Differential diagnosis with different types of secondary headache

■ **Trigeminal neuralgia** - pain is similar to electrical current and is shorter (seconds to minutes). There are no autonomic symptoms and periodicity of the attacks. They rarely occur at night and may be triggered by trigger zones on the face.

■ **Horton's temporal arteritis** - manifested by unilateral pain that persists throughout the day, although decreasing and weakening. The pain is moderately strong, burning and localized in the temporal artery. It increases when chewing. Affected artery is tight and sensitive to palpation, often the pulse cannot be palpated. Diagnosis is confirmed by increased ESR rates and finding of giant cells in a biopsy.

■ **Raeder's syndrome** - resembles a cluster headache with its unilateral pain with localization around the eye and the onset of partial Horner syndrome. The pain, however, is persistent, and while at the beginning it is strong, it decreases in the coming weeks.

■ **Pheochromocytoma** - manifested by a bilateral, severe burning headache, mainly occipital, accompanied by pallor, sweating, tachycardia and high blood pressure.

■ **Symptomatic cluster headache** due to paracellar meningioma, pituitary adenoma, anterior communicating artery aneurysm, arteriovenous malformations and other processes located near the cavernous sinus.

- **Tolosa-Hunt syndrome** - apart from constant pain, there is a lesion of one or more ocular nerves (III, IV, VI). It is well-influenced by corticosteroids.

- **Glaucoma** and other eye diseases should also be considered. Pain in acute glaucoma is prolonged and is associated with visual disturbance, pupil enlargement, photophobia and increased intraocular pressure. Differential diagnosis with chronic glaucoma, which is characterized by intermittent, sometimes very severe pain, is more difficult. The corneitis can also simulate cluster headaches due to unilateral pain, lacrimation, reddening of the eye and frequent night pain lasting up to 1 hour. However, the pain is too local and is often accompanied by blepharospasm; in addition, the corneal lesion can be seen by an ophthalmologist. A similar clinical picture is found in the posterior scleritis, but the pain is longer.

- when pain is localized in the gums and jaw may occur differential diagnosis problems with **toothache** and other dental diseases.

- sometimes a differential diagnosis with **sinusitis** is necessary, at least because some patients think that after having symptoms of the nose, they have sinusitis.

## 2. Paroxysmal hemicrania

### Definition

- Paroxysmal hemicrania manifest with attacks with a characteristic of pain and accompanying symptoms as with cluster headaches, but with shorter duration (2-30 minutes) and more frequent, completely affected by indomethacin.

**The morbidity** is 1 in 25,000 people and affects 3 times more women.

**Pathophysiology** is as in the case of cluster headache. It is considered as its variant.

It is **classified** as episodic (remission periods) and chronic (no remission). Both forms can evolve into each other. A secondary form is described for arteriovenous malformations, cerebral aneurysms in the circle of Willis, cerebrovascular accidents, infarctions, collagen vascular diseases, Pancoast tumor, pituitary, frontal, cervical, sella turcica and cavernosal sinus, intracranial hypertension, thrombocytopenia and after injuries.

**Clinically**, it occurs at about the age of 34, but it can start between the age of 1 and 81. The headache is very strong, localized in the eye, the frontal or temporal area, and less frequently in the infraorbital, ear, mastoid area or the neck. Pain never changes its side, attacks are shorter (15 to 30 minutes), at regular intervals, mostly during the day and their number is greater (from 8 to 16 daily). Typical is the varying frequency and severity of attacks

on different days. In contrast to cluster headache, triggering factors are flexion and neck rotations. The headache is accompanied by cranial autonomic symptoms.

The **diagnosis of paroxysmal hemicrania** requires the headache to fulfill the following **criteria**:

1. At least 20 attacks fulfilling criteria 2-5.
2. Attacks of severe unilateral orbital, supraorbital or temporal pain lasting 2-30 minutes.
3. Fulfills either or both of the following:
  - at least one of the following symptoms, ipsilateral to the headache is available:
    - Conjunctival injection and/or lacrimation
    - Nasal congestion and/or rhinorrhea
    - Eyelid edema
    - Forehead and facial sweating
    - Miosis and/or ptosis
  - A sense of restlessness or agitation
4. Attacks occur with a frequency of >5 per day
5. Attacks are affected absolutely by therapeutic doses of indomethacin.
6. Symptoms cannot be better explained by another type of headache.

In order to exclude incomplete therapeutic response, indomethacin should be administered at doses above 150 mg daily orally (to 225 mg if necessary) or 100-200 mg by injection.

**Episodic paroxysmal hemicrania** should fulfill the criteria for paroxysmal hemicrania and also with at least 2 periods of 7 to 365 days, separated by pain-free periods lasting at least 3 months.

**Chronic paroxysmal hemicrania** should fulfill the criteria the criteria for paroxysmal hemicrania with attacks occurring for 1 year without remission, or with remission periods lasting less than 3 months.

**Differential diagnosis** is primarily done with secondary (*symptomatic*) paroxysmal hemicrania. It is relatively common and is caused by pathological processes with different localization. Even patients with a typical clinical course and response to indomethacin may be symptomatic. It is also important to differentiate vascular disease of the brain. This requires MRT testing in any newly diagnosed patient, even if they are well affected by indomethacin. Blood scanning (thrombocythemia), pituitary hormones, vasculitis and

coagulopathy workup, lumbar puncture for intracranial hypertension and chest X-ray are necessary.

*Cluster headache* is the next important differential diagnosis, given the different treatment of both types of headache. Both types of headache are very similar in their clinical course. The frequency of the attacks in patients with paroxysmal hemicrania is greater (6 to 1 attacks on average) and the duration of the attacks is shorter (26 to 60 minutes on average). Despite these differences, it is desirable for all patients to try the efficacy of indomethacin therapy.

*Hemicrania continua* is also affected by indomethacin. The differentiation from paroxysmal hemicrania, which has intermittent pain, is difficult. Distinctive features are weaker intermittent pain than with hemicrania continua. Exacerbated pain with paroxysmal hemicrania is shorter but stronger than that of hemicrania continua

SUNCT syndrome is does not respond to indomethacin.

### 3. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)

#### Definition

- It is characterized by attacks of moderate or severe, strictly unilateral headache, lasting seconds to minutes, occurring at least once daily and accompanied by lacrimation and redness of the ipsilateral eye.

The disease is rare, occurs a little more often (1.5:1) in male patients.

It is **classified** as an idiopathic and symptomatic form. The symptomatic form is observed in patients with arteriovenous malformations and aneurysms in the pontocerebellar angle, pituitary adenoma, basilar impression, stem infarctions, HIV infection, tumors or other brain damage.

It is subdivided into episodic and chronic forms. Episodic is more common, with symptomatic periods alternating with remissions in a random pattern.

**Pathophysiology**, as with other trigeminal autonomic cephalalgies, is probably associated with activation of the hypothalamus.

**Clinically**, it starts between the age of 35 and 65 (at the age of 48 on average), but there are cases reported for onset at the age of 10 and 77. The pain is short, unilateral, strong and neuralgic - sharp, burning, shocking, like electric current or piercing. It starts suddenly, reaches its maximum for 1-2 seconds and remains as strong as possible until the moment it suddenly stops. Localized in the area innervated by the ophthalmic branch of the

trigeminal nerve - the eye, the temple, the forehead or the face. It can also irradiate in other ipsilateral regions, innervated by the maxillary and mandibular branch of the trigeminal nerve (the nose and the teeth) and, less often, in the ear and neck. Pain rarely (20%) changes its side or is bilateral. Attacks occur mostly during the day, with 17% of patients having only daytime attacks, some patients (66%) sometimes having night attacks. The average number of daily attacks is 16 but from 1 to 100 attacks can occur. The attacks are either spontaneous or triggered by touching certain zones in the innervating area of the trigeminal nerve. The accompanying autonomic symptoms are unilateral and ipsilateral. They start 1-2 seconds after the pain occurs and end seconds after its disappearance.

The syndrome with a typical headache but without conjunctival injection and lacrimation is considered a subtype and is called **SUNA**.

It is subdivided into episodic and chronic form.

**Diagnostic criteria** require headaches to fulfill the following criteria:

1. At least 20 attacks fulfilling criteria 2-4.
2. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal or other trigeminal localization, lasting for 1–600 seconds and occurring as single stabs or series of stabs.
3. At least one of the autonomic symptoms occur, ipsilateral to the pain
  - Conjunctival injection and/or lacrimation
  - Nasal congestion and/or rhinorrhea
  - Eyelid edema
  - Forehead and facial sweating
  - Miosis and/or ptosis
4. Occurring with a frequency of at least one a day
5. Symptoms cannot be better explained by another type of headache.

**Episodic form** of SUNCT is diagnosed with at least two attacks continuing without treatment from 7 days to 1 year and separated by a remission period of  $\geq 3$  months.

**Chronic form** of SUNCT is diagnosed with headache without remission or with remission lasting less than 3 months for one year.

**Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)** is diagnosed in patients who fulfill the SUNCT criteria and have no more than one of the symptoms ipsilaterally to the headache:

- Conjunctival injection

- Lacrimation

**Episodic form** of SUNA is diagnosed with periods of headache lasting from 7 days to 1 year, separated by remission periods lasting more than three months.

**Chronic form** of SUNA is diagnosed with headache without remission or with remission lasting less than 3 months, for at least one year.

**Differential diagnosis** requires first of all differentiation of a secondary (*symptomatic*) SUNCT syndrome. Brain MRI, prolactin, thyroid stimulating hormone, free thyroxine, cortisol, adrenocorticotrophic hormone, luteinizing hormone, follicle-stimulating hormone, estrogen, testosterone and growth factor tests are required. A diagnostic test with indomethacin should also be conducted to exclude the headaches responding to it.

*Trigeminal neuralgia* is difficult to differentiate due to the similar clinical course.

*The idiopathic (primary) stabbing headache* is more common in women, the pain is spontaneous, with different localization in each attack, and cranial autonomic symptoms are absent. Responding to indomethacin.

*Paroxysmal hemicrania* occurs with longer attacks occurring both during the day and at night and rarely provoked by trigger factors. Responding to indomethacin.

#### 4. Hemicrania continua

##### Definition

- Characterized with a persistent strictly unilateral headache accompanied by ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, sweating of the forehead and face, myositis, ptosis and/or eyelid edema, and/or a feeling of restlessness or agitation completely sensitive to indomethacin.

**It affects** up to 1% of the population but is difficult to diagnose. It occurs twice as often in women.

**Classified** according to its course as remitting (12%), secondary chronic (35%) or primary chronic (53%) form.

**Pathophysiology** is unknown, activation has been established in the contralateral posterior hypothalamus and the ipsilateral rostral part of the pons.

**Clinically**, it occurs at the age of about 34 (between the age of 11 and 58). The persistent headache is dull and compulsive, constant, with moderate intensity. It is strictly unilateral and does not change its side for at least 3 months. Localized in the eye, temporal or maxillary area. In most cases, it is unremitting, and periods of intensified pain overlap with it.



Exacerbations, with moderate to severe pain lasting from 20 minutes to several days, overlap with the dull headache. The frequency of exacerbations ranges from several times a week, up to once in 3 months. They are localized in the front of the head, but also in the occipital and auricular area or the neck. In 30% of patients, the exacerbations occur at night and wake up the patient. During exacerbations it is similar to migraine, with sudden punctures (20-40%), which last up to 1 minute or a feeling of a foreign body in the eye. Before the headache is exacerbated, there may be an aura or a specific feeling of sand in the eyes. It is not provoked by any of the known triggers that exacerbate other headaches.

Ipsilateral autonomic symptoms may accompany pain during exacerbations. They are not as pronounced as in the cluster headache and paroxysmal hemicrania. 75% of patients have at least one autonomic symptom, most often conjunctival injection and lacrimation. Nasal congestion, rhinorrhea, eyelid edema, ptosis and miosis may be added. During migraine attacks, there may be migraine symptoms such as photophobia and phonophobia.

**Diagnostic criteria** require headaches to fulfill the following criteria:

1. Availability of unilateral headache fulfilling criteria 2-4.
2. Lasting for >3 months, with exacerbations of moderate or greater intensity
3. At least one of the or two of the following symptoms are present:
  - at least one of the symptoms occurs, ipsilateral to the headache
    - Conjunctival injection and/or lacrimation
    - Nasal congestion and/or rhinorrhea
    - Eyelid edema
    - Forehead and facial sweating
    - Miosis and/or ptosis
  - A sense of restlessness or agitation, or aggravation of the pain by movement
4. Responds absolutely to indomethacin
5. Symptoms cannot be better explained by another type of headache

In order to exclude an incomplete therapeutic response, indomethacin should be administered at doses above 150 mg daily orally (to 225 mg if necessary) or 100-200 mg by injection.

**The remitting form** of the headache is diagnosed in patients who fulfill the criteria for hemicrania continua in which the headache left untreated is not daily and continuous but is separated by remission periods lasting 24 hours or more.

**The unremitting form** is diagnosed in patients who fulfill the criteria for hemicrania continua in which the headache is daily and prolonged for at least 1 year, with no remission periods for at least 24 hours.

**Differential diagnosis** is performed with chronic unilateral headaches (chronic migraine, new daily and cervicogenic headaches) and unilateral short-term headaches with ocular-facial autonomic symptoms (trigeminal autonomic cephalgia). It responds to indomethacin as opposed to chronic migraine, cervicogenic and new daily headaches. Paroxysmal hemicrania is also affected by indomethacin, but the attacks are shorter and with more pronounced autonomic symptoms.

The secondary form due to brain tumor, HIV infection, etc., should be also differentiated.

■ **General practitioner should:**

- refer the patient for diagnosis and treatment by a neurologist.

■ **The neurologist** should:

- determine whether there is a form of trigeminal autonomic cephalgia, using the diagnostic criteria;
- refine the diagnosis by performing appropriate pharmacological tests, paraclinical examinations or consultations with other specialists if necessary.

- **The neurologist** should refer the patient to an office or clinic for the treatment of pain in case of establishing anamnestic and clinical evidence of secondary headache or a change in the characteristics of an already established trigeminal autonomic cephalgia.

- **The neurologist** in office or clinic for the treatment of pain should refine the diagnosis by performing appropriate pharmacological tests, paraclinical examinations or consultations with other specialists, as appropriate, in the light of the changes that have occurred or the data of secondary headaches that were collected from the case-history, clinical examination and paraclinical studies.

## Treatment

### 1. Treatment of the cluster headache attacks

It should be considered that the attack pain is so intense that it requires the immediate attention of the physician.

- **Inhalation of 100% oxygen** through a mask at a rate of 12-15 L/min for 15 minutes. It suppresses the headache in about 15 minutes if it is applied at the onset of the attack. Sometimes after a few hours the headache returns. Oxygen use is efficient primarily in patients less than 50 years old and those with episodic headaches. An advantage of this treatment is the lack of contraindications. The effect is due to the oxygen-induced vasoconstriction.

- **Corticosteroids** (Prednisone 40-60 mg) influence the attack quickly and efficiently.

- **Serotonin agonists (triptans)** - Sumatriptan and Zolmitriptan 10 mg in the form of a nasal spray affect the headache quickly and efficiently. Sumatriptan in the form of subcutaneous injection is efficient in 75% of patients

- **Ergotamine derivatives** - the administration of Ergotamine tartarate or Dihydroergotamine 1 mg via a nasal spray shields effectively the acute attack. Applying the preparation on several consecutive days does not cause headache recurrence, as is the case with migraine patients. Ergotamine derivatives are also successfully administered as sublingual tablets (1-2 mg daily) or rectal suppositories (2 mg).

- **Local anesthetics:**

- Cocaine intranasally, ipsilateral to the headache in the form of a 10% solution on cotton swabs for 2 - 5 minutes is efficient, mainly due to the local anesthetic effect and less due to the sympathomimetic effect of the drug. A problem is the high risk of addiction.

- Lidocaine 4% 1 ml of an aqueous solution administered as nasal drops as the patient is lying on the back with an oblique head to the side of the pain reduces the headache. The effect is weaker than that of cocaine.

- **Neuromodulatory methods** are non-invasive (vagus nerve stimulation) and invasive (deep brain stimulation/DBS, occipital nerve stimulation/ONS and sphenopalatine ganglion stimulation/SPG). Invasive methods are costly, have side effects and therefore have very little clinical use.

- non-invasive vagus stimulation in the cervical branch of n. vagus. 3 consecutive 2-minute stimulations at the onset of pain are performed via a portable device. After 3 minutes, if necessary, it can be repeated. Up to 4 attacks (up to 24 stimulations) per day are treated.

- With **children**, oxygen and indomethacin are used.

- **During pregnancy**, oxygen and prednisone may be used.

- Oxygen, sumatriptan and prednisone can be used **during breastfeeding**.

***During breastfeeding, oxygen,*** sumatriptan and prednisone can be used.

- Treatment of cluster headache attacks is performed by a neurologist. If they do not respond to the classical medication, the patient is referred for consultation in a specialized office or clinic for the treatment of pain.

### 3. Prophylactic treatment during the cluster period

In order to be efficient, prophylactic treatment should have a rapid effect in order to prevent attacks within the onset of the cluster period. Applying prophylaxis to prevent the period is not efficient unless the period always starts at a specific time of the year. In these cases, prophylaxis can be started before the onset of the period. Two weeks after the end of the period, prophylactic treatment is stopped because it cannot prevent a further period

**1. The lifestyle** changes during the cluster period include stopping the intake of any alcohol products and smoking. It is necessary to retain a certain cycle of sleep and wakefulness, because long-term sleep triggers attacks. One should not sleep in the afternoon because this will increase the number of attacks. Avoid vasodilator (nitroglycerin) and antihypertensive drugs, as well as long-term exposure to volatile substances such as solvents and oil paints.

**2. Corticosteroids** are the fastest acting prophylactic medication. They are used together with another prophylactic medication at the onset of the cluster period for 5-7 days to achieve the effect more quickly and are gradually decreased when the other drug starts acting. They can be used for a period of 10 to 20 days around the attack period.

- Prednisone – 40 – 80 mg daily

**3. Calcium antagonists** are very efficient. Clinical efficacy is achieved in a few weeks.

- verapamil (tabl. 40 и 80 mg) at a dose of 120 to 160 mg 3-4 times a day. Treatment is started with 240 mg daily at normal ECG. The dose is increased by 80 mg every week at normal ECG until the effect is achieved.

**4. Anticonvulsants** are administered with good effect

- valproates - at a daily dose of 600 to 1200 mg divided into 3-4 intakes (plasma level 60-75 mg/ml)
- topiramate 100-200 mg daily
- gabapentin 900 – 1800 mg daily

**5. Lithium carbonate** 300 mg 2 to 4 times a day is efficient in 60% of patients, mostly with chronic headaches. If necessary, the dose may be increased to 1200 mg daily after a

few weeks, but the serum concentration should be maintained below 1,2 mEq/l. In patients with chronic headache, treatment lasts for 6-12 months after which the doses are slowly reduced. Serum concentration should be measured every week in the first month, then - every month.

**6. Local nerve blockades** of n. occipitalis major, ipsilateral to pain attacks, with corticosteroid and local anesthetic are efficient. Applied in 3 consecutive days.

Verapamil or gabapentin can be used **during pregnancy**, as well as occipital nerve blockades with anesthetic and corticosteroid.

**During breastfeeding**, prednisone, prednisolone, verapamil and lithium carbonate can be used, as well as occipital nerve blockades with anesthetic and corticosteroid.

■ **The neurologist** makes the decision to include one or another drug for the prophylactic treatment of cluster headaches. Prophylactic treatment is continued as long as the cluster period commonly lasts with any individual patient, or until a break occurs in the chronic form.

■ **The neurologist** should examine the patient with cluster headache weekly during the cluster period and in case of any worsening. The patient should be monitored for:

- effect of the applied symptomatic treatment
- effect of the applied prophylactic treatment
- secondary chronification
- No therapy should be prescribed without a personal examination of the patient.

■ **The neurologist** should refer the patient for consultation in an office or clinic for the treatment of pain in case of:

- insufficient effect of the prophylactic treatment at an optimal dose
- presence of symptoms of overdose of therapy.
- chronic cluster headache not responding to therapy.

#### 4. Treatment of paroxysmal hemicrania

It is treated prophylactically because the attacks are too short to rely on a therapeutic response. It is affected dramatically 48 hours after starting treatment with indomethacin 25-50 mg 3-4 times daily orally or rectally. The dose should be maintained at 150 mg daily for the first 3-4 days until the effect is achieved. Thereafter, an individual maintenance dose is

adjusted, depending on the frequency and severity of the attacks. With episodic patients, the treatment should be slightly longer than the usual period, and then the dose should be gradually reduced. With the chronic form, treatment lasts for at least 6 months and attempts are made to lower the doses and withdraw the drug.

### 5. Treatment of SUNCT

It is treated only prophylactically because the attacks are too short to rely on their therapeutic response. Long-term and short-term prophylactic treatment is used.

*Long-term prophylactic treatment* is performed first with lamotrigine (100-400 mg/daily). Drugs of second choice are topiramate (50-300 mg/daily) and gabapentin (800-2700 mg/daily), which is more efficient in SUNA. Thirdly, in case of absence of efficacy, carbamazepine may be administered alone or in combination with lithium, naloxone, verapamil or prednisolone.

*Short-term prophylactic treatment* is administered during the symptomatic period and the patient is hospitalized. In these cases, patients are severely disabled because they cannot often eat and drink fluids, which triggers a new attack. Intravenous lidocaine or corticosteroids are administered, while optimizing the basic long-term prophylactic treatment.

### 6. Hemicrania continua

It responds to prophylactic treatment with indomethacin 25-300 mg. The effect occurs 1-2 days to 2 weeks after reaching the required therapeutic dose. Every 6 months treatment is discontinued/withdrawn to check for spontaneous remission.

- **The neurologist** performs the treatment of paroxysmal hemicrania, hemicrania continua and SUNCT.
- In case of no response to classical medications, the patient is referred for consultation in a specialized office or clinic for the treatment of pain.

## The International Classification of Headache Disorders,3rd edition

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### Primary headaches

#### 1. Migraine

Migraine without aura

Migraine with aura

Migraine with typical aura

Typical aura with headache

Typical aura without headache

Migraine with brainstem aura

Hemiplegic migraine

Familial hemiplegic migraine (FHM)

Familial hemiplegic migraine type 1 (FHM1)

Familial hemiplegic migraine type 2 (FHM2)

Familial hemiplegic migraine type 3 (FHM3)

Familial hemiplegic migraine, other loci

Sporadic hemiplegic migraine (SHM)

Retinal migraine

Chronic migraine

Complications of migraine

Status migrainosus

Persistent aura without infarction

Migrainous infarction

Migraine aura-triggered seizure

Probable migraine

Probable migraine without aura

Probable migraine with aura

Episodic syndromes that may be associated with migraine

Recurrent gastrointestinal disturbance

Cyclical vomiting syndrome

Abdominal migraine

Benign paroxysmal vertigo

Benign paroxysmal

## **2. Tension-type headache (TTH)**

Infrequent episodic tension-type headache

Infrequent episodic tension-type headache associated with pericranial tenderness

Infrequent episodic tension-type headache not associated with pericranial tenderness

Frequent episodic tension-type headache

Frequent episodic tension-type headache associated with pericranial tenderness

Frequent episodic tension-type headache not associated with pericranial tenderness

Chronic tension-type headache

Chronic tension-type headache associated with pericranial tenderness

Chronic tension-type headache not associated with pericranial tenderness

Probable tension-type headache

Probable infrequent episodic tension-type headache

Probable frequent episodic tension-type headache

Probable chronic tension-type headache

## **3. Trigeminal autonomic cephalalgias (TACs)**

Cluster headache

Episodic cluster headache

Chronic cluster headache

Paroxysmal hemicrania

Episodic paroxysmal hemicrania

Chronic paroxysmal hemicrania

Short-lasting unilateral neuralgiform headache attacks

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)

Episodic SUNCT

Chronic SUNCT

Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)

Episodic SUNA

Chronic SUNA

Hemicrania continua

Hemicrania continua, remitting subtype

Hemicrania continua, unremitting subtype

Probable trigeminal autonomic cephalalgia

Probable cluster headache



Probable paroxysmal hemicrania

Probable short-lasting unilateral neuralgiform headache attacks

Probable hemicrania continua

#### **4. Other primary headache disorders**

Primary cough headache

Probable primary cough headache

Primary exercise headache

Probable primary exercise headache

Primary headache associated with sexual activity

Probable primary headache associated with sexual activity

Primary thunderclap headache

Cold-stimulus headache

Headache attributed to external application of a cold stimulus

Headache attributed to ingestion or inhalation of a cold stimulus

Probable cold-stimulus headache

Headache probably attributed to external application of a cold stimulus

Headache probably attributed to ingestion or inhalation of a cold stimulus

External-pressure headache

External-compression headache

External-traction headache

Probable external-pressure headache

Probable external-compression headache

Probable external-traction headache

Primary stabbing headache

Probable primary stabbing headache

Nummular headache

Probable nummular headache

Hypnic headache

Probable hypnic headache

New daily persistent headache (NDPH)

Probable new daily persistent headache

#### **Secondary headaches**

##### **5. Headache attributed to trauma or injury to the head and/or neck**

Acute headache attributed to traumatic injury to the head

Acute headache attributed to moderate or severe traumatic injury to the head  
Acute headache attributed to mild traumatic injury to the head  
Persistent headache attributed to traumatic injury to the head  
Persistent headache attributed to moderate or severe traumatic injury to the head  
Persistent headache attributed to mild traumatic injury to the head  
Acute headache attributed to whiplash  
Persistent headache attributed to whiplash  
Acute headache attributed to craniotomy  
Persistent headache attributed to craniotomy

## **6. Headache attributed to cranial and/or cervical vascular disorder**

Headache attributed to cerebral ischaemic event  
Headache attributed to ischaemic stroke (cerebral infarction)  
Acute headache attributed to ischaemic stroke (cerebral infarction)  
Persistent headache attributed to past ischaemic stroke (cerebral infarction)  
Headache attributed to transient ischaemic attack (TIA)  
Headache attributed to non-traumatic intracranial haemorrhage  
Acute headache attributed to non-traumatic intracerebral haemorrhage  
Acute headache attributed to non-traumatic subarachnoid haemorrhage (SAH)  
Acute headache attributed to non-traumatic acute subdural haemorrhage (ASDH)  
Persistent headache attributed to past non-traumatic intracranial haemorrhage  
Persistent headache attributed to past non-traumatic intracerebral haemorrhage  
Persistent headache attributed to past non-traumatic subarachnoid haemorrhage  
Persistent headache attributed to past non-traumatic acute subdural haemorrhage  
Headache attributed to unruptured vascular malformation  
Headache attributed to unruptured saccular aneurysm  
Headache attributed to arteriovenous malformation (AVM)  
Headache attributed to dural arteriovenous fistula (DAVF)  
Headache attributed to cavernous angioma  
Headache attributed to encephalotrigeminal or leptomeningeal angiomatosis (Sturge Weber syndrome)  
Headache attributed to arteritis  
Headache attributed to giant cell arteritis (GCA)  
Headache attributed to primary angiitis of the central nervous system (PACNS)  
Headache attributed to secondary angiitis of the central nervous system (SACNS)

Headache attributed to cervical carotid or vertebral artery disorder

Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection

Acute headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection

Persistent headache or facial or neck pain attributed to past cervical carotid or vertebral artery dissection

Post-endarterectomy headache

Headache attributed to carotid or vertebral angioplasty or stenting

Headache attributed to cranial venous disorder

Headache attributed to cerebral venous thrombosis (CVT)

Headache attributed to cranial venous sinus stenting

Headache attributed to other acute intracranial arterial disorder

Headache attributed to an intracranial endarterial procedure

Angiography headache

Headache attributed to reversible cerebral vasoconstriction syndrome (RCVS)

Acute headache attributed to reversible cerebral vasoconstriction syndrome (RCVS)

Acute headache probably attributed to reversible cerebral vasoconstriction syndrome (RCVS)

Persistent headache attributed to past reversible cerebral vasoconstriction syndrome (RCVS)

Headache attributed to intracranial artery dissection

Headache and/or migraine-like aura attributed to chronic intracranial vasculopathy

Headache attributed to Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

Headache attributed to mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)

Headache attributed to Moyamoya angiopathy (MMA)

Migraine-like aura attributed to cerebral amyloid angiopathy (CAA)

Headache attributed to syndrome of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCLSM)

Headache attributed to other chronic intracranial vasculopathy

Headache attributed to pituitary

## **7. Headache attributed to non-vascular intracranial disorder**

Headache attributed to increased cerebrospinal fluid (CSF) pressure

Headache attributed to idiopathic intracranial hypertension (IIH)

Headache attributed to intracranial hypertension secondary to metabolic, toxic or hormonal cause

Headache attributed to intracranial hypertension secondary to chromosomal disorder

Headache attributed to intracranial hypertension secondary to hydrocephalus

Headache attributed to low cerebrospinal fluid (CSF) pressure

Post-dural puncture headache

Cerebrospinal fluid (CSF) fistula headache

Headache attributed to spontaneous intracranial hypotension

Headache attributed to non-infectious inflammatory intracranial disease

Headache attributed to neurosarcoidosis

Headache attributed to aseptic (non-infectious) meningitis

Headache attributed to other non-infectious inflammatory intracranial disease

Headache attributed to lymphocytic hypophysitis

Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)

Headache attributed to intracranial neoplasia

Headache attributed to intracranial neoplasm

Headache attributed to colloid cyst of the third ventricle

Headache attributed to carcinomatous meningitis

Headache attributed to hypothalamic or pituitary hyper- or hyposecretion

Headache attributed to intrathecal injection

Headache attributed to epileptic seizure

Ictal epileptic headache

Post-ictal headache

Headache attributed to Chiari malformation type I (CM1)

Headache attributed to other non-vascular intracranial disorder

## **8. Headache attributed to a substance or its withdrawal**

Headache attributed to use of or exposure to a substance

Nitric oxide (NO) donor-induced headache

Immediate NO donor-induced headache

Delayed NO donor-induced headache

Phosphodiesterase (PDE) inhibitor-induced headache

Carbon monoxide (CO)-induced headache

Alcohol-induced headache

Immediate alcohol-induced headache  
Delayed alcohol-induced headache  
Cocaine-induced headache  
Histamine-induced headache  
Immediate histamine-induced headache  
Delayed histamine-induced headache  
Calcitonin gene-related peptide (CGRP)-induced headache  
Immediate CGRP-induced headache  
Delayed CGRP-induced headache  
Headache attributed to exogenous acute pressor agent  
Headache attributed to occasional use of non-headache medication  
Headache attributed to long-term use of non-headache medication  
Headache attributed to use of or exposure to other substance  
Medication-overuse headache (MOH)  
Ergotamine-overuse headache  
Triptan-overuse headache  
Non-opioid analgesic-overuse headache  
Paracetamol (acetaminophen)-overuse headache  
Non-steroidal anti-inflammatory drug (NSAID)-overuse headache  
Acetylsalicylic acid-overuse headache  
Other non-opioid analgesic-overuse headache  
Opioid-overuse headache  
Combination-analgesic-overuse headache  
Medication-overuse headache attributed to multiple drug classes not individually overused  
Medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes  
Medication-overuse headache attributed to other medication  
Headache attributed to substance withdrawal  
Caffeine-withdrawal headache  
Opioid-withdrawal headache  
Oestrogen-withdrawal headache  
Headache attributed to withdrawal from chronic use of other substance

**9. Headache attributed to infection**  
Headache attributed to intracranial infection

Headache attributed to bacterial meningitis or meningoencephalitis  
Acute headache attributed to bacterial meningitis or meningoencephalitis  
Chronic headache attributed to bacterial meningitis or meningoencephalitis  
Persistent headache attributed to past bacterial meningitis or meningoencephalitis  
Headache attributed to viral meningitis or encephalitis  
Headache attributed to viral meningitis  
Headache attributed to viral encephalitis  
Headache attributed to intracranial fungal or other parasitic infection  
Acute headache attributed to intracranial fungal or other parasitic infection  
Chronic headache attributed to intracranial fungal or other parasitic infection  
Headache attributed to localized brain infection  
Headache attributed to systemic infection  
Headache attributed to systemic bacterial infection  
Acute headache attributed to systemic bacterial infection  
Chronic headache attributed to systemic bacterial infection  
Headache attributed to systemic viral infection  
Acute headache attributed to systemic viral infection  
Chronic headache attributed to systemic viral infection  
Headache attributed to other systemic infection  
Acute headache attributed to other systemic infection  
Chronic headache attributed to other systemic infection

#### **10. Headache attributed to disorder of homoeostasis**

Headache attributed to hypoxia and/or hypercapnia  
High-altitude headache  
Headache attributed to aeroplane travel  
Diving headache  
Sleep apnoea headache  
Dialysis headache  
Headache attributed to arterial hypertension  
Headache attributed to pheochromocytoma  
Headache attributed to hypertensive crisis without hypertensive encephalopathy  
Headache attributed to hypertensive encephalopathy  
Headache attributed to pre-eclampsia or eclampsia  
Headache attributed to autonomic dysreflexia

Headache attributed to hypothyroidism

Headache attributed to fasting

Cardiac cephalalgia

Headache attributed to other disorder of homeostasis

**11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure**

Headache attributed to disorder of cranial bone

Headache attributed to disorder of the neck

Cervicogenic headache

Headache attributed to retropharyngeal tendonitis

Headache attributed to craniocervical dystonia

Headache attributed to disorder of the eyes

Headache attributed to acute angle-closure glaucoma

Headache attributed to refractive error

Headache attributed to ocular inflammatory disorder

Trochlear headache

Headache attributed to disorder of the ears

Headache attributed to disorder of the nose or paranasal sinuses

Headache attributed to acute rhinosinusitis

Headache attributed to chronic or recurring rhinosinusitis

Headache attributed to disorder of the teeth

Headache attributed to temporomandibular disorder (TMD)

Head or facial pain attributed to inflammation of the stylohyoid ligament

Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure

**12. Headache attributed to psychiatric disorder**

Headache attributed to somatization disorder

Headache attributed to psychotic disorder

**13. Painful lesions of the cranial nerves and other facial pain**

Pain attributed to a lesion or disease of the trigeminal nerve

Trigeminal neuralgia

Classical trigeminal neuralgia  
Classical trigeminal neuralgia, purely paroxysmal  
Classical trigeminal neuralgia with concomitant continuous pain  
Secondary trigeminal neuralgia  
Trigeminal neuralgia attributed to multiple sclerosis  
Trigeminal neuralgia attributed to space-occupying lesion  
Trigeminal neuralgia attributed to other cause  
Idiopathic trigeminal neuralgia  
Idiopathic trigeminal neuralgia, purely paroxysmal  
Idiopathic trigeminal neuralgia with concomitant continuous pain  
Painful trigeminal neuropathy  
Painful trigeminal neuropathy attributed to herpes zoster  
Trigeminal post-herpetic neuralgia  
Painful post-traumatic trigeminal neuropathy  
Painful trigeminal neuropathy attributed to other disorder  
Idiopathic painful trigeminal neuropathy  
Pain attributed to a lesion or disease of the glossopharyngeal nerve  
Glossopharyngeal neuralgia  
Classical glossopharyngeal neuralgia  
Secondary glossopharyngeal neuralgia  
Idiopathic glossopharyngeal neuralgia  
Painful glossopharyngeal neuropathy  
Painful glossopharyngeal neuropathy attributed to a known cause  
Idiopathic painful glossopharyngeal neuropathy  
Pain attributed to a lesion or disease of nervus intermedius  
Nervus intermedius neuralgia  
Classical nervus intermedius neuralgia  
Secondary nervus intermedius neuralgia  
Idiopathic nervus intermedius neuralgia  
Painful nervus intermedius neuropathy  
Painful nervus intermedius neuropathy attributed to herpes zoster  
Post-herpetic neuralgia of nervus intermedius  
Painful nervus intermedius neuropathy attributed to other disorder  
Idiopathic painful nervus intermedius neuropathy  
Occipital neuralgia



Neck-tongue syndrome

Painful optic neuritis

Headache attributed to ischaemic ocular motor nerve palsy

Tolosa–Hunt syndrome

Paratrigeminal oculosympathetic (Raeder's) syndrome

Recurrent painful ophthalmoplegic neuropathy

Burning mouth syndrome (BMS)

Persistent idiopathic facial pain (PIFP)

Central neuropathic pain

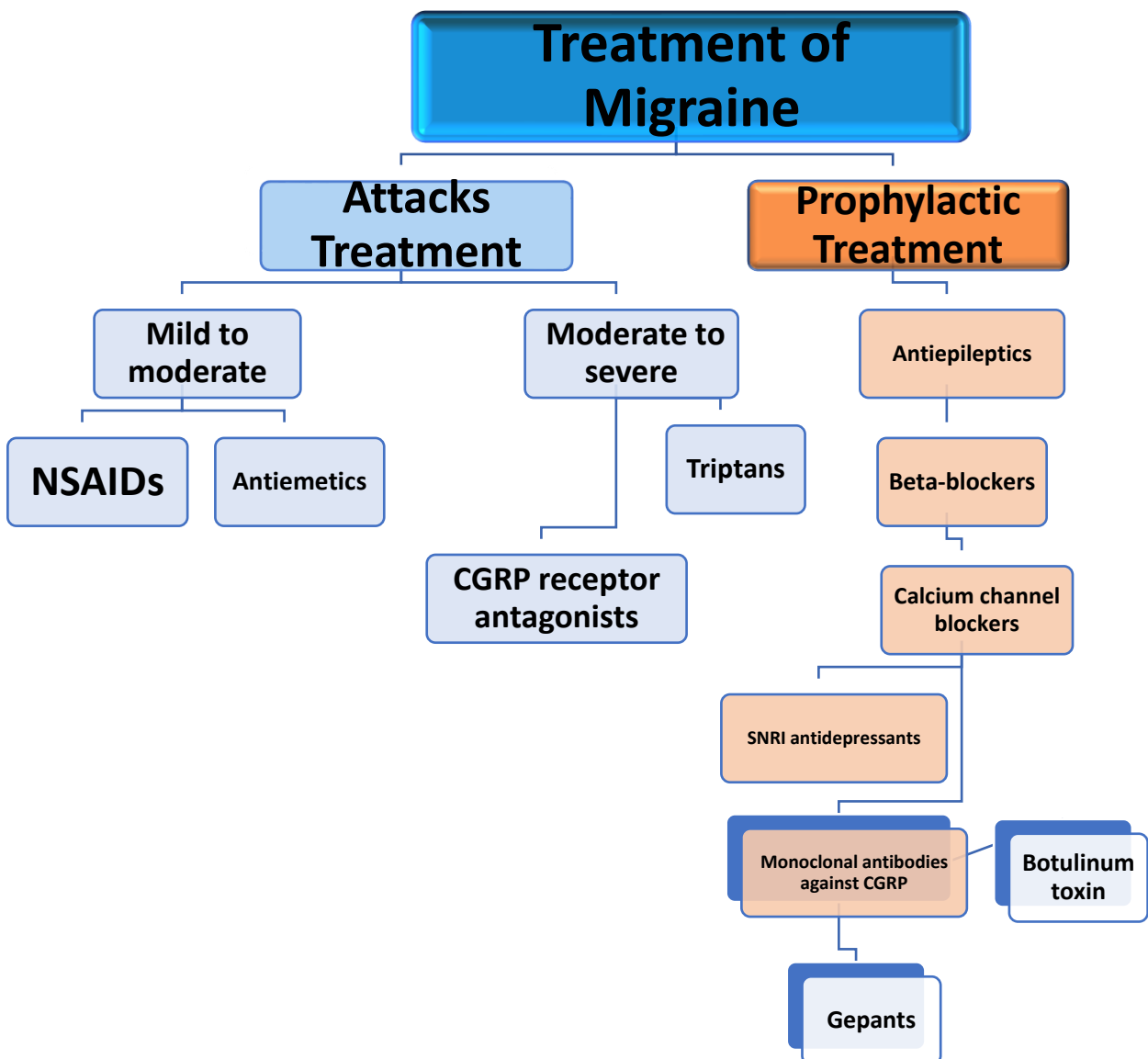
Central neuropathic pain attributed to multiple sclerosis (MS)

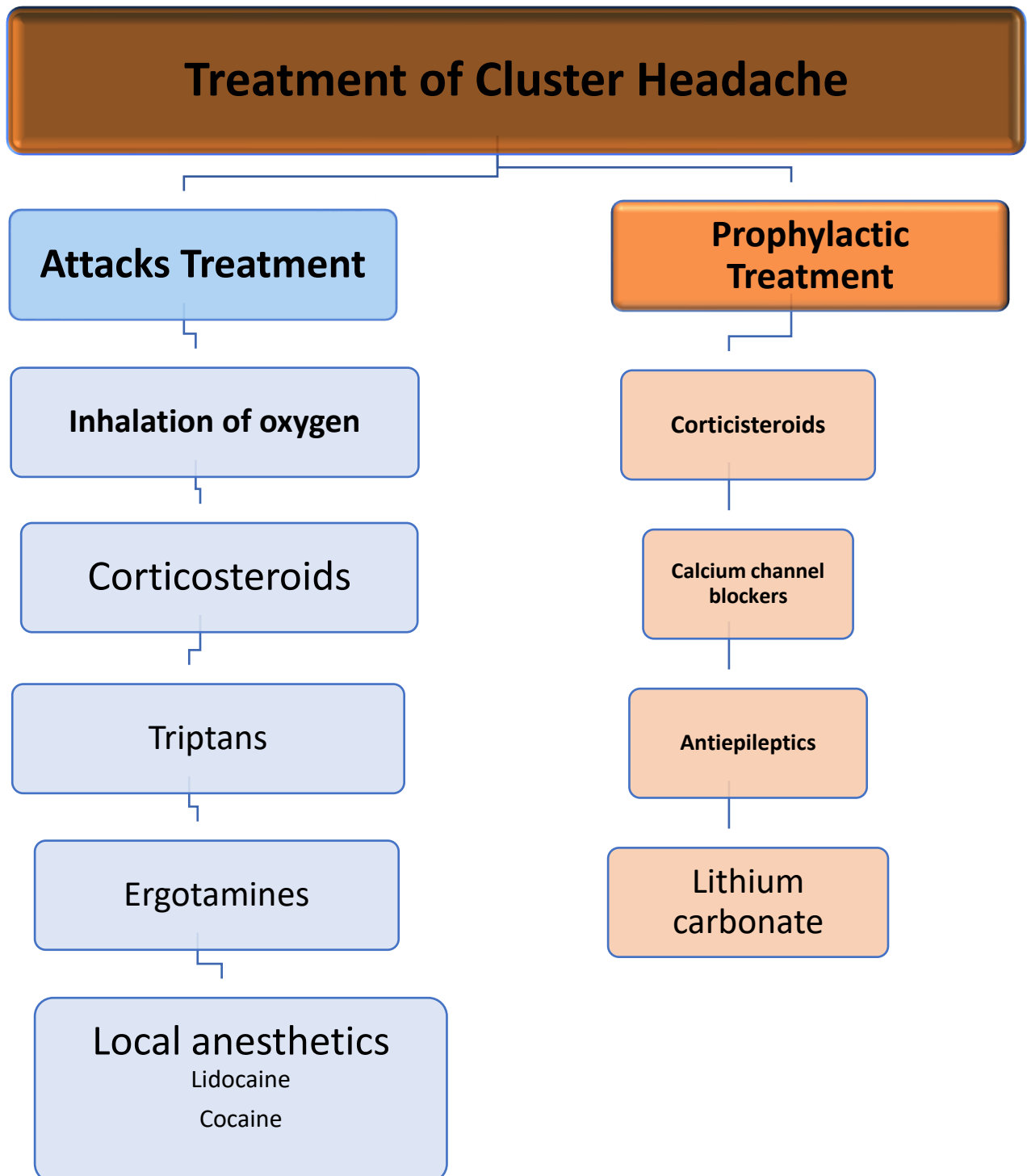
Central post-stroke pain (CPSP)

#### **14. Other headache disorders**

Headache not elsewhere classified

Headache unspecified





## Treatment of Tension-type Headache

