EVIDENCE BASED GUIDELINES FOR TREATMENT OF PRIMARY HEADACHES

Report of the Croatian Neurovascular Society of the Croatian Medical Association

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SUMMARY – A proportion of headache patients should be evaluated by a neurologist. These guidelines are developed to help physicians in making appropriate choice in the work-up and treatment of headache patients. Most migraine sufferers have not been diagnosed by a physician and are not receiving medical guidance to effectively address their migraine attacks. In the past 15 years new therapies (acute and preventive) have been introduced. In migraine patients nonresponders to analgesics, especially in patients with moderate to severe migraine, triptans should be introduced. In migraine with frequent attacks or long lasting attacks, preventive treatment according to comorbid diseases should be recommended. In tension type headache, an underlying pathology should be excluded; management includes pharmacological and non-pharmacological treatment. Although rare, patients with cluster headache experience major pain and disability; in acute management oxygen inhalation or triptans are recommended, in certain cases prophylaxis is indicated. These guidelines contain classification, diagnostic criteria, and principles of management of all primary headaches. These recommendations for headache treatment are based on a comprehensive review and meta-analysis of scientific literature with regard to treatment possibilities in Croatia.

Key words: *migraine; tension headache; cluster headache; headache management; pharmacotherapy*

Introduction

Headache disorders constitute a public health problem with an impact on both individuals and society. The socio-economic burden includes costs associated with health care utilization and economic costs due to reduced productivity or sickleave. A large proportion of headache sufferers are never diagnosed or regularly treated.

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A patient may present for care of headaches during an attack or during a headache-free period. If the patient presents during a headache, appropriate evaluation (history, examination, appropriate testing) needs to be undertaken acutely. The primary headache disorders, which include migraine and tension-type headache, account for the majority of headaches; those with underlying pathology are by far less common (tumor, giant cell arteritis, aneurysm)[1].

Once the diagnosis has been established, acute treatment should be instituted. If the patient has a history of recurrent headaches, a plan of treatment (acute and/or prophylactic) needs to be established.

Guidelines are developed to assist the physician in making appropriate choice in the work-up and treatment of patients. The specific aim of the Evidence Based Guidelines for treatment of primary headaches is to provide recommendations for diagnostic testing in the group of primary headache patients based on a comprehensive review and meta-analysis of scientific evidence.

OVERVIEW, DIAGNOSIS, AND CLASSIFICATION

General Rules for Classification

Classification of a headache disorder requires the following rules to be applied[2]:

1. To make a diagnosis, all diagnostic criteria must be fulfilled. Physicians must diagnose or exclude secondary headaches and diagnose the specific form of primary headache.
2. If one headache type fits the diagnostic criteria for different categories of headache, code it to the first headache category in the classification for which the criteria are fulfilled.
3. If the patient has more than one headache disorder, all should be diagnosed in the order of importance indicated by the patient.
4. If the patient has a form of headache that fulfills one set of diagnostic criteria, similar episodes that do not quite satisfy the criteria also usually occur. This can be due to treatment, inability to remember symptoms exactly, and other factors. Ask the patient to describe a typical untreated attack or an unsuccessfully treated attack, and ascertain that there have been enough of these attacks to establish the diagnosis. Then, estimate the days *per* year with this type of headache, adding treated attacks and less typical attacks.
5. A major obstacle to an exact diagnosis is reliance on the patient's history to determine whether the criteria are met. In less clear cases, have the patient record the attack characteristics prospectively, using a headache diary, before the diagnosis is made.
6. Patients who develop a particular form of headache for the first time in close temporal relation to the onset of one of the disorders listed in groups 5-11 are coded to these groups. However, a causal relationship is not necessarily indicated. Pre-existing migraine, tension type headache, or cluster headache aggravated in close temporal relation to one of the disorders listed in groups 5-11 are still coded as migraine, tension-type headache, or cluster headache (groups 1-3).

Criteria for Hospitalization

General criteria for urgent and non-urgent admission are as follows)[3]:

I Emergency or urgent admission

1. Medical emergency presenting with a severe headache.
2. Severe headache associated with intractable nausea and vomiting producing dehydration or postural hypotension, or unable to retain oral medication and unable to be controlled in an outpatient setting.
3. Failed outpatient treatment of an exacerbation of episodic headache disorder with failure to respond to "rescue" or backup medications.
4. Certain migraine variants (e.g., hemiplegic migraine, suspected migrainous infarction, basilar migraine with serious neurologic symptoms such as syncope, confusional migraine, etc.)
   a) when a diagnosis has not been established during a previous similar occurrence
   b) when the established outpatient treatment plan has failed
5. Diagnostic suspicion of infectious disorder involving central nervous system (CSF) (e.g., brain abscess, and meningitis) with initiation of appropriate diagnostic testing.
6. Diagnostic suspicion of acute vascular compromise (e.g., aneurysm, subarachnoid hemorrhage, and carotid dissection) with initiation of appropriate diagnostic testing.
7. Diagnostic suspicion of a structural disorder causing symptoms requiring an acute setting (e.g., brain tumor, increased intracranial pressure) with initiation of appropriate diagnostic testing.
8. Low cerebrospinal fluid headache when an outpatient blood patch has failed and an outpatient treatment plan has failed.

II Non-emergency admission

1. Impaired daily functioning (e.g., many lost days at work or school due to headache, threatened relationships, etc.), with a failure to respond to 2 days of outpatient treatment with IV analgesics.
2. Severe chronic daily headaches involving chronic medication overuse when there is
   a) daily use of potent opioids and/or barbiturates
   b) daily use of triptans, simple analgesics, or ergotamine in a patient with a documented failed trial of withdrawal of these medications

3. Coexistent psychiatric disease documented by psychologic or psychiatric evaluation with sufficient severity of illness, so that failure to admit could pose a health risk to the patient or impair the implementation of outpatient treatment.
4. Coexistent or risk of disease (e.g., unstable angina, unstable diabetes, recent transient ischemic attack, myocardial infarction in the past 6 months, renal failure, hypertension, age >65) necessitating monitoring for treatment of headache significant enough to warrant admission.

Diagnostic Work-up in Patients with Headache

I Detailed history

Assessment of the headache characteristics requires determination of the following:

- Temporal profile:
  - o Time from onset to peak
  - o Usual time of onset (season, month, menstrual cycle, week, hour of day)
  - o Frequency
  - o Duration
  - o Stable or changing over past 6 months and lifetime
- Descriptive characteristics (pulsatile, throbbing, pressing, sharp, etc.)
- Location (uni- or bilateral, changing sides)
- Severity
- Precipitating features
- Aggravating factors
- Factors which relieve the headache
- Pharmacological and non-pharmacological treatments which are effective or ineffective
- Aura (present in approximately 15% of migraine patients)
- Functional disabilities at work, school, housework or leisure activities during the past 3 months (informally or using well-validated disability questionnaire)

II Neuroimaging

Detection of treatable lesions remains the primary reason to obtain neuroimaging studies[4,5]. Neuroimaging may also relieve the patient's anxiety about having an underlying pathologic condition, therefore neuroimaging may improve the patient's overall satisfaction and medical care.

In adult patients with recurrent headaches defined as migraine, including those with visual aura, with no recent change in headache pattern, no history of seizures, and no other focal neurologic signs or symptoms, the routine use of neuroimaging is not warranted. In patients with atypical headache patterns, a history of seizures or focal neurologic signs and symptoms, computerized tomography (CT) or magnetic resonance imaging (MRI) may be indicated. Neuroimaging should be considered when risk factors for intracranial pathology exist. Testing should be avoided if it will not lead to a change in management. Testing that normally may not be recommended as a population-policy may make sense at an individual level (exceptions may be considered for patients who are disabled by their fear of serious pathology, or for whom the physician in charge is suspicious even in the absence of known predictors of abnormalities on neuroimaging studies[4,5].

Neurologic examination

An abnormal neurologic examination increases the likelihood of finding significant intracranial pathology (brain tumor, AVM, hydrocephalus) on neuroimaging. The absence of any abnormalities on neurologic examination reduces the odds of finding a significant abnormality on imaging studies.

Recommendation: neuroimaging should be considered in patients with non-acute headache and an unexplained abnormal finding on the neurologic examination (Level B)

Neurologic symptoms

Headache worsened by Valsalva maneuver, headache causing awakening from sleep, new headache in the older population, or progressively worsening headache may indicate a higher likelihood of significant intracranial pathology. In general, the absence of signs and symptoms is less reliable and informative than their presence.

Recommendation: evidence is insufficient to make specific recommendations regarding neuroimaging in the presence or absence of neurologic symptoms (Level C).

Reasons to consider neuroimaging for headaches

Temporal profile and headache features

1. The "first or worst" headache
2. Subacute headache with increased frequency or severity
3. A progressive or new daily persistent headache
4. Chronic daily headache
5. Headache always on the same side
6. Headache not responding to treatment
7. History of headache causing awakening from sleep

Demographics

1. New onset headache in a patient who has cancer or is human immunodeficiency virus (HIV) positive
2. New onset headache after age 50
3. Patients with headaches and seizures

Associated symptoms and signs

1. Headache associated with symptoms and signs such as fever, stiff neck, nausea, vomiting
2. Headaches other than migraine with aura associated with focal or generalized neurologic symptoms and signs
3. Headaches associated with papilledema, cognitive impairment, personality change or seizures

Effectiveness of CT vs MRI

Finding: MRI appears to be more sensitive in finding white matter lesions and developmental venous abnormalities than CT, a result that could be expected based upon the characteristics of the two technologies. The greater resolution and discrimination of MRI appears to be of little clinical importance in the evaluation of patients with non-acute headache. Data are lacking comparing enhanced with unenhanced CT scan.

Recommendation: data are insufficient to make any evidence-based recommendations regarding the relative sensitivity of MRI compared with CT in the evaluation of migraine or other non-acute headache (Level C).

Which patients with headache require neuroimaging at emergency department (ED)?

Patients presenting to the emergency department with headache and abnormal findings on a neurologic examination (i.e. focal deficit, altered mental status, and altered cognitive function) should undergo emergent* non-contrast CT scan of the head. HIV-positive patients with a new type of headache should be considered for an urgent* neuroimaging study. Patients presenting with acute sudden-onset headache should be considered for an emergent* head CT scan[4,5] (Level B).

**Emergent studies are those essential for a timely decision regarding potentially life-threatening or severely disabling entities. Urgent studies are those that are arranged prior to discharge from ED (scan appointment is included in the disposition) or performed prior to disposition when follow-up cannot be assured.*

Patients who are older than 50 years presenting with a new type of headache without abnormal findings on neurologic examination should be considered for an urgent neuroimaging study (Level C).

III Electroencephalography (EEG)

EEG is not indicated in the routine evaluation of headache. This does not exclude the use of EEG to evaluate headache patients with associated symptoms suggesting a seizure disorder such as atypical migrainous aura or episodic loss of consciousness. Assuming head imaging capabilities are readily available, EEG is not recommended to exclude a structural cause of headache[4] (Level C).

IV Lumbar puncture (LP)

LP is indicated in the evaluation of:

- meningitis, encephalitis
- meningeal carcinomatosis or lymphomatosis
- subarachnoid hemorrhage (SAH) (when CT scan is negative)
- high (benign intracranial hypertension) or low CSF pressure

Adult patients with headache exhibiting signs of increased intracranial pressure including papilledema, absent venous pulsations on funduscopic examination, altered mental status, or focal neurologic deficits should undergo a neuroimaging study before having an LP. In the absence of findings suggestive of increased intracranial pressure, an LP can be performed without obtaining a neuroimaging study[4]. (Note: An LP does not assess for all causes of a sudden severe headache) (Level C).

V Angiography

Patients with a thunderclap headache who have negative findings on head CT scan, normal opening pressure, and negative findings on CSF analysis do not need emergent angiography and can be discharged from ED with follow-up arranged with their primary care provider or neurologist[4] (Level C).

VI Laboratory studies

Routine clinical laboratory studies followed by specific laboratory studies are recommended if indicated[4].

Diagnostic alarms in the evaluation of headache disorders

Patient history or certain signs and symptoms should alert the physician in the evaluation of a headache disorder[4]:

Symptom	Suspected diagnosis
• headache begins after age 50	– temporal arteritis, mass lesion
• sudden onset headache	– SAH, pituitary apoplexy, bleed into a mass or AVM, mass lesion (especially posterior fossa)
• accelerating pattern of headaches	– mass lesion, subdural hematoma, medication overuse
• new onset headache in patient with cancer or HIV	– meningitis (chronic or carcinomatous), brain abscess (including toxoplasmosis), metastasis
• headache with systemic illness	– meningitis, encephalitis, Lyme disease, systemic infection, collagen vascular disease
• focal or generalized neurologic symptoms or signs of disease	– mass lesion, AVM, stroke, collagen vascular disease
• papilledema	– mass lesion, pseudotumor, meningitis

International Headache Society Classification System

(Headache Classification Committee, 2004)

The second edition of the International Headache Society classification system has been recently released[2]. The diagnosis of headache disorders should be made as accurately as possible according to the following classification:

A. Primary headache disorders

l.	[G43]	Migraine
1.1	[G43.0]	Migraine without aura
1.2	[G43.1]	Migraine with aura
1.2.1	[G43.10]	Typical aura with migraine headache
1.2.2	[G43.10]	Typical aura with non-migraine headache
1.2.3	[G43.104]	Typical aura without headache
1.2.4	[G43.105]	Familial hemiplegic migraine (FHM)
1.2.5	[G43.105]	Sporadic hemiplegic migraine
1.2.6	[G43.103]	Basilar-type migraine
1.3	[G43.82]	Childhood periodic syndromes that are commonly precursors of migraine
1.3.1	[G43.82]	Cyclic vomiting
1.3.2	[G43.820]	Abdominal migraine
1.3.3	[G43.821]	Benign paroxysmal vertigo of childhood
1.4	[G43.81]	Retinal migraine
1.5	[G43.3]	Complications of migraine
1.5.1	[G43.3]	Chronic migraine
1.5.2	[G43.2]	Status migrainosus
1.5.3	[G43.3]	Persistent aura without infarction
1.5.4	[G43.3]	Migrainous infarction
1.5.5	[G43.3]	Migraine-triggered seizure
1.6	[G43.83	Probable migraine
1.6.1	[G43.83]	Probable migraine without aura
1.6.2	[G43.83]	Probable migraine with aura
1.6.5	[G43.83]	Probable chronic migraine
2.	**[G44.2]**	**Tension-type headache (TTH)**
2.1	[G44.2]	Infrequent episodic tension-type headache
2.1.1	[G44.20]	Infrequent episodic tension-type headache associated with pericranial tenderness
2.1.2	[G44.21]	Infrequent episodic tension-type headache not associated with pericranial tenderness
2.2	[G44.2]	Frequent episodic tension-type headache
2.2.1	[G44.20]	Frequent episodic tension-type headache associated with pericranial tenderness
2.2.2	[G44.21]	Frequent episodic tension-type headache not associated with pericranial tenderness
2.3	[G44.2]	Chronic tension-type headache
2.3.1	[G44.22]	Chronic tension-type headache associated with pericranial tenderness
2.3.2	[G44.23]	Chronic tension-type headache not associated with pericranial tenderness
2.4	[G44.28]	Probable tension-type headache
2.4.1	[G44.28]	Probable infrequent episodic tension-type headache
2.4.2	[G44.28]	Probable frequent episodic tension-type headache
2.4.3	[G44.28]	Probable chronic tension-type headache
3.	**[G44.0]**	**Cluster headache and other trigeminal autonomic cephalalgias**
3.1	[G44.0]	Cluster headache
3.1.1	[G44.01]	Episodic cluster headache
3.1.2	[G44.02]	Chronic cluster headache
3.2	[G44.03]	Paroxysmal hemicrania
3.2.1	[G44.03]	Episodic paroxysmal hemicrania
3.2.2	[G44.03]	Chronic paroxysmal hemicrania (CPH)

3.3	[G44.08]	Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT)
3.4	[G44.08]	Probable trigeminal autonomic cephalalgia
3.4.1	[G44.08]	Probable cluster headache
3.4.2	[G44.08]	Probable paroxysmal hemicrania
3.4.3	[G44.08]	Probable SUNCT
4.	**[G44.80]**	**Other primary headaches**
4.1	[G44.800]	Primary stabbing headache
4.2	[G44.803]	Primary cough headache
4.3	[G44.804]	Primary exertional headache
4.4	[G44.805]	Primary headache associated with sexual activity
4.4.1	[G44.805]	Preorgasmic headache
4.4.2	[G44.805]	Orgasmic headache
4.5	[G44.80]	Hypnic headache
4.6	[G44.80]	Primary thunderclap headache
4.7	[G44.80]	Hemicrania continua
4.8	[G44.2]	New daily-persistent headache (NDPH)
B.	**Secondary headache disorders**	
5.	[G44.88]	Headache attributed to head and/or neck trauma
6.	[G44.81]	Headache attributed to cranial or cervical vascular disorder
7.	[G44.82]	Headache attributed to non-vascular intracranial disorder
8.	[G44.4 or G44.83]	Headache attributed to a substance or its withdrawal
9.	[G44.821]	Headache attributed to infection
10.	[G44.882]	Headache attributed to disorder of homeoeostasis
11.	[G44.84]	Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures
12.	(R 51)	Headache attributed to psychiatric disorder
13.	[G44.847, G44.848 or G44.85]	Cranial neuralgias and central causes of facial pain
14.	[R51]	Other headache, cranial neuralgia, central or primary facial pain

1. MIGRAINE

Migraine is a common neurologic disorder that results in a spectrum of disability within and among different individuals. Migraine causes significant burden for both the individual and the society. Calculations of direct costs generally include physician visits, emergency department treatment, inpatient care, and pharmacotherapy. Indirect costs include lost work days and reduced performance at work; two-thirds of the financial burden are linked to indirect costs[6]. Approximately 3/4 of migraine sufferers have a reduced ability to function during attacks with more than half reporting severe disability or need of bed rest. Therefore it is plausible that many headache sufferers are unaware that effective treatment exists and do not consult a physician. Most migraine sufferers have not been officially diagnosed by a physician; therefore, many patients are lacking medical guidance to effectively address their migraine attacks. Over half of all migraine sufferers deny having received a migraine diagnosis from a physician, and of those patients who receive an accurate diagnosis, many do not receive appropriate therapy.

Prevalence estimates for women range from 12.9% to 17.6%; the range for men is 3.4%-6.1%[7,8]. Migraine is consistently found to be more prevalent in females than in males, with a female to male ratio ranging from 2:1 to 3:1. Migraine prevalence has also been found to be age dependent. In women, the prevalence appears to increase with age until the peak prevalence is reached during the fourth or fifth decade of life. A similar trend is seen in men, although the peak prevalence occurs earlier. Thereafter, the prevalence decreases for both sexes but remains higher in women than in men[9,10].

Migraine prevalence is significantly higher in Caucasians (20.4%) than in African Americans (16.2%) or Asian Americans (9.2%)[11].

The mechanism of migraine pain development is not fully understood. The theory of neurogenic inflammation proposes that the main event is inflammation in the vessel wall, which leads to leakage of nociceptive substances, causing thickening of the vessel wall and dilatation of vascular smooth muscles. The release of vasoactive neuropeptides causes depolarization of trigeminal perivascular axons, thus causing pain[12]. Epidemiologic studies of the vessel lumen diameter and studies of changes in cerebral hemodynamics and vasoreactivity during migraine attack and in free periods contribute to the understanding of the migraine pathomechanism[13-17].

There is a longstanding belief that hereditary factors are involved in migraine, this view being supported by the re-

sults of recent genetic mapping studies. Migraine is a polygenic multifactorial disorder; it seems likely that a combination of genetic factors interact with environmental triggers to produce migraine in susceptible patients. Genetic factors likely account for 30% of the risk, with environmental factors contributing 70% of the risk[18]. A gene for familial hemiplegic migraine has been mapped to chromosome 19 in most families. The genetics of the more frequent variants, migraine with and without aura, is more complex[19].

Diagnostic testing

There are, as yet, no tests that confirm the diagnosis of migraine[4,20,21]. The headache diary is the most important diagnostic tool and should be filled in for at least 3 months; the frequency, duration and intensity of migraine attacks are recorded in the diary. The total number of hours with headache *per* month, the presence of accompanying symptoms, and the use of symptomatic therapy should be listed. Selective testing, including neuroimaging (CT or MRI), electroencephalogram, lumbar puncture, cerebrospinal fluid and blood studies, may be indicated to evaluate for secondary headache if causes of concern have been identified in the patient history or by physical examination. Diagnosis may be complicated if several headache types coexist in the same patient.

Neuroimaging is unlikely to reveal an abnormality on MRI or CT scanning in patients with migraine and normal neurologic examination[5].

Neuroimaging is not usually warranted for patients with migraine and normal neurologic examination (Level B). For patients with atypical headache features or patients who do not fulfill the strict definition of migraine (or have some additional risk factors), a lower threshold for neuroimaging may be applied (Level C).

Prodromes

Premonitory symptoms include changes in mood or behavior that precede the onset of migraine attack by a short time interval. Many suspected precipitants have been reported. Environmental factors (emotional upset, weather changes, lack of sleep, skipping meals) and hormonal fluctuations may trigger or aggravate migraine in susceptible individuals. Migraine with aura is more frequently associated with precipitating factors than migraine without aura[22]. In case of suspected food triggers, the migraine prodrome (the initial stage of the attack before headache develops) can sometimes cause craving for certain food. Therefore, a particular food may be blamed for the migraine, when craving and consumption of the food are actually a consequence of the start of the attack. Certain migraineurs appear to be sensitive to some sorts of red wine in normal amounts, and several aspects of the pharmacology of red wine may contribute to this effect[23,24].

Premonitory symptoms in migraine include:

- psychologic: depression, hyperactivity, euphoria, talkativeness, irritability, drowsiness, restlessness
- neurologic: photophobia, difficulty in concentrating, phonophobia, dysphasia, hyperosmia, yawning
- general: stiff neck, food craving, cold feeling, anorexia, sluggishness, diarrhea or constipation, thirst, urination, fluid retention

Migraine types

1.1. Migraine without aura – diagnostic criteria

Previously used term: common migraine

A. At least 5 attacks fulfilling B-D
B. Headache lasting 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe intensity (inhibits or prohibits daily activities)
   4. Aggravation by walking stairs or similar routine physical activity
D. During headache, at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not attributed to another disorder

1.2 Migraine with aura – diagnostic criteria

Previously used terms: classic migraine, hemiplegic migraine, hemiparesthetic migraine, aphasic migraine, migraine accompagnee

The migraine headache may be preceded by aura; approximately 10%-25% of migraine sufferers report aura[4]. Aura is a focal neurologic deficit that usually precedes the onset of headache by 5-60 minutes. Aura is both more sensitive and specific than premonitory symptoms in the diagnosis of migraine.

Aura symptoms:

Visual: scotoma; photopsia or phosphenes; geometric forms; fortification spectra; objects may rotate, oscillate, or shimmer; brightness appears often very bright.

Visual hallucinations or distortions: metamorphopsia; macropsia; zoom or mosaic vision

Sensory: paresthesias, often migrating, often lasting for minutes (cheiro-oral), and can become bilateral olfactory hallucinations

Motor: weakness or ataxia

Language: dysarthria or aphasia

Delusions and disturbed consciousness: deja vu, multiple conscious trance-like states

A. There have been at least two attacks fulfilling criterion B listed below

B. At least three of the following characteristics are present:

1. There are one or more fully reversible aura symptoms indicating focal cerebral cortical or brain stem dysfunction
2. Either at least one aura symptom develops gradually over more than 4 minutes, or two or more symptoms occur in succession
3. No aura symptom lasts more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased
4. Headache follows aura with a free interval of less than 60 minutes (it may also begin before or simultaneously with the aura)

C. No evidence of organic disease – history, physical examination and diagnostic tests exclude a secondary cause

1.2.1. Typical aura with migraine headache

A. At least 2 attacks fulfilling criteria B-D

B. Aura consisting of at least one of the following but no motor weakness:

1. fully reversible visual symptoms including positive features (flickering lights, spots or lines) and/or negative features (loss of vision)
2. fully reversible sensory symptoms including positive symptoms (pins and needles) and/or negative features (numbness)
3. fully reversible dysphasic speech disturbances

C. At least two of the following:

1. homonymous visual symptoms and or unilateral sensory symptoms
2. at least one aura symptom develops gradually over >5 minutes and/or different aura symptoms occur in succession over >5 minutes
3. each symptom lasts >5 and <60 minutes

D. Headache fulfilling criteria B-D for *1.1 Migraine without aura* begins during the aura or follows aura within 60 minutes

E. Not attributed to another disorder

1.2.2. Typical aura with non-migraine headache

A, B, C as in 1.2.1.

D. Headache not fulfilling criteria B-D for *1.1 Migraine without aura* begins during the aura or follows aura within 60 minutes

E. Not attributed to another disorder

1.2.3. Typical aura without headache

A, B, C as in 1.2.1.

D. Headache does not occur during aura nor follows aura within 60 minutes

E. Not attributed to another disorder

1.2.4. Familial hemiplegic migraine (FHM) (1, 17a)

A. At least 2 attacks fulfilling criteria B and C

B. Aura consisting of fully reversible motor weakness and at least one of the following:

1. fully reversible visual symptoms including positive features (flickering lights, spots or lines) and/or negative features (loss of vision)
2. fully reversible sensory symptoms including positive symptoms (pins and needles) and/or negative features (numbness)
3. fully reversible dysphasic speech disturbances

C. At least two of the following:

1. at least one aura symptom develops gradually over >5 minutes and/or different aura symptoms occur in succession over >5 minutes
2. each aura symptom lasts >5 minutes and <24 hours
3. headache fulfilling criteria B-D for *1.1. Migraine without aura* begins during the aura or follows onset of aura within 60 minutes

D. At least one first- or second-degree relative has attacks fulfilling these criteria A-E

E. Not attributed to another disorder

Comment:

- in FHM 1 there are mutations in the calcium-channel gene CACNA1A on chromosome 19, and in FHM 2 on chromosome 1. FHM is the only known autosomal dominant subtype of migraine
- during FHM 1 attacks, disturbances of consciousness (sometimes including coma), fever, CSF pleocytosis and

confusion can occur; attacks can be triggered by mild trauma
- FHM is very often mistaken for epilepsy (and unsuccessfully treated as such)

1.2.5. Sporadic hemiplegic migraine

A, B, C as in 1.2.4.

D. No first- or second-degree relative has attacks fulfilling these criteria A-E

E. Not attributed to another disorder

1.2.6. Basilar-type migraine

A. At least 2 attacks fulfilling criteria B-D

B. Aura consisting of at least two of the following fully reversible symptoms but no motor weakness:
   1. Dysarthria
   2. Vertigo
   3. Tinnitus
   4. Hypacusia
   5. Diplopia
   6. Visual symptoms simultaneously in both temporal and nasal fields of both eyes
   7. Ataxia
   8. Decreased level of consciousness
   9. Simultaneously bilateral paresthesias

C At least one of the following:
   1. At least one aura symptom develops gradually over >5 minutes and/or different aura symptoms occur in succession over >5 minutes
   2. Each aura symptom lasts >5 and <60 minutes

D. Headache not fulfilling criteria B-D for *1.1 Migraine without aura* begins during the aura or follows aura within 60 minutes

E. Not attributed to another disorder

Comment

- basilar-type migraine should be diagnosed only when no motor weakness occurs, since familial hemiplegic migraine has basilar-type symptoms in 60% of cases.

1.3. Childhood periodic syndromes

Childhood periodic syndromes will not be discussed in these guidelines.

1.4. Retinal migraine – diagnostic criteria

A At least 2 attacks fulfilling criteria B and C

B. Fully reversible monocular positive and/or negative visual phenomena (scintillations, scotomata or blindness) confirmed by examination during attack or (after proper instruction) by the patient's drawing of a monocular field defect during an attack

C. Headache fulfilling criteria B-D for *1.1 Migraine without aura* begins during the visual symptoms or follows them within 60 minutes

D. Normal ophthalmologic examination between attacks

E. Not attributed to another disorder

1.5. Complications of migraine – diagnostic criteria

1.5.1. Chronic migraine

A. Headache fulfilling criteria C and D for *1.1. Migraine without aura* on >15 days/month for >3 months

B. Not attributed to another disorder

Comment:

- when medication overuse is present, this is the most likely cause of chronic symptoms

1.5.2. Status migrainosus

The IHS defines status migrainosus as an attack of migraine in which the headache phase lasts more than 72 hours whether treated or not. The headache is continuous throughout the attack or is interrupted by the headache-free intervals that last less than 4 hours. Short-lasting relief due to medication is also disregarded.

A. The present attack in a patient with *1.1. Migraine without aura* is typical of previous attacks except for its duration

B. Headache has both of the following features:
   1. unremitting for >72 hours
   2. severe intensity

C. Not attributed to another disorder

Comment:

- non-debilitating attacks lasting >72 hours but otherwise meeting these criteria are coded as 1.6.1. Probable migraine without aura

1.5.3. Persistent aura without infarction

Aura symptoms persisting for more than 1 week without radiographic evidence of infarction

A. The present attack in a patient with *1.2. Migraine with aura* is typical of previous attacks except that one or more aura symptoms persist for >1 week

B. Not attributed to another disorder

Comment:

- persistent aura symptoms are often bilateral and may last for months or years
- exclude posterior leukoencephalopathy and migrainous infarction by MRI

1.5.4. Migrainous infarction

A. The present attack in a patient with *1.2. Migraine with aura* is typical of previous attacks except that one or more aura symptoms persist for >60 minutes

B. Neuroimaging demonstrates ischemic infarction in a relevant area

C. Not attributed to another disorder

Comment:

- only cerebral infarction occurring during the course of a typical migraine with aura attack fulfills criteria for migrainous infarction
- ischemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with migraine or cerebral infarction of other cause presenting with symptoms resembling migraine with aura

1.5.5. Migraine-triggered seizure

A seizure triggered by a migraine aura. While migraine-like headaches are frequently seen in the postictal period, sometimes a seizure occurs during or following a migraine attack.

A. Migraine fulfilling criteria for *1.2. Migraine with aura*

B. A seizure fulfilling diagnostic criteria for one type of epileptic attack occurs during or within 1 hour after a migraine aura

1.6. Probable migraine

1.6.1. Probable migraine without aura

A. Attacks fulfilling all but one of criteria A-D for *1.1. Migraine without aura*

B. Not attributed to another disorder

1.6.2. Probable migraine with aura

A. Attacks fulfilling all but one of criteria A-D for *1.1. Migraine with aura* or any of its subforms

B. Not attributed to another disorder

1.6.5. Probable chronic migraine

A. Headache fulfilling criteria C and D for *1.1. Migraine without aura* on >15 days/month for >3 months

B. Not attributed to another disorder, but there is, or has been within last 2 months, medication overuse fulfilling criterion B for any of the subforms of *8.2. Medication-overuse headache*

Treatment of migraine

Migraine sufferers in need of medical care should be encouraged to enter the health care system, consult their physicians, and obtain appropriate treatment. Improved migraine diagnosis is required and improved strategies for treating migraine are needed, because many migraine sufferers are dissatisfied with current treatment.

Most migraine sufferers rely on over-the-counter (OTC) medications and many do not achieve effective relief. About half of all migraine sufferers do not consult their physicians for headache[25].

General principles of management

1. Establish the right diagnosis – an accurate diagnosis facilitates successful management of migraine.
2. Educate migraine patients about their headache type and possibilities of treatment; discuss the pros and cons for a particular treatment, how and when to use it, and possible adverse events.
3. Discuss the expected benefits and goals of therapy and the expected time to achieve them (give realistic information).
4. Treatment choice depends on the frequency and severity of attacks, the presence and degree of temporary disability and associated symptoms such as nausea and vomiting; therefore encourage patients to take an active part in the management of the headache by using diary cards, headache calendars – writing down possible triggers, days of dissability or missed work, school or social activities.
5. Educate the patient to identify and avoid possible triggers.
6. Develop an appropriate, individualized management plan: consider the individual patient response and tolerance to specific medications. The program should include behavioral and educational issues, acute treatment and preventive pharmacotherapy in selected patients.
7. Consider comorbidity (coexisting conditions) such as heart disease, uncontrolled hypertension, thyroid disease, pregnancy, severe liver/kidney damage, as they may limit treatment choices.

Each individual headache must be evaluated in the context of the patient's prior migraine attacks. The practitio-

ner must always remain alert to the possibility of secondary causes of headache, particularly when there is a previously established history of a primary headache disorder such as migraine.

Categorize according to peak severity based on functional impairment, duration of symptoms, and time to peak impairment.

Severity levels:

Mild – Patient is aware of a headache but is able to continue daily routine with minimal alteration.

Moderate – The headache is significant enough to interfere substantially with daily activities but is not completely incapacitating.

Severe – The headache is significant enough to limit all activities or greatly alter them.

Status – A severe headache that has lasted more than 72 hours.

This categorization influences choice of treatment method. For example, parenteral administration (subcutaneous, nasal) should strongly be considered for people whose time to peak disability is <1 hour, who awaken with headache, and for those with severe nausea and vomiting.

I Recommendations for acute treatment of migraine attacks

Principles and recommendations for treatment of acute migraine attacks are as follows[4,26-29]:

1. Treat attacks rapidly (educate the patient to begin treatment as soon as possible); failure to use an effective treatment promptly may increase and prolong the pain and disability.
2. Use medications and dosages that will have no or minimal adverse events (individual approach). The administered dose should be in therapeutic range. Migraine treatment requires higher doses of analgesics than usually recommended for other headaches.
3. a) patients with mild to moderate headache – use nonsteroidal anti-inflammatory drugs (NSAIDs) or combinations such as aspirin plus paracetamol plus caffeine and antiemetics; if response to these medications is poor – use triptans (or dihydroergotamine, DHE).
   b) patients with moderate to severe headache – use migraine specific agents (triptans, DHE)
   c) select a non-oral route of administration for patients with migraine associated with severe nausea or vomiting; nausea is one of the most disabling symptoms of a migraine attack and should be treated appropriately – therefore antiemetics should not be recommended only to patients who are vomiting or are likely to vomit.
4. Minimize the use of back-up and rescue medications, better use higher initial dose (a rescue medication is used at home when other treatments fail and permits the patient to achieve relief without the discomfort and expense of a visit to the physician's office or ED).
5. Educate patients against medication overuse (do not induce "rebound headache" or "drug-induced headache"); frequent use of acute medications such as ergotamines (not DHE), opiates, triptans, simple analgesics and mixed analgesics containing butalbital, caffeine or isometheptene) is generally thought to cause medication overuse headache.
6. Be cost-effective for overall management.

Acute treatment can be nonspecific (analgesics, NSAIDs, opioids, combinations) or specific (triptans, ergot alkaloids and derivatives). Nonspecific drugs control a whole spectrum of pain disorders and in some cases the migraine pain, whereas specific drugs are effective in migraine but are not effective in non-headache pain disorders. The choice of treatment depends on the severity and frequency of attacks, associated symptoms, coexistent disorders, previous treatment response, efficacy of the drug, potential for overuse and adverse events.

A non-oral route of administration combined with an antiemetic should be used in cases of severe nausea and vomiting. Triptans or DHE are first-line drugs for severe attacks and for less severe attacks that do not adequately respond to analgesics[26].

Nonspecific medications

NSAIDs and non-opioid analgesics

Analgesics, NSAIDs and ***acetysalicylic acid*** (ASA) are thought to act *via* inhibition of prostaglandin synthesis and can affect peripheral receptors and the release of inflammatory mediators.

The most consistent evidence of efficacy is available for ASA, ***naproxen sodium***, ***ibuprofen*** (Level A) and ***diclofenac potassium*** (Level B); these medications have good tolerability, wide dose range and relatively few side effects.

NSAIDs and combination analgesics containing caffeine, paracetamol, ASA are a reasonable first-line treatment for mild to moderate migraine attacks or severe atacks that have been responsive in the past to similar NSAIDs or non-opioid analgesics (Level A)[26].

The combination of aspirin and metoclopramide is almost as effective as sumatriptan[30].

Paracetamol (acetaminophen) alone is not recommended for migraine, except in pregnant migraine sufferer (Level B).

It should be noted that daily or almost daily intake of analgesics, NSAIDs or combination of analgesics can induce chronic daily headache[2].

General rule: give the adequate dose as early as possible (avoid overuse!).

Contraindications: analgesics and NSAIDs – in patients with hemorrhagic diathesis or hemocoagulative pathologies, gastric or duodenal ulcer, in patients with severe liver or kidney insufficiency; ibuprofen, naproxen, piroxicam, diclofenac and ketorolac – in congestive heart failure. Pregnancy (except paracetamol) – especially in the first trimester.

Caution is advised in children <16 years; ASA should not be continuously used because of potential danger of Reye's syndrome.

Adverse effects: gastrointestinal symptoms; somnolence, asthenia, blood cell disturbances occur less frequently; skin rashes, urticarial reactions, asthmatic crisis and anaphylactic reactions are rare.

*The majority of NSAIDs and non-opioid analgesics are available in Croatia, some of them are partially covered by Croatian Institute of Health Insurance, a prescription is usually not needed

Barbiturate hypnotics – no randomized, placebo controlled trials have established the efficacy of butalbital containing agents. Because of the potential of drug-overuse headache and withdrawal, their use should be restricted and carefully monitored[31].

Opioids are effective in the treatment of migraine attacks for patients who do not respond to simple analgesics or cannot take ergots or triptans, or as a rescue drug. Because of the risk of drug overuse they should be used less than twice a week in patients who have severe infrequent headaches[26,32]. Use of parenteral and oral combination should only be considered when the risk of abuse has been addressed and sedation will not put the patient at risk.

Combination drugs

Combination of mild opioid (such as codein) enhances analgesic effectiveness up to 40%[29]. Propiphenazone has a high potential of adverse events, but is a relatively common drug used in combination drugs. Combination drugs should best be avoided because certain compounds may be hypodosed and other should not be taken in excess.

Combination drugs common on the market:

ASA 200 mg + paracetamol 200 mg + caffeine 60 mg
Paracetamol 210 mg + propiphenazone 250 mg + caffeine 50 mg + codeine 10 mg
Paracetamol 200 mg + propiphenazone 200 mg + caffeine 50 mg
Paracetamol 500 mg + caffeine 65 mg

*all combinations are available in Croatia as OTC

Other medications

Corticosteroids (dexamethasone or hydrocortisone) are a treatment choice for rescue therapy for patients with status migrainosus[33].

Lidocaine intranasal or lidocaine IV – there is insufficient evidence at this time for their use in the management of acute migraine, although a modest but signifiacant effectiveness has been shown[34].

Antiemetics

Relatively few studies have investigated their effectiveness in migraine attacks; in the majority of cases such studies include a combination of analgesics or NSAIDs with antiemetics. These associations have been proposed to improve the absorption of the symptomatic drugs and to act as adjuvants in reducing nausea and vomiting (Level C).

Metoclopramide IM/IV is an adjunct to control nausea (Level C) and may be considered as IV monotherapy for migraine pain relief (Level B).

Metoclopramide (10 mg) is given either by direct IV injection over 2 to 3 minutes, or in 50 mL of normal saline and infused intravenously over 15 minutes. Each dose of metoclopramide should be administered 15 minutes prior to each DHE injection.

Tietilperazine and ***prochlorperazine*** are adjuncts in the treatment of acute migraine with nausea and vomiting[26,35]. ***Chlorpromazine*** IV may be a therapeutic choice for migraine in the appropriate setting (Level B).

Current evidence does not support the use of ***granisetron*** or ***zatosetron*** (5-HT_3 antagonists) for the symptomatic treatment of migraine attacks as monotherapy (Level B); such drugs could be considered as adjuvants in relieving nausea and vomiting (Level C).

Contraindications: metoclopramide is contraindicated in patients with pheochromocytoma, epilepsy, in patients in whom it may potentially induce extrapyramidal reactions.

Domperidone is not recommended in patients with prolactinoma.

All medications from this group should be used in pregnancy only in cases of extreme necessity.

Adverse effects: metoclopramide, tietilperazine – acute extrapyramidal side effects such as dystonia, akathisia, and oculogyric crisis may occur. Prochlorperazine, chlorpromazine – drowsiness, sedation, postural hypotension

* Metoclopramide and tietilperazine are covered by Croatian Institute of Health Insurance (100% and partial), a prescription is needed. Granisetron is on Hospital Medication List.

Specific medications

Triptans ($5HT_1$ agonists, serotonin 1B/1D receptor agonists)

Triptans are effective and relatively safe for the acute treatment of migraine and are an appropriate initial treatment choice in patients with moderate to severe migraine who have no contraindications for its use and when nonspecific medication has failed to be efficient in the past. A number of controlled studies have demonstrated the efficacy of triptans not only in headache but also for accompanying symptoms (photophobia, phonophobia, nausea and vomiting) and in functional disability[4,36-60].

Triptans may be used during the established headache phase of an attack and are the preferred treatment in those who fail to respond to conventional analgesics. Triptans are effective in the range of mild, moderate and severe migraine attacks[61]. Triptans should be used as soon as possible after headache onset. To date, no evidence supports their use during tha aura phase of a migraine attack. Sumatriptan was the first $5HT_1$ agonist to be introduced for treating migraine; zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan have been introduced more recently.

Contraindications: all triptans have the same contraindications and safety concerns. $5HT_1$ agonists should not be used for prophylaxis. They are contraindicated in ischemic heart disease, previous myocardial infarction, coronary vasospasm (including Prinzmetal's angina), uncontrolled hypertension, previous cerebrovascular incident or transient ischemic attack, basilar or hemiplegic migraine, peripheral vascular disease, Wolf-Parkinson-White syndrome, arrhythmias associated with accessory cardiac conduction pathways, pregnancy, breast feeding.

$5HT_1$ agonists should not be taken with ergotamins concurrently, or within 6 hours.

Sumatriptan, zolmitriptan and rizatriptan should not be taken with MAO inhibitors, SSRIs and lithium. Rizatriptan and zolmitriptan are contraindicated in patients with liver dysfunction.

Caution: $5HT_1$ agonists should be used with caution in conditions which predispose to coronary artery disease (preexisting cardiac disease), hepatic and liver impairment, pregnancy and breast feeding. Triptans can cause drowsiness. Triptans are not recommended for use in children.

Caution should be exercised in patients over 65 years. Sumatriptan and naratriptan contain the sulfonamide component, which may cause an allergic reaction.

Adverse effects: include sensations of tingling, heat, heaviness, pressure or tightness of any body part (including throat and chest – should be discontinued if intense, may be due to coronary vasoconstriction or to anaphylaxis); flushing, dizziness, feeling of weakness, fatigue, nausea, vomiting, drowsiness, transient increase in blood pressure, hypotension, bradycardia or tachycardia, altered liver function tests, erythema at injection site, seizures.

In general practice, triptan treatment in migraine does not increase the risk of stroke, myocardial infarction, cardiovascular death or mortality[62]. The safety of triptans was evaluated in a study measuring coronary artery diameter after intravenous eletriptan administration. The study demonstrated that in patients with normal coronary arteries eletriptan administered at plasma concentrations in excess of 3 times resulted in only mild and clinically insignificant degree of coronary vasoconstriction[63].

When deciding which triptan to recommend, migraine severity, rapidity of onset and duration are important factors. An individual response to a triptan cannot be predicted, if the first triptan is not efficient another triptan should be recommended; thus physicians need more than one triptan to treat migraine patients optimally. Patients who do not have vomiting may be given oral triptans. Patients with nausea and vomiting or rapid onset of headache may be given intranasal or subcutaneous formulations[26,36].

The response to triptans is often idiosyncratic; one triptan might be more suitable for one patient and other triptans for other patients. In an individual patient the triptan of choice is the one that relieves pain and associated symptoms quickly with minimum adverse events and without recurrence of symptoms.

Seven $5\text{-}HT_{1B/1D}$ agonists are available on the market; they differ in pharmacokinetics, pain response, recurrence and adverse events[4,26,36-66]:

Naratriptan, rizatriptan and zolmitriptan are full agonists while eletriptan is a partial agonist. Almotriptan,

eletriptan, rizatriptan, sumatriptan and zolmitriptan have the highest 2-hour effectiveness, provide headache relief within 30-60 minutes and have the least recurrences. The meta-analysis suggests that almotriptan 12.5 mg, eletriptan 80 mg and rizatriptan 10 mg offer the highest likelihood of success. The lower doses of these agents (rizatriptan 5 mg and eletriptan 40 mg) may be good starting doses.

Sumatriptan 100 mg and 50 mg (oral) provide good efficacy and tolerability. The 50 mg dose was comparable with 100 mg and superior to 25 mg in 4-hour headache relief. Recurrences respond well to a second dose of sumatriptan. Subcutaneous sumatriptan (6 mg) is the most effective acute treatment for migraine attacks, reaching peak plasma concentrations within 12 min but is also associated with more intense AEs and the need of self-injection. Several placebo controlled trials support the efficacy of sumatriptan NS for headache relief at 1 and 2 hours; a dose-response relationship was demonstrated, with superiority to placebo at the 10 mg, 20 mg and 40 mg doses. Sumatriptan is metabolized mainly by the monoamine oxidase (MAO-A) and is contraindicated in patients using MAO inhibitors. No substantial drug interaction with other traditional migraine-preventive medications, including beta blockers, calcium channel antagonists, selective serotonin reuptake inhibitors and tricyclic antidepresants has been found.

Zolmitriptan has oral bioavailability of 40%, half life of about 2.5 hours and is metabolized by the cytochrome P450 system. No significant difference was found between 2.5 mg and 5 mg dose. The recommended starting dose of 2.5 mg provides the best balance of benefit and side effects, although some patients may benefit from the 5 mg dose. Both 2.5 mg and 5 mg doses of zolmitriptan were comparable to sumatriptan 50 mg and 100 mg for headache relief, consistency of response and 24-hour headache relief rates. Nasal spray (available in some countries) is detectable in blood within 5 minutes.

Naratriptan has a longer half life (6 hours) and higher oral bioavailability (70%). Relief rates were found to be lower than with other oral triptans. Compared with sumatriptan, one-third fewer patients experienced recurrence headache. Naratriptan 2.5 mg offers very good tolerability coupled with a slower onset of improvement, thus naratriptan can be offered to patients with mild to moderate migraine.

Rizatriptan has rapid oral absorption and high oral bioavailabilty (45%) for the 10 mg dose. There is no significant difference at 2 hours between sumatriptan and the lower doses of rizatriptan. Rizatriptan is metabolized mainly by MAO-A, plasma concentrations are increased in patients taking propranolol (in which cases the recommended dose should not exceed 5 mg); no interaction with other beta-blockers has been observed.

Almotriptan 6.25 mg and 12.5 mg is clinically significant in relieving migraine symptoms. Almotriptan does not interact with propranolol, selective serotonin reuptake inhibitors or MAO.

Frovatriptan was effective and well tolerated across a wide range of doses (2.5 mg, 5 mg, 10 mg, 20 mg or 40 mg) and low recurrence rates were observed. Frovatriptan is metabolized by the cytochrome P450 system.

Eletriptan is rapidly absorbed, with high bioavailability (50%) and long half life (5 hours); interacts with drugs that are metabolized by the cytochrome P450 system. Headache response rates were higher in eletriptan (40 to 80 mg) than in sumatriptan (50 to 100 mg) group at 1 and 2 hours. Adverse events are more common with eletriptan 80 mg than with other triptans.

The triptans which had a longer half life and higher 5-HT_{1B} receptor potency – frovatriptan 2.5 mg, naratriptan 2.5 mg and eletriptan 80 mg, had the lowest rates of headache recurrence.

Seven triptans are available on the market (Europe, USA):

* Sumatriptan 50 mg, 100 mg PO, maximum daily dose 300 mg

* Sumatriptan 10 mg, 20 mg NS, 1 single dose spray; maximum daily dose 40 mg
Sumatriptan 6 mg SC, maximum daily dose 12 mg
Sumatriptan 25 mg supp, maximum daily dose 50 mg
Zolmitriptan 2.5 mg, 5 mg PO, maximum daily dose 5 mg
Zolmitriptan 5 mg NS

** Naratriptan 1 mg, 2.5 mg PO, maximum daily dose 5 mg

** Rizatriptan 5 mg, 10 mg PO, maximum daily dose 30 mg

** Rizatriptan rapid disk (RPD) 10 mg, maximum daily dose 30 mg
Eletriptan 20 mg, 40 mg, 80 mg PO, maximum daily dose 80 mg
Almotriptan 6.25 mg, 12,5 mg, 25 mg PO, maximum daily dose 25 mg
Frovatriptan 2.5 mg PO

Tables 1 and 2 show the pharmacokinetic variables for 5-$HT_{1B/1D}$ agonists[39].

Table 1. Pharmacokinetic variables for oral 5-$HT_{1B/1D}$ agonists

	Tmax (h)	T½	Bioavailability (%)
Sumatriptan	2.5	2.5	15
Zolmitriptan	2	2.5-3	40-48
Rizatriptan	1-1.5	2-3	45
Naratriptan	2-4	5.6-6.3	74 (women), 63 (men)
Eletriptan	1-2	3.6-5.5	50
Frovatriptan	2-4	25	24-30
Almotriptan	1.4-3.8	3.2-3.7	70

* Sumatriptan 50 mg PO, sumatriptan 20 mg NS and zolmitriptan 2.5 mg and 5 mg PO and rizatripan 10 mg RPD are available in Croatia, covered by Croatian Institute of Health Insurance (partial), a prescription is needed

** Naratriptan 2.5 mg PO, rizatriptan 10 mg PO are available in Croatia, NOT covered by Croatian Institute of Health Insurance, a prescription is needed

An economic analysis of a prospective observational 6-month outcome study of patients with migraine showed that initiation of sumatriptan in patients previously receiving non-triptan therapy was cost-effective and had an economic benefit for patients, employers and society by reducing patients' disability and thus improving their ability to function at work and non-work activities[67].

Ergot alkaloids and derivatives

Ergotamine tartarate, in association with caffeine or not (caffeine doubles the rate of absorption of ergotamine and increases the peak in blood concentration), is significantly effective in reducing head pain in migraine attack; a low incidence of headache recurrence has been observed[68]. The value of ergotamine in the treatment of migraine is limited by difficulties in absorption and by its side effects. Ergots have a much greater receptor affinity at 5-HT_1a, 5-HT_2, adrenergic and dopaminergic receptors than triptans, leading to more adverse events. Ergot derivatives may worsen nausea nad vomiting, thus co-administration of an antiemetic is indicated. Ergot derivatives are vasospastic and may cause a rise in blood pressure level. Co-administration with triptans is contraindicated within 6 hours.

Table 2. Pharmacokinetic variables for 5-$HT_{1B/1D}$ agonists

	Dose mg	Pain response 2 h (%)	Pain response 4 h (%)	Pain free 2 h (%)	Recurrence (%)
Sumatriptan PO	50	63	77	28	28
Sumatriptan PO	100	59	–	29	30
Sumatriptan NS	20	61	–	27-37	–
Sumatriptan SC	6	69	–	49	–
Zolmitriptan PO	2.5	64	73	25	30
Zolmitriptan PO	5	66	73-77	34	34
Rizatriptan PO	5	62	–	30	39
Rizatriptan PO	10	69	84	40	37
Naratriptan PO	2.5	49	60-68	22	21
Eletriptan PO	40	60	–	27	21
Eletriptan PO	80	66	88	33	20
Almotriptan PO	12.5	61	–	36	26
Frovatriptan PO	2.5	42	64	–	–

DHE (Dihydroergotamine) by parenteral route has been the choice treatment for migraine attack until the introduction of triptans. DHE is effective in alleviating head pain during migraine attack and is better tolerated than ergotamine tartarate[69]. DHE SC and NS formulation is less effective than subcutaneously administered sumatriptan in relieving head pain and accompanying symptoms, but is associated with a small percentage of headache recurrence[70]. DHE nasal spray is safe and effective for the treatment of acute migraine attacks and should be considered for use in patients with moderate to severe migraine with or without nausea and vomiting, or in migraine of any severity when nonspecific medication (or triptans) has failed to provide adequate relief in the past.

The recommended doses of ergotamine preparations should not be exceeded and treatment should not be repeated at intervals of less than 4 days. Patients who regularly use ergot derivatives for more than 2-3 days/week can develop rebound headache[71]. The abuse of ergot derivatives may induce an increase in attack frequency and develop into chronic daily headache. To avoid habituation, the frequency of administration of ergotamine should be limited to no more than twice a month. Their use is not recommended in the treatment of attacks of medium or high frequency, for the potential risk of abuse. Ergotamine should be best avoided if possible (consider other therapies such as triptans).

Contraindications: peripheral vascular disease, cerebrovascular disease, coronary heart disease, mitral stenosis, obliterative vascular disease and Raynaud's syndrome, hepatic and renal impairment, sepsis, severe or inadequately controlled hypertension, hyperthyroidism, pregnancy and breast feeding, porphyria, liver and renal failure.

DHE is relatively contraindicated if blood pressure is sustained ≥165/95[72].

Caution: risk of peripheral vasospasm (in patients who are concomitantly using beta blockers), elderly, dependence, should not be used for migraine prophylaxis.

Ergot derivatives should not be administered within 6 hours of the administration of triptans.

Macrolide antibiotics increase plasma levels of ergotamine derivatives.

Adverse events: nausea, vomiting, abdominal pain, diarrhea, muscle cramps, occasionally increased headache, distal paresthesias, precordial pain, myocardial ischemia – rarely infarction; chronic use or repeated high doses may cause ergotism with gangrene and confusion, ischemic neuropathies, pericardial, pleural and peritoneal fibrosis[72].

Table 3. Evidence summary for treatment of acute attacks of migraine

Drug	Level of evidence	Clinical effectiveness
Triptans		
Sumatriptan SC	A	+++
Sumatriptan NS	A	+++
Sumatriptan oral	A	+++
Zolmitriptan oral	A	+++
Rizatriptan oral	A	+++
Naratriptan oral	A	++
Eletriptan oral	A	+++
Almotriptan oral	A	+++
Ergot alkaloids and derivatives		
Ergotamine oral, suppository, IM, SC	B	+
Ergotamine+caffeine	B	+
DHE IV, IM, SC	B	+++
DHE NS	A	++
Antiemetics		
Chlorpromazine	C/B	++
Metoclopramide IM	B	+
Prochlorperazine IM	B	+/++
NSAIDs and non-opiate analgesics (oral)		
Paracetamol	B	+
Aspirin	A	++
Diclofenac	B	++
Ibuprofen	A	++
Naproxen	B	++
Naproxen sodium	A	++
Indomethacin oral, supp.	C	+
Ketoprofen (parenteral)	B	++
Ketorolac IM	B	++
Combination of:		
Paracetamol, aspirin, caffeine	A	++
Barbiturate hypnotics		
Butalbital, ASA, caffeine	C	+++
Opiates		
Opiates oral	A	++
Opiates parenteral	B	++
Other		
Corticosteroids	C	++
Lidocaine intranasal	B	?

* Ergotamine is not registered in Croatia.
* DHE aerosol 1 ml/4 mg is available in Croatia, NOT covered by Croatian Institute of Health Insurance, a prescription is needed.

Treatment of acute migraine attacks according to levels of evidence and clinical effectiveness is listed in Table 3[73].

Clinical stratification of acute migraine treatment is listed in Table 4.

Migraine status

The principles of treatment for status migrainosus include the following:

Table 4. Clinical stratification of acute migraine treatment

Drug	Recommended dosage	Maximum daily dose
1. Analgesics, NSAID		
1) Paracetamol	500-1000 mg PO	2000 mg
2) Acetylsalicylic acid	500-1000 mg PO	2000 mg
3) Ibuprofen	400-800 mg PO	1800 mg
4) Diclofenac	50-100 mg PO, IM, supp	200 mg
5) Ketoprofen	50-100 mg PO, IM, supp	200 mg
6) Naproxen	500-1000 mg PO, supp	1500 mg
7) Piroxicam	20 mg PO, IM, supp	40 mg
combination: paracetamol, aspirin, caffeine with or without antiemetic		
Antiemetics		
1) Metoclopramide	10 mg PO, IV, IM	30 mg
2) Tietilperazine	6.5 mg PO	13 mg
3) Prochlorperazine	10 mg Supp	20 mg
4) Chlorpromazine	0.1 mg/kg IM	1 mg/kg
2. Analgesics or NSAID failed, try		
1) Sumatriptan	50 –100 mg PO	300 mg
2) Zolmitriptan	2.5-5.0 mg PO	5 mg
3) Rizatriptan	5-10 mg PO, MLT wafer	30 mg
4) Naratriptan	2.5 mg PO	5 mg
5) Eletriptan	80 mg PO	80 mg
6) Almotriptan	12.5-25 mg PO	25 mg
3. Early nausea, vomiting or problem taking tablets		
1) Sumatriptan	20 mg NS	40 mg
2) Sumatriptan	6 mg SC if available	12 mg
3) Rizatriptan	10 mg MLT wafer	30 mg
4) DHE	0.5-2 mg NS	2 mg
4. Headache recurrence or long lasting headache		
1) Naratriptan	2.5 mg PO	5 mg
2) Other triptans		
3) DHE	0.5-2 mg NS	2 mg
5. Very rapidly developing symptoms		
1) Sumatriptan 6 mg SC		
2) Sumatriptan 20 mg NS		
6. Tolerating triptans poorly		
DHE	0.5-2 mg NS	2 mg

1. Consider brain imaging
2. Fluid replacement and correction of metabolic parameters (if indicated) for 24-48 hours
3. Drug detoxification
4. Parenteral pharmacotherapy
   a) analgesics, NSAIDs and antiemetics up to maximum daily dose
   b) sedatives (diazepam) 5-10 mg IM (or IV)
   c) consider oral, IM or IV neuroleptics in an inpatient setting (the patient should be observed in a medical setting and should be monitored for hypotension, sedation and dystonic reactions)
   d) parenteral corticosteroids alone or in combination with other symptomatic medications may be used to treat severe, resistant headaches: prednisone up to 100 mg/day rapidly tapering short course will assist in terminating an otherwise refractory migraine
5. Concurrent implementation of migraine prophylaxis (if indicated)
6. Consider admission in case of
   a) drug abuse
   b) exacerbation of comorbid diseases
   c) therapy that requires inpatient monitoring

*Patients to whom IV sedatives and neuroleptics have been administered should not drive for at least 24 hours.

II Recommendations for preventive therapy of migraine attacks

Principles and recommendations for preventive treatment of migraine attacks are as follows[4,73-76]:

Prior to instituting prophylactic therapy for migraine, it is an imperative that realistic goals and expectations be established. Patients should have clear understanding that the goals of preventative therapy are to:

1. reduce attack frequency, severity and duration; it is generally accepted that good response to prophylactic therapy is at least a 50% reduction in the frequency or severity of migraine attacks,
2. improve responsiveness to treatment of acute attacks, and
3. improve function and quality of life.

Who should be offered a prophylactic treatment and when:

- frequent headaches, >2-3 migraine attacks *per* month
- attacks lasting >48 hours
- attacks described by patients as unbearable, or that significantly interfere with daily activities despite acute treatment
- contraindication to, or failure or overuse of acute therapies
- adverse events with acute therapies
- patient preference
- presence of uncommon migraine conditions including hemiplegic migraine, basilar migraine, migraine with prolonged aura or migrainous infarction (to prevent neurologic damage)

Principles of preventive treatment:

1. Medication use:

- initiate therapy with medications that have the highest level of evidence-based efficacy
- initate therapy with the lowest effective dose of the drug; increase it slowly until clinical benefits are achieved until limited by adverse events
- give each drug an adequate trial; it may take 2 to 3 months to achieve clinical benefit
- avoid interfering medications (overuse of acute medications)
- use of a long-acting formulation may improve compliance

2. Evaluation:

- monitor the patient's headache frequency through a headache diary
- re-evaluate therapy; if after 6-12 months headaches are well controlled, consider tapering or discontinuing treatment

3. Take coexisting conditions into account. Several conditions are more common in persons with migraine: stroke in certain subgroups of patients, myocardial infarction, Raynaud's phenomenon, epilepsy, affective and anxiety disorders. These conditions present both treatment opportunities and limitations:

- select a drug that will treat the coexistent condition and migraine, if possible
- establish that the treatment being used for migraine is not contraindicated for the coexisting disease
- establish that the tretament being used for coexisting condition does not exacerbate migraine attacks
- beware all drug interactions

4. Special attention should be paid to pregnant women or women who wish to become pregnant in near future. Preventive medications may have teratogenic effects. If treatment is absolutely necessary, select a treatment with the lowest risk of adverse effects to the fetus.

5. Nonpharmacologic treatment

Over the past two decades, several behavioral treatments for migraine prevention have been used widely as independent therapies or combined with pharmacologic therapy. These therapies may be particularly well suited as treatment options for headache sufferers who have one or more of the following characteristics:

- patient preference for nonpharmacologic treatment
- poor tolerance of specific pharmacologic treatments
- medical contraindications for specific pharmacologic treatments
- insufficient or no response to pharmacologic treatment
- pregnancy, planned pregnancy, or nursing
- history of long-term, frequent, or excessive use of analgesics or acute medications that can aggravate headache problems
- significant stress

The choice of prophylactic medication should be individualized according to the potential efficacy and side effect profile of the medication as well as the presence of any associated comorbid medical conditions or medication interactions. For example, a tricyclic antidepressant may be especially useful in a patient with migraine and depression. Similarly, divalproex sodium would be an optimal choice when epilepsy is a comorbid illness. On the other hand, some comorbid illnesses affect prophylactic choices. Caution should be exercised with beta-blockers, for example, which would not be a prudent choice in patients with diabetes, asthma, Raynaud's phenomenon, etc. (Level A, C).

Prophylactic treatment should be started at low doses, possibly as monotherapy; doses can be slowly increased until therapeutic goals are achieved and side effects are minimal. Patients should also understand that there is usually a latency of at least 3 to 6 weeks between the initiation of medication and recognizable efficacy. Often, an 8- to 12-week trial is necessary, allowing for an adequate period for drug titration to a dosage likely to attain efficacy. Long-acting formulations can improve compliance. It is also not uncommon for initial side effects to subside after continued therapy, and patients should be made aware of this so as to avoid premature discontinuation of a potentially effective medication.

Prophylactic treatment during pregnancy should best be avoided, if necessary, limited to special situations; in these cases drugs with lowest risk to the fetus should be selected.

Patients should carefully fill out headache diaries where the frequency, duration of attack, severity of pain, functional impairment, disability as well as drugs taken and possible adverse events are recorded.

Pharmacologic treatment

Beta blockers

Prophylaxis of migraine headache by beta blockers was incidentally detected in patients treated for hypertension who also had migraine headaches. The mechanism is not clear, although it is probably by acting on the central monoaminergic system and serotonin receptors. The beta blockers considered efficient in migraine prophylaxis are propranolol, atenolol, metoprolol, nadolol and timolol[27,73,74,77].

A meta-analysis of 74 controlled studies showed propranolol to be consistently effective for migraine prevention in a daily dose of 120-240 mg. There was no absolute correlation between the dose of propranolol and its clinical efficacy. On an average, propranolol yielded a 44% reduction in migraine activity compared with a 14% reduction on placebo[74,78,79].

Therapy should be started with low doses and then slowly increased if necessary. When migraine attacks are controlled, doses can be slowly reduced. An abrupt cessation of therapy with beta blockers may induce rebound effects by increasing migraine attacks and inducing adrenergic side effects and hypertension.

Propranolol. The therapeutically effective dose of propranolol ranges from 40 to 400 mg a day; therapy should be started at a dose of 40 mg/day in 2 doses and slowly increased to tolerance. The short-acting form can be given four times a day, although we recommend twice a day, and the long-acting form once or twice a week[73].

Nadolol has a long half-life, the dose ranges from 20 mg to 160 mg a day given once daily or in split doses. It has fewer side effects than propranolol[73].

Timolol has a short half-life, doses range from 20 mg to 60 mg a day in divided doses[73].

Atenolol has fewer side effects than propranolol, the dose ranges from 50 mg to 200 mg a day once daily[73].

Metoprolol has short half-life, doses range from 100 mg to 200 mg a day in divided doses, long-acting preparation may be given once a day[73].

No migraine prophylaxis activity has been shown for acebutol, alprenolol, oxprenolol and pindolol[80].

Contraindications: congestive heart failure, asthma, insulin dependent diabetes, Raynaud's disease.

Caution: abrupt stopping of therapy with beta blockers can cause increased headache, withdrawal symptoms of tachycardia and tremulousness[81,82].

Adverse events: drowsiness, dizziness, nausea, fatigue, lethargy, sleep disorder, nightmares, depression, memory disturbance, hallucinations, orthostatic hypotension, significant bradycardia, impotence.

*Propranolol and atenolol are available in Croatia, covered by Croatian Institute of Health Insurance (100%), a prescription is needed. Metoprolol is available in Croatia, NOT covered by Croatian Institute of Health Insurance, a prescription is needed.

Antidepressants

Only tricyclic antidepressants have proven efficacy in migraine. The mechanism by which antidepressants effect headache prophylaxis is uncertain, but does not result from treating masked depression. Amitriptyline modulates monoaminergic pathways by inhibitng the reuptake of both adrenaline and serotonin.

Amitriptyline is the only antidepressant with fairly consistent support for efficacy in migraine prevention; placebo controlled trials found amitriptyline significantly better than placebo in reducing headache index or frequency[83,84].

The effective dose varies; treatment should be started with an initial dose of 10 mg in the evening, to be increased by 10 mg *per* week up to a maximum of 50 mg *per* day[73,83]. High doses may be necessary in the presence of depression.

One trial comparing propranolol and amitriptyline suggested that propranolol was more efficacious in patients with migraine alone, whereas amitriptyline was superior for patients with the phenotypes of migraine and tension type headache[85].

Contraindications: severe cardiac, liver, renal, prostatic nad thyroid diseases, glaucoma, hypotension, convulsive disorders, concomitant use of MAO inhibitors.

Caution in elderly patients because of anticholinergic effects. Antidepressant treatment may also reduce seizure threshold.

Adverse effects: orthostatic hypotension, dry mouth, metallic taste, epigastric distress, constipation, dizziness, mental confusion, tachycardia, blurred vision, urinary retention.

*Amitriptyline is available in Croatia, covered by Croatian Institute of Health Insurance (100%), a prescription is needed.

Selective serotonin-reuptake inhibitors (*fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram*). At the moment there is no definitive evidence supporting the use of these drugs in preventing migraine attacks[86,87].

Calcium channel antagonists

Calcium channel blockers act by modulating neurotransmission, inducing vasodilatation and exerting a cytoprotective effect by preventing the influx of calcium ions into the cells and reducing cell damage due to hypoxia.

Nifedipine and nimodipine have been shown to be ineffective, whereas ***verapamil*** has been shown to be marginally effective; there are no randomized controlled trial evidence to support the use of verapamil in migraine[74,76]. ***Cyclandelate*** has comparable efficacy with that of beta blockers and only a few side effects[88].

Flunarizine. Among all available drugs of this class (flunarizine, nimodipine, nifedipine, verapamil, cyclandelate, nicardipine), flunarizine was the most effective drug showing no significant differences when compared with beta blockers[74,89-93]. The recommended dose of flunarizine is 5-10 mg a day. Flunarizine is not available in Croatia.

Contraindications: pregnancy, hypotension, heart failure, atrioventricular block, Parkinson's disease, depression.

Adverse effects: weight gain, somnolence, dry mouth, dizziness, hypotension, occasional extrapyramidal reactions, exacerbation of depression, abdominal pain.

*Verapamil is available in Croatia, covered by Croatian Institute of Health Insurance (100%), a prescription is needed; nifedipine and nimodipine are available in Croatia, partially covered by Croatian Institute of Health Insurance, a prescription is needed.

Serotonin antagonists

Pizotifen and methysergide are 5-HT_{2B} and 5-HT_{2C} receptor antagonists. Both substances are effective but have a high frequency of side effects[94,95].

Pizotifen. Controlled and uncontrolled studies have shown that pizotifen is of benefit in 40%-79% of patients[96]. Analysis of the placebo controlled trials suggested a large clinical effect that was statistically significant; in direct comparisons with other agents for migraine prevention, no significant differences were demonstrated with flunarizine, methysergide, or metoprolol[97-99]. However, in 26 trials reviewed, pizotifen was generally poorly tolerated.

The dose recommendatin is 0.5-1 mg 1-3 times daily by titration[74].

Adverse effects: drowsiness, asthenia, increased appetite, weight gain.

Methysergide. Four placebo controlled trials suggested that methysergide was significantly better than placebo in reducing headache frequency; there was no difference in comparison with propranolol and pizotifen[98,100]. The use of methysergide should be restricted to patients who do not respond to other prophylactic treatments, taking carefully into account the risk-benefit ratio. The dose ranges from 2 to 8 mg a day (maximum 14 mg *per* day), higher dosage has to be split in 3 doses; starting dose is 1 mg, increased by 1 mg every 2-3 days.

Contraindications: pregnancy, severe arteriosclerosis, coronary heart disease, severe hypertension, peptic ulcer, fibrotic disorders, lung diseases, collagen diseases, liver and renal impairment, valvular heart disease.

Adverse effects: transient muscle aching, claudication, abdominal distress, nausea, weight gain, hallucinations. Major complications are rare and include retroperitoneal, pulmonary and endocardial fibrosis (estimated frequency of 1 *per* 5000 treated patients)[95]. A 4-week drug free interval is recommended after 6 months of continuous treatment to prevent such complications.

*Pizotifen and methysergide are NOT available in Croatia.

Anticonvulsants

Anticonvulsant medication is increasingly recommended for migraine prevention based on the placebo-controlled, double blind trials that proved it to be effective.

Studies with ***divalproex sodium*** and ***sodium valproate*** provided strong and consistent support of their efficacy[101-104]. Divalproex sodium was found to be more effective compared with placebo, but not significantly different compared with propranolol for the prevention of migraine in patients without aura[105]. Starting dose is 250-500 mg in divided doses, the dose is slightly increased usually up to 1000 mg daily[65]. Baseline liver function studies should be obtained.

Contraindications: pregnancy, as divalproex carries a high risk of congenital abnormality; history of pancreatitis, chronic hepatitis, hematologic disorders including thrombocytopenia, pancytopenia and bleeding disorders. Hyperandrogenism resulting from elevated testosterone levels, ovarian cysts and obesity are of particular concern in young women with epilepsy who use valproate.

Adverse effects: nausea, vomiting, gastrointestinal distress, somnolence, asthenia, tremor, alopecia, weight gain. Severe adverse reactions such as hepatitis or pancreatitis are rare[106].

Gabapentin was effective in several trials. Gabapentin 600-1800 mg was effective in a 12-week open label study, and in dose of 1800-2400 gabapentin was superior to placebo in reducing the frequency of migraine attacks by 50% in about 1/3 of patients[107,108]. Gabapentin was not effective in one placebo-controlled, double blind study[109].

Addverse effects: dizziness, drowsiness.

Topiramate is effective in migraine prophylaxis. Topiramate in a range of 25-200 mg was associated with 33% reduction in monthly headache rate *vs* 8% in placebo group; >50% reduction in migraine frequency was reported by 47% of patients in topiramate group (dose 200 mg in divided doses in 6 weeks) as compared with 6.7% of patients from placebo group[10,111]. Starting dose is 25 mg, the dose is elevated by 25 mg every 7 days up to a dose of 200 mg.

Adverse effects: weight loss, cognitive dysfunction, sedation, dizziness, diarrhea.

Lamotrigine showed lower efficacy in preventing migraine without aura, whereas it was efficacious in the prevention of high frequency migraine attacks with aura[112-114].

Adverse effects: rash, fatigue, dizziness, headache, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions.

*Gabapentin, topiramate and lamotrigine are available in Croatia but are NOT covered by Croatian Institute of Health Insurance for migraine prophylaxis.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The main mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) is the inhibition of cyclooxygenase in both isoforms; NSAIDs are active in reduction of migraine pain even in the absence of inflammation. Some NSAIDs show discrete effectiveness in migraine prophylaxis; these include ASA, flurbiprofen, ketoprofen; naproxen and naproxen sodium are, however, useful in the prevention of menstrual migraine[115-120]. NSAIDs should be used for intermittent prophylaxis in menstrual migraine, not for prolonged periods of time because of their gastric side effects.

Complementary drugs

Vitamin B2 (riboflavin)

A recent randomized, placebo-controlled study found daily supplements of riboflavin 400 mg to be moderately effective in reducing the frequency and severity of migraine, however, the effect was not apparent until the fourth month of treatment[121]. However, riboflavin is not available in most countries in such high doses.

Adverse effects: mild abdominal pain and diarrhea.

Feverfew

This herbal therapy is made from crushed chrysanthemum leaves; 250 micrograms of the active ingredient, parthenolide, are considered necessary for therapeutic effectiveness. Feverfew is considered to be an anti-inflammatory medication with serotonin effects. The role of feverfew in migraine prophylaxis is not well established. Despite studies showing superiority to placebo, a recent meta-analysis suggests that the evidence for it is weak and that trial designs were poor. In addition, the demonstrated effects were poor[122,123].

Magnesium

Low magnesium certainly is a fundamental mechanism of neuronal excitability; migraine patients have lower circulating magnesium levels than normal. Studies with P-spectroscopy revealed consistent and profound changes in posterior brain regions of patients with hemiplegic migraine and spectroscopic images of family members showed low magnesium levels. Regarding these observations, supplementing magnesium would make sense. Daily oral dosages of 400 to 600 mg have been shown to be of benefit in migraine prevention[124-126].

Coenzyme Q-10

Magnetic resonance spectroscopy (MRS) studies and DNA analysis suggest that migraine, at least in a subset of individuals, may be the result of mitochondrial impairment. On this basis coenzyme Q-10 could be used as a preventive treatment for migraine. So far, coenzyme Q-10 has been successfully used in the treatment of mitochondrial disorders; MRS studies have identified improvement in both brain and muscle energy metabolism after coenzyme Q-10 administration[127-129]. In one open-label study migraine patients were treated with 150 mg daily of coenzyme Q-10, by the end of 3 months there was a 55% reduction in the frequency of migraine; no side effects were noted[130].

Other therapies

Certain forms of treatment listed below show promising results in clinical trials but their use is still not recommended.

Botulinum toxin

Several retrospective open label chart reviews and 4 double-blind, placebo-controlled studies have demonstrated the efficacy of botulinum toxin type A in migraine prophylaxis. Botulinum toxin significantly reduced the frequency, severity and disability associated with migraine headaches, and its efficacy was good and consistent through the studies[128-133].

The mode of action by which botulinum toxin is effective in migraine prophylaxis is not fully understood. Migraine patients with certain characteristic features may be given an attempt with botulinum toxin for pain relief: muscular stress as migraine trigger (cervicocranial dystonia, pericranial painful muscular trigger points or tender points, oromandibular dysfunction), concurrent chronic tension-type headache, chronic migraine with frequent migraine attacks on more than 15 days *per* month for longer than 3 months and if other therapeutic options have been either ineffective or have not been tolerated[136].

Adverse effects: to date, neither organic damage nor allergic complications have been reported, or CNS side effects have been noticed.

The tolerability and safety of botulinum toxin type A seem to be high. There is a number of ongoing clinical trials to evaluate the efficacy, optimal dosing and side effect profile of botulinum toxin type A in the prophylaxis of migraine and other headache entities.

Hyperbaric oxygen therapy (HBO)

A double blind, placebo controlled study in which the treatment group received 100% oxygen during 30 minutes on 3 consecutive days (control group received air) showed a nonsignificant reduction in hours of headache *per* week; the authors concluded that the test protocol did not show a prophylactic effect on migraine[137]. However, HBO showed significant effect in acute migraine attacks[138,139].

Lisuride

Lisuride has been proved to be effective and well tolerated for migraine prophylaxis: in an open study, attack reduction by more than 50% was observed in 61.4% of patients treated for a 3-month period, with good tolerance[140].

Triptans

Naratriptan 2.5 mg twice daily in patients with chronic migraine refractory to other commonly used preventive therapies was associated with a significant reduction in the frequency of headache days at 1 month and 1 year of therapy initiation. After 6 months of continuous therapy, 65% of patients reverted to the episodic pattern of migraine, and at 1 year 55% still had episodic headache. None of the patients showed intolerance to naratriptan[141].

Antipsychotic drugs

Olanzapine (thienobenzodiazepine) may be effective for patients with refractory headache who have not responded to other prophylactic agents. An open-label study with olanzapine in daily doses from 2.5 mg to 35 mg for 3 months resulted in a significant decrease in the number of headache days and headache severity. Olanzapine may be considered in patients with refractory headaches who have mania, bipolar disorder or psychotic depression[142].

Medications with proven high efficacy and mild to moderate adverse events are:

1) beta blockers: propranolol, atenolol
2) antidepressants: amitriptyline
3) anticonvulsants: divalproex sodium

If the prophylactic therapy is successful, continue treatment for 6-12 months, then reassess

If success is achieved with a particular prophylactic medication after approximately 6 to 12 months, gradual tapering is recommended and the patient should be observed for increased headache frequency or intensity.

Try different first line medication or different drug of the same class

Monotherapy is generally recommended. A single agent is employed at a gradually increasing dosage (within prescribed limits) until dose-limiting side effects or therapeutic efficacy occurs. It is important to remember that a therapeutic failure with one medication does not preclude the potential for benefit with another medication from the same class.

Try combination of beta-blockers and tricyclics

It is an established observation that certain combinations, particularly a beta-blocker and a tricyclic antidepressant, may be more efficacious and produce fewer side effects in combination (at lower doses) than either medication in isolation (at higher single doses).

Prophylactic drug treatment in migraine according to levels of evidence and clinical effectiveness are listed in Table 5[73].

Table 5. Evidence for prophylactic drug treatment in migraine

Drug	Level of evidence	Clinical effectiveness
Beta blockers		
Atenolol	A	+++
Propranolol	A	+++
Nadolol	B	++
Metoprolol	B	++
Ca channel blockers		
Flunarizine	A	+++
Nimodipine	B	+
Verapamil	B	+
Antidepressants		
Amitriptyline	A	+++
Nortriptyline	C	+
Doxepine	C	+
Imipramine	C	+
SSRIs		
Fluoxetine	B	+
Paroxetine	B	+
Antiepileptics		
Sodium valproate	A	++
Gabapentine	A	++
Topiramate	B	?
Lamotrigine	B	?
Serotonin antagonists		
Pizotifen	A	+++
Lisuride	A	+
Dihydroergotamine	A	+++
NSAIDs	B	?
Other		
Estradiol	B	++
Vitamin B2	B	++
Magnesium	B	+
Tanacetum Parthenium	B	?
Botulinum toxin	B	++

Why treatment fails

Treatment of acute attacks or prophylactic treatment of migraine may fail because of the following[143]:

1. Diagnosis is incomplete or incorrect
   a) an undiagnosed secondary headache disorder is present
   b) a primary headache disorder is misdiagnosed
   c) two or more different headache disorders are present
2. Important exacerbating factors may have been missed
   a) medication overuse (including OTC drugs)
   b) caffeine overuse
3. Dietary or lifestyle triggers
4. Hormonal triggers
5. Psychosocial factors
6. Other medications that trigger headache; pharmacotherapy has been inadequate
7. Ineffective drug; at least 3 attacks should be treated before deciding that a drug is ineffective
8. Inappropriate initial doses (low, excessive)
9. Inadequate duration of treatment
10. Unrealistic expectations
11. Comorbid conditions complicate therapy
12. Inpatient treatment required
13. Inappropriate formulation or route of administration
14. There is an analgesic abuse

Nonpharmacologic treatments include:

Behavioral treatments

It is extremely difficult to design studies with matching placebo, since double blinding is impossible, thus the majority of studies compared active treatments *vs.* control groups consisting of patients in an outpatient setting (mostly prospective, controlled "randomized" studies)[144].

A) Relaxation training

Relaxation training includes progressive muscular relaxation, autogenic training, breathing exercises, and directed imagery. Patients learn to control muscle tension, to use mental relaxation and/or visual imagery to achieve treatment goals. The goal is to develop long-term skills rather than to treat individual events. Repetitive sessions and practice by the patient increase the successfulness of these therapies in reducing headache frequency. Patients need to be motivated and to appreciate the potential long-term benefits of this type of therapy. It may be especially beneficial for patients who cannot take prophylactic medication or who have been unsuccessful with prophylactic pharmacologic treatment. Studies showed 41% mean headache improvement[145-147].

B) Psychotherapy

Cognitive behavioral therapy is based on the premise that anxiety and distress aggravate an evolving migraine, and has the potential of helping the patient recognize maladaptive responses that may trigger a headache. Cognitive-behavioral training (stress management training) teaches skills for identifying and controlling stress and minimizing the effects of stress[147].

C) Biofeedback therapy

1) thermal biofeedback (TBR), (hand warming) – consists of teaching the patient to warm the hands (vasodilatation) by using rapid sensory feedback;
2) electromyographic (EMG) biofeedback training.

The results obtained by electromyographic biofeedback and TBR showed that neither technique is superior. The mean headache improvement when EMG biofeedback was applied using the headache index was 23%-51%; positive and negative results were achieved for TBR. However, the combination of TBR and EMG biofeedback yielded best results[145,148-152]. Recently, TBR associated with relaxation techniques has been recommended as a first-choice nonpharmacologic treatment for migraine, and physical therapy has been indicated as a second-choice treatment for migraineurs who do not sufficiently improve with TBR[153]. The association of TBR with medication therapy can further improve the headache index, as seen in one study which showed a positive effect of the addition of propranolol to the treatment[154].

D) Hypnosis

Hypnosis has a long tradition but few controlled studies are available regarding its effectiveness in migraine treatment. On considering the possibility of combining hypnosis with other nonpharmacologic therapies, a meta-analysis of a broad number of controlled studies suggested that hypnosis could be of benefit in the treatment of headache when combined with cognitive-behavioral therapy[155].

Physical treatment

A) Acupuncture

This therapy has been found to be expensive and of variable availability. Controlled studies specifically applied to

migraine produced mixed findings, positive studies had some methodologic doubts[156].

B) Cervical manipulation

Cervical mobilization (movement of a joint within the normal range of movement) and cervical manipulation (movement of a joint beyond its normal range of oscillation) provided little advantage for the use of these techniques in patients with migraine. Previous studies suggested potentially high levels of risk associated with improper application of this modality. Although more recent studies report few complications, there is well documented evidence of cerebral infarction and death from cervical manipulation.The scientific evidence is not convincing to show significant benefits[157,158].

C) Transcutaneous electrical nerve stimulation (TENS)

TENS units for migraine or muscle contraction headache have not been found to be more beneficial than placebo when evaluated in a controlled study.

D) Massage, homeopathy and naturopathy

Massage, homeopathy and naturopathy have been found to be without supporting evidence.

Recommendation for nonpharmacologic treatment:

1. Relaxation training, TBR combined with relaxation training, EMG biofeedback and cognitive-behavioral therapy may be considered as treatment options for prevention of migraine (Level A). Specific recommendations on which of these to use for specific patients cannot be made.
2. Behavioral therapy (relaxation, biofeedback) may be combined with preventive drug therapy (propranolol, amitriptyline) to achieve additional clinical improvement for migraine relief (Level B)
3. Evidence-based treatment recommendations are not yet posssible for: hypnosis, acupuncture, TENS, chiropractic or osteopathic cervical manipulation, and hyperbaric oxygen (Level C).

Menstrual migraine

"Menstrual migraine," a term misused by both patients and doctors, lacks precise definition. The literature has proposed that menstrual-only migraine be defined as attacks exclusively starting on day 1±2 of the menstrual cycle; the woman should be free from attacks at all other times of the cycle[159]. Many women who do not have attacks exclusively with menses have menstrual associated migraines. Clinical experience suggests that menstrual migraine attacks are more severe, longer in duration, and more difficult to treat than migraine attacks at other times of the month.

A diagnosis of menstrual migraine should be confirmed with calendar record. The provider and patient need to discuss diary documentation. The patient should keep continuous daily records for at least 2 months to include the following:

- day/time of headache
- severity of headache
- duration
- onset of menstrual flow

Screening tests in women with migraine prior to use of combined oral contraceptives (COCs):

No specific tests need to be undertaken other than those routinely performed or indicated by the patient's history or the presence of specific symptoms[160].

Migraine-related symptoms that may necessitate further evaluation and/or cessation of COCs:

- new persisting headache
- new onset of migraine aura
- increased headache frequency or severity
- development of unusual aura smyptoms, particularly prolonged aura

Treatment of menstrual migraine – cyclic prophylaxis

Acute attacks of menstrual migraine should be treated as usual. Prophylactic treatment includes NSAIDs and hormonal prophylaxis[161-165]:

1) Short-term prophylactic perimenstrual treatment:

NSAIDs should be considered as first-choice approaches in the prophylactic treatment of migraine associated with menses. Naproxen sodium 550 mg twice a day (*bid*) has been used as a preventive agent. Other NSAIDs may also be effective 3-7 days before menstruation until 1-7 days after. Typically, the agent is initiated two to three days before the anticipated onset of headache and continued throughout the risk period.

2) Hormonal prophylaxis

Oral contraceptives have a variable effect on migraines, causing worsening of headaches in some patients, improvement of headaches in a small percentage of patients, and no change in migraines in other patients[165]. Estrogen levels decrease during the late luteal phase of the menstrual cy-

cle, likely triggering migraine. Estrogen replacement prior to menstruation has been used to prevent migraine.

Estradiol patches are applied 48 hours prior to the expected onset of migraine and used daily for the next 7 days; it is the treatment of choice in women taking COCs since the expected date of attack is precisely known. A relatively high dose of this hormone (1.5 mg *per* day) may be efficacious since low doses such as 50 mcg *per* day are not as efficacious.

Migraine and menopause

Although migraine prevalence decreases with advancing age, migraine can either regress or worsen at menopause. Women with prior migraine generally improve with physiologic menopause; in contrast, surgical menopause usually results in worsening of migraine[166].

Treatment of hormonal replacement headache

In the treatment of hormonal replacement headache try the following[166,167]:

Estrogens

- reduce estrogen dose
- change estrogen type from conjugated estrogen to pure estradiol to synthetic estrogen or to pure estrone
- convert from interrupted to continuous dosing
- convert from oral to parenteral dosing
- add androgens
- switch to selective estrogen receptor modulator

Progestin

- switch from interrupted (cyclic) to continuous lower dose
- change progestin type
- change delivery system (vaginal)
- discontinue progestin

Migraine and risk of stroke in women using COCs or hormone replacement therapy (HRT)

Data from observational studies suggest that migraine may be a risk factor in developing stroke[168]. Migraine is frequent in young patients with ischemic stroke; the posterior circulation involvement and the presence of patent foramen ovale (PFO) is characteristic suggesting PFO as a possible risk factor for stroke[169]. However, there is no evidence that migraine is a risk factor for ischemic stroke in women over age 45 years[167,170]. The absolute risk of stroke among young women is low: 5-20 *per* 100 000 women years. In women with migraine, the risk has been estimated to 17-19 *per* 100 000 women years.

There are insufficient data to support an increased risk of ischemic stroke in women with any type of migraine who are using HRT. There is no contraindication to the use of COCs in women with migraine in the absence of migraine aura or other risk factors. Women should be advised and regularly assessed for the development of additional risk factors. Currently, the usual indications and contraindications for HRT should be applied[167,170].

There is a potentially increased risk of ischemic stroke in women with migraine who are using COCs and have additional risk factors which cannot be easily controlled, including migraine with aura. The risks must be individually assessed. In certain cases COCs may be contraindicated.

Women who have migraine with a relatively brief common aura type (e.g., visual aura under 30 minutes) probably have significantly increased ischemic stroke risk if estrogen-containing oral contraceptives (OCPs) are used. This risk probably increases with age as baseline stroke rates increase, so that the increased risk may be acceptable to the younger patient (e.g., under age 30), but not to the older patient. It is probably too simplistic to say that no patient with migraine with aura should take estrogen-containing OCPs. The decision should be individualized and should be made with the patient.

It appears reasonable that women who have prolonged migraine auras (certainly those beyond 60 minutes), multiple aura symptoms, or less common aura symptoms (e.g., dysphasia, hemiparesis) should be strongly discouraged from using estrogen-containing OCPs.

Patients who develop a migraine aura for the first time while taking estrogen-containing OCPs, or whose previous typical migraine aura becomes more prolonged or complex, should discontinue estrogen-containing OCPs (Level C).

Practical management:

- diagnose migraine type, particularly the presence of aura
- identify and evaluate risk factors
- risk factors such as hypertension and hyperlipidemia should be treated
- women with migraine who smoke should stop smoking before starting COCs
- consider non-ethinylestradiol methods in women who are at an increased risk of ischemic stroke, particularly those who have multiple risk factors. Observational studies suggest that progesteron-only hormonal contraceptive use is not associated with an increased risk of ischemic stroke, although quantifiable data are limited

Additional risk factors for ischemic stroke in women with migraine using COCs:

- age >35 years
- ischemic heart disease or cardiac disease with embolic potential
- diabates mellitus
- family history of arterial disease <45 years
- hyperlipidemia
- hypertension
- migraine aura
- obesity (body mass index >30)
- smoking
- systemic disease associated with stroke (connective tissue disorders)

Migraine and pregnancy

Most women with migraine improve during pregnancy, however, some women have their first attack during pregnancy[171]. Migraine often recurs during postpartum and can begin for the first time in general. The major concern in managing the pregnant migraineur is the effect of both medication and migraine on the fetus. Because of the possible risk of injury to the fetus, medication use should be limited; however, it is not contraindicated during pregnancy.

Since migraine usually improves after the first trimester, many women can manage their headaches with this reassurance along with nonpharmacologic means of coping such as ice, massage, and biofeedback. Some women continue to have severe headaches that may not only be disruptive to the patient, but they pose a risk to the fetus that is greater than the potential risk of the medications used to treat the pregnant patient. Symptomatic drugs are indicated for headaches that do not respond to nonpharmacologic treatment.

Proposed drugs for the treatment of acute attacks[164]:

Paracetamol (alone or with codeine)
NSAIDs

Caution: aspirin in low intermittent doses does not pose a significant teratogenic risk, whereas large doses, especially near term, may be associated with maternal and fetal bleeding.

To avoid: ergotamine, DHE, triptans, barbiturates, benzodiazepines.

Nausea: promethazine, prochlorperazine suppositories.

Severe attacks of migraine should be treated aggressively; intravenous fluids should be administered for hydration and in conjunction with prochlorperazine IV to control both nausea and pain.

Principles of migraine management: clinical highlights

1. Migraine is diagnosed by history and physical examination with a limited need of imaging or laboratory tests.
2. Consider additional testing if necessary.
3. Acute migraine therapy should be started with non-opioid analgesics (with or without antiemetics) as early as possible in attack. Adequate dosage should be administered; keep in mind that the dosage is higher than the usual analgesic/antipyretic dose. Appropriate pharmacologic or analgesic treatment of acute migraine should generally not exceed >2 days *per* week on a regular basis. More than this may result in chronic daily headaches.
4. Consider triptans if NSAR fails.
5. Consider which patients require prophylactic therapy. Depending on the comorbid disease, beta blockers, antidepressants or anticonvulsants are first line therapy to be introduced. Most prophylactic medications should be started in a low dose, titrated to a therapeutic dose to minimize side effects, and maintained at target dose for at least 12 weeks to assess efficacy.
6. Migraines occurring in association with menses and not responsive to standard cyclic prophylaxis may respond to hormonal prophylaxis with the use of estradiol patches or oral contraceptives.
7. Additional lifestyle modifications or risk factor avoidance should be discussed.

2. TENSION-TYPE HEADACHE

Previously used terms: psychomyogenic headache, stress headache, muscle contraction headache, ordinary headache, essential headache

This is the most common type of primary headache; lifetime prevalence in the general population ranges in different studies from 30% to 80%[172]. In the general population 4%-5% suffer from chronic daily headache and about half of them have chronic tension-type headache (CTTH) with more than 15 headaches *per* month[173].

The pathophysiology of CTTH is unknown; it has been suggested that increased myofascial tenderness and muscle hardness play an important role, although evidence for a centrally mediated origin of CTTH is increasing[174-176]. Increased pericranial tenderness recorded by manual palpation is the most significant abnormal finding in patients with tension-type headache. The tenderness increases with the severity and frequency of headache.

Diagnosic criteria for tension type headache are as follows[2]:

2.1 Infrequent episodic tension-type headache (ETTH) – diagnostic criteria

A. At least 10 previous headache episodes occurring on <1 day *per* month on an average (<12 days *per* year) and fulfilling criteria B-D
B. Headache lasting from 30 minutes to 7 days
C. At least 2 of the following characteristics:
   1. Pressing/tightening (nonpulsating) quality
   2. Mild or moderate severity (may inhibit but does not prohibit activities)
   3. Bilateral location
   4. No aggravation by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. No nausea or vomiting (anorexia may occur)
   2. Photophobia and phonophobia are absent, or one but not the other is present
E. Not attributed to another disorder

2.1.1.Infrequent episodic tension-type headache associated with pericranial tenderness

A. Episodes fulfilling criteria A-E for *2.1. Infrequent episodic tension-type headache*
B. Increased pericranial tenderness on manual palpation

2.1.2. Infrequent episodic tension-type headache not associated with pericranial tenderness

A. Episodes fulfilling criteria A-E for *2.1. Infrequent episodic tension-type headache*
B. No increased pericranial tenderness on manual palpation

2.2. Frequent episodic tension-type headache – diagnostic criteria

A. At least 10 previous headache episodes occurring on =1 day but <15 days *per* month for at least 3 months (≥12 and <180 days *per* year) and fulfilling criteria B-D

B, C, D, E as in 2.1.

Comment:

- frequent tension-type headache often coexists with migraine without aura, these two types of headache should be distinguished best by a diagnostic headache diary in order to select the right treatment and to prevent medication-overuse headache

2.2.1. Frequent episodic tension-type headache associated with pericranial tenderness

A. Episodes fulfilling criteria A-E for *2.2. Frequent episodic tension-type headache*
B. Increased pericranial tenderness on manual palpation

2.2.2. Frequent episodic tension-type headache not associated with pericranial tenderness

A. Episodes fulfilling criteria A-E for *2.2. Frequent episodic tension-type headache*
B. No increased pericranial tenderness on manual palpation

2.3. Chronic tension-type headache (CTTH) – diagnostic criteria

A. Average headache frequency ≥15 days/month for >3 months (≥180 days/year), fulfilling criteria B-D
B. Headache lasts for hours or may be continuous
C. At least 2 of the following characteristics:
   1. Pressing/tightening quality
   2. Mild or moderate severity (may inhibit but does not prohibit activities)
   3. Bilateral location
   4. No aggravation on climbing stairs or similar routine physical activity
D. Both of the following:
   1. no more than one of photophobia, phonophobia or mild nausea
   2. neither moderate or severe nausea, nor vomiting
E. Not attributed to another disorder

2.3.1. Chronic tension-type headache associated with pericranial tenderness

A. Headache fulfilling criteria A-E for *2.3. Chronic tension-type headache*
B. Increased pericranial tenderness on manual palpation

2.3.2. Chronic tension-type headache not associated with pericranial tenderness

A. Headache fulfilling criteria A-E for *2.3. Chronic tension-type headache*
B. No increased pericranial tenderness on manual palpation

2.4. Probable tension-type headache – diagnostic criteria

2.4.1. Probable infrequent tension-type headache

A. Episodes fulfilling all but one of criteria A-D for *2.1. Infrequent episodic tension-type headache*
B. Episodes do not fulfill criteria for *1.1. Migraine without aura*
C. Not attributed to another disorder

2.4.2. Probable frequent tension-type headache

A. Episodes fulfilling all but one of criteria A-D for *2.2. Frequent episodic tension-type headache*
B. Episodes do not fulfill criteria for *1.1. Migraine without aura*
C. Not attributed to another disorder

2.4.3. Probable frequent tension-type headache

A, B, C, D as in 2.3.

E. Not attributed to another disorder but there is, or has been within the last 2 months, medication overuse fulfilling criterion B for any of the subforms of *8.2 Medication-overuse headache*

Diagnosis

There is no laboratory test that will make the diagnosis; underlying structural or metabolic disease should be considered when evaluating a patient who fulfills the diagnostic criteria for TTH.

Neuroimaging is unlikely to reveal an abnormality on MRI or CT scanning in patients with tension-type headache and normal neurologic examination[5].

Recommendation: data are insufficient to make an evidence-based recommendation regarding the use of neuroimaging for tension-type headache.

Therapy

Treatment of tension-type headache is mostly unsatisfactory and includes physical therapy, simple analgesics or antidepressants[177,178]. The vast majority of people with tension-type headache take simple analgesics or no medicine at all; people may seek help if episodic TTHs occur with unusual frequency or severity.

As a general rule, medications used for an acute headache should be taken at a relatively high dose and as early as possible[4].

I Acute treatment

1) Analgesics
   a) paracetamol 500-1000 mg
   b) aspirin 500-1000 mg
2) NSAIDs
   a) diclofenac 50-100 mg
   b) ketoprofen 25-50 mg
   c) naproxen 500-750 mg
   d) ibuprofen 400-800 mg
3) Combination drugs (see Migraine – acute therapy)

*The majority of NSAIDs and non-opioid analgesics are available in Croatia, some of them are partially covered by Croatian Institute of Health Insurance, a prescription is usually not needed

II Preventive treatment

Most preventive agents used for primary tension-type headache have not been examined in well-designed double-blind studies.

Pharmacologic treatment

Antidepressants

Antidepressants are most commonly used since many patients have comorbid depression and anxiety. In an open label study in nondepressed patients with either ETTH or CTTH, ***amitriptyline*** 25 mg/day significantly reduced analgesic consumption and the frequency and duration of headache in CTTH but not in ETTH[179].

Fluoxetine (SSRI) is coming into wider use for daily headaches, evidence from a double blind study demonstrates its efficacy in primary chronic headache disorders[180].

*Amitriptyline is available in Croatia, covered by Croatian Institute of Health Insurance (100%), a prescription is needed. Fluoxetine is available in Croatia, covered by Croatian Institute of Health Insurance (partially), a prescription is needed.

Botulinum toxin

Recently, five open label, double-blind, placebo-controlled studies of botulinum toxin type A (Botox) have been carrried out[181-185]. Four of them were positive and one was negative. In one study 200 U of Botox were injected and after 12-week follow-up headache-free days had improved in the Botox group and strongly tended to improve over the entire period[181]. Improvement was observed in a study where the dose range was 40-95 U; all of the patients showed reduced severity of headache, reduced pericranial muscle tenderness and increased headache-free days[182]. No proven efficacy has been shown at 12 weeks of injection of up to 100 U[185].

*Botulinum toxin is available in Croatia, NOT covered by Croatian Institute of Health Insurance for the treatment of tension type headaches

Nonpharmacologic treatment

a) Teaching healthy habits with regard to sleep, meals, exercise and eliminating unhealthy habits such as smoking and drinking
b) Psychological and behavioral techniques (see Migraine – nonpharmacologic treatment)

3. CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

Previously used terms: Horton's headache, migrainous neuralgia, petrosal neuralgia, hemicrania neuralgiformis chronica, ciliary neuralgia, erythromelalgia of the head.

Cluster headache (CH) is characterized by attacks of severe, strictly unilateral pain, located orbitally, supraorbitally, temporally or combined but may be spread to other regions of the head; the attacks are accompanied by autonomic features on the pain side. Most patients are restless or agitated during the attack. Attacks usually occur in series (cluster periods) lasting for weeks or months separated by remission periods usually lasting for months or years. Pain almost invariably recurs on the same side during an individual cluster period. About 10%-15% of patients have chronic symptoms without remissions, conversion to a chronic form seems to be related to a long (>20 years) duration of the disease and to a late age at onset[186]. A single cluster period is present in 27% of patients. During the cluster period, attacks may be provoked by alcohol (not during remission periods), histamine or nitroglycerine, or sudden variation in temperature. Cluster periods usually last between 2 weeks and 3 months. The frequency of attacks varies between one every other day and two a day, the duration of attacks is about 30-120 minutes (minimum 15 minutes, maximum 180 minutes). The individual attacks show a defined temporal profile, they often occur with "clock-like" regularity; cluster periods often begin in spring or autumn[187]. The usual age at onset is in the 20s-40s, and is older in chronic than in episodic CH; the prevalence is 5-6 times higher in men than in women[188,189].

The estimated prevalence is 3-5.6 *per* 100 000 population[190,191]. Studies suggest that there is an increased familial risk of CH, the mechanism of which remains to be fully elucidated. CH is inherited in only a minority of cases with an autosomal dominant pattern, and it seems that CH results from the interaction of more than one gene (polygenic inheritance)[192]. Epidemiologic studies found an increased prevalence among CH patients with cigarette smoking, previous head trauma (but not head trauma associated with loss of consciousness) and family history of headache[193].

The diagnosis of CH is mainly based on accurate description of the headache and associated symptoms; neurophysiologic tests are not warranted in the routine work-up of such patients[194,195].

Diagnosic criteria for cluster headache are as follows[2]:

3.1. Cluster headache – diagnostic criteria

A. At least 5 attacks fulfilling B-D
B. Severe unilateral orbital, supraorbital, and/or temporal pain lasting for 15 to 180 minutes if untreated
C. Headache associated with at least one of the following:
   1. ipsilateral conjunctival injection and/or lacrimation
   2. ipsilateral nasal congestion and/or rhinorrhea
   3. ipsilateral forehead and facial sweating
   4. ipsilateral miosis and/or ptosis
   5. ipsilateral eyelid edema
   6. a sense of restlessness or agitation
D. Frequency of attacks: from 1 every other day to 8/day
E. Not attributed to another disorder

3.1.1 Episodic cluster headache

A. Attacks fulfilling criteria A-E for *3.1. Cluster headache*
B. At least 2 cluster periods lasting from 7 days to 1 year, separated by remissions of at least 31 month

3.1.2 Chronic cluster headache

A. Attacks fulfilling criteria A-E for *3.1. Cluster headache*
B. Attacks recur >1 year without remission periods or with remission periods lasting ≥1 month

Comment:

- chronic cluster headache may evolve from episodic subtype, or arise as such from the first cluster period

Therapy

I Acute treatment

In all cases, patients should be instructed to avoid afternoon naps and alcoholic beverages; alcohol may induce acute attacks during active cluster periods. Patients should be cautioned about prolonged exposure to certain substances such as solvents, gasoline or oil-based paints during cluster periods. Altitude hypoxemia may induce attacks during clus-

ter periods. Bursts of anger, prolonged anticipatory anxiety, and excessive physical activity should be avoided because cluster attacks are apt to occur during the relaxation period that follows.

Two clinical trials, controlled *versus* placebo, investigated the efficacy of ***sumatriptan*** 6 mg SC in relieving a CH crisis and confirmed significant efficacy[196,197]. Observational studies also confirmed the effectiveness of sumatriptan in treating multiple attacks over time, with a good safety profile[198,199]. Another observational study also demonstrated the effectiveness of sumatriptan on the accompanying vegetative symptoms[200]. Sumatriptan nasal spray, in a dosage of 20 mg in comparison to the 6 mg SC formulation was investigated in one open controlled study; the results indicated a lower efficacy of the sumatriptan nasal spray[201].

One clinical trial of ***zolmitriptan*** 10 mg *versus* placebo has reported the drug appeared to be efficacious; 5 mg formulation has not been tested so far[202].

The efficacy of inhalatory ***oxygen*** at 100% for 15 minutes with a facial mask at a rate of 6-7 l/min in CH was evaluated in one clinical trial and one open study[203-206].

In 2 open studies the efficacy of ***ergotamine and caffeine*** combined, both in tablets (1 mg ergotamine +100 mg caffeine)[207] and suppositories (2 mg ergotamine + 100 mg caffeine)[208] was tested. The results failed to demonstrate clear efficacy in the treatment of CH attacks.

One placebo controlled clinical trial investigated the efficacy of ***dihydroergotamine*** in the nasal spray formulation at a dose of 0.5 mg *per* spray *per* nostril in the attack of CH. Dihydroergotamine was not able to stop CH crisis, but only to reduce the severity of symptoms[209].

An uncontrolled open study of 4% ***lidocaine*** in the nasal spray formulation did not provide definite clinical evidence of its efficacy[210].

*Oxygen inhalation is available only as a treatment in hospital, portable inhalators are NOT covered by Croatian Institute of Health Insurance for treatment of cluster headaches. For the availability of other medications see Migraine treatment.

Evidence for acute medication in acute cluster headache attacks are listed in Table 6[194].

To treat acute attacks, try the following:

1) Oxygen inhalation at a flow rate of 7 l/min for 15 minutes
2) Sumatriptan 6 mg SC (caution: cluster predominates in middle aged men with tobacco abuse)
3) Sumatriptan 20 mg nasal spray
4) Zolmitriptan 5-10 mg PO
5) DHE 1 mg IV or 20 mg nasal spray

II Preventive treatment

The objectives of prophylactic therapy are aimed at reducing the frequency, severity and duration of attacks, and consequently to end the cluster phase.

The principles of prophylactic therapy are[194]:

- Begin treatment early, particularly in the episodic forms
- Continue treatment for at least 10-14 days after the disappearance of the crisis
- Gradually suspend treatment
- If the crises reappear, increase dosages to therapeutic levels

The drug choice depends on different factors:

- Age and lifestyle of the patient
- Expected duration of the cluster phase
- Type of CH (episodic or chronic)
- Response to previous treatments
- Possible reported side effects
- Contraindications to the use of the drug
- Comorbid pathologies

Pharmacologic treatment

Calcium channel blockers

Verapamil is considered the first-choice drug for the prophylactic treatment of CH, both the episodic and chronic

Table 6. Evidence for acute medication in acute cluster headache attacks

Drug	Level of evidence	Clinical effectiveness
Triptans		
Sumatriptan SC	A	+++
Sumatriptan NS	C	?
Zolmitriptan	B	?
Oxygen inhalation	B	++
Hyperbaric oxygen therapy	B	?
Ergotamine and derivatives		
Ergotamine+caffeine	C	+
DHE NS	B	0
DHE IV	C	++
Lidocaine IN	C	+
Capsaicin	C	?

forms. In an open study (48 patients), 69% of patients reported an improvement greater than 75% during treatment with a dosage of 360 mg/day[211]. A double-blind *versus* placebo study with the same dosage showed a significant reduction in the frequency of crisis and use of analgesics, most evident in the second week of treatment[212].

The initial dose of a delayed-release preparation is 120 mg, which should be gradually increased to 3 times daily. Two thirds of patients show an improvement greater than 50% with a daily dose of 240 mg. Verapamil is generally well tolerated, and there are no interactions with sumatriptan, corticosteroids or other prophylactic drugs.

Adverse effects: constipation

Special caution is necessary if the drug is administered together with beta-blockers. An electrocardiogram is advisable before administration of the drug (to exclude atrioventricular block).

*Verapamil is available in Croatia, covered by Croatian Institute of Health Insurance (100%), a prescription is needed.

Corticosteroids

Prednisone is considered to be a second-choice drug. In chronic CH the drug induces rapid relief of the crises, and is useful in the early phase of treatment. It can be used for inducing remission in most serious cases with high attack frequency and severity, particularly in the central phase of the cluster period. A large open study showed a marked improvement in 77% of patients with episodic CH, and a partial benefit in another 12%[213]. Prednisone is used at doses of 50-60 mg/day for 2-3 days, then decreasing the dose by 10 mg/day every 2-3 days. The treatment period should not exceed 3 weeks. Headache may reappear when the dose is less than 25 mg/day; in this case another first-choice prophylactic drug may be added along with prednisone.

Dexamethasone. In an open study dexamethasone administered parenterally at a dose of 4 mg two times *per* day for 2 weeks followed by 4 mg *per* day in the 3rd week was able to interrupt the cluster period[214].

*Prednisone and dexamethasone are available in Croatia, covered by Croatian Institute of Health Insurance (100%), a prescription is needed.

Antipsychotics

Lithium is considered to be effective in the prophylaxis of both chronic and episodic CH. In clinical studies involving 428 patients, improvement was recorded in 78% of patients with chronic form; upon treatment suspension, a shift from the chronic to the episodic form was demonstrated[215]. In a group of patients with episodic form, a significant improvement was observed in 63%[216]. A double blind study in patients with chronic CH compared verapamil (360 mg/day) and lithium (900 mg/day), and found an equal efficacy but fewer side effects and a shorter latency period with verapamil[217]. One double blind study was unable to show greater efficacy of lithium *versus* placebo[218].

The initial dose is 300 mg, which should be increased to 900/day (maximum dose is 1200 mg/day). The efficacy is seen after a few days of treatment (at dosages of 600-900 mg/day). Serum levels should be measured 12 hours after the last dose and should not exceed 1.2 mEq/l (lithium is effective at serum concentrations od 0.4-1.2 mEq/l). It is necessary to periodically measure serum lithium levels and to check for thyroid and renal functional parameters before and during treatment.

Adverse effects: tremor, diarrhea, mental confusion.

Caution if used with some SSRIs, thiazide diuretics, indomethacin and diclofenac.

*Lithium is available in Croatia, NOT covered by Croatian Institute of Health Insurance for the treatment of cluster headaches

Serotonin antagonists

Pizotifen. In a single blind study in patients with episodic CH, the disappearance of the crises has been reported in 21% of patients, and 36% showed an improvement of the crises greater than 50%[219]. The maintenance dose of pizotifen was 3 mg/day (reached progressively).

Methysergide. A review of studies before 1967 showed a methysergide efficacy of 73%; however, another review study conducted later found the efficacy percentage to range from 20% to 30%. The dosage range was 4-10 mg/day. The drug should be suspended for at least 2 months after a treatment period of 4 months, due to the adverse effects of retroperitoneal, pleuropulmonary and endocardiac fibrosis[220,221].

* Pizotifen and methysergide are not available in Croatia

Anticonvulsants

Valproic acid. In an open study involving 13 patients with episodic CH receiving 600-1200 mg of valproic acid / day, disappearence of the crises was observed in 9 patients after 1-4 days of treatment[222].

Topiramate. In an open study, an improvement was observed after 2-week administration of 50-125 mg of topiramate; the most common adverse events reported were somnolence, stupor, ataxia, cognitive disturbances[223].

* Valproic acid and topiramate are available in Croatia, NOT covered by Croatian Institute of Health Insurance for the treatment of cluster headaches

Other

Melatonin. On the observation that serum and urinary levels of melatonin are reduced in patients with CH[224], a double-blind study of melatonin 10 mg *per os versus* placebo was carried out in patients with episodic CH and showed its efficacy[225]. The remission phase was obtained in 3-5 days in half of the patients treated with melatonin, in contrast to CH patients treated with placebo.

Capsaicin. In a double-blind study, capsaicin at a concentration of 0.025% applied 2 times *per* day for 7 days into the ipsilateral nostril was shown to be more efficacious than placebo in reducing the frequency and severity of the crises[226]. Long-term use of capsaicin is inappropriate because of the unpleasant local reactions induced by the drug.

Dihydroergotamine. Dihydroergotamine administered intravenously was demonstrated to induce rapid disappearance of cluster attacks when administered daily (0.5-0.8 mg in 8 h) in patients with episodic CH[227].

Evidence for prophylactic medication in episodic and chronic cluster headache are listed in Tables 7 and 8[194].

In prophylactic therapy try the following:

1) Verapamil 80 mg *tid* or 240 mg sustained release; dosages employed range from 240 to 720 mg/day in divided doses
2) Prednisone 60 mg/day for 3 days, followed by 10 mg decrements every 3 days over an 18-day period
3) Dexamethasone 4 mg *bid* for 2 weeks followed by 4 mg/day for 1 week
4) Lithium carbonate 300 mg *tid* or 450 mg sustained release (effective at serum concentrations of 0.4-0.8 mEq/l, which is less than usually required for bipolar disorder); most patients will benefit from dosages between 600 and 900 mg/day. Lithium has the potential for many side effects and has a narrow therapeutic window. The serum concentration should be measured 12 hours after the last dose and should not exceed 1.0 mEq/l. Renal and thyroid function must be assessed prior to and during treatment.
5) Valproic acid 250 mg *bid* followed by 250 mg increments *per* dose to find the lowest effective dose
6) Topiramate 50-125 mg/day in 2 divided doses

Table 7. Evidence for prophylactic medication in episodic cluster headache

Drug	Level of evidence	Clinical effectiveness
Verapamil	B	+++
Prednisone	C	+++
Lithium	C	+++
Melatonin	B	?
Pizotifen	B	?

Nonpharmacologic treatment

Refractory patients

Approximately 10% of patients develop chronic cluster headache which does not respond to monotherapy. In patients with chronic cluster headache, surgical treatment may be the only alternative therapy when medical therapy is ineffective, is limited by contraindications, or is poorly tolerated[228].

The following criteria should be applied in carefully selected patients:

1) Total resistance to pharmacologic treatment (severe side effects and contraindications to therapy)
2) Headache strictly located on the same side
3) Pain primarily in the region of the ophthalmic branch of the trigeminal nerve
4) Patients with stable personality and psychological profile with little tendency to somatization

Options to consider:

1) Radiofrequency thermocoagulation of the trigeminal ganglion
2) Gamma knife radiosurgery
3) Microvascular decompression
4) Section of the sensory trigeminal nerve at the root exit zone

Table 8. Evidence for prophylactic medication in chronic cluster headache

Drug	Level of evidence	Clinical effectiveness
Verapamil	C	+++
Prednisone	C	?
Lithium	C	+++
Methysergide	C	+

The surgical procedures that yield best results are those involving the sensory component of the trigeminal nerve:

Rhizotomy with radiofrequencies

This techique is based on the demonstration that the nociceptive C fibers, being thinner than the A fibers responsible for tactile sensitivity, may be destroyed with a gradual thermal lesion, leaving tactile sensitivity intact. The results are encouraging: at least 75% of patients have good to excellent results[229,230]. The duration of the procedure is also favorable, with recurrence in the long-term follow-up of only 20%, while some patients remain pain-free for 20 years[231].

Percutaneous retrogasserian rhizolysis with glycerol

This method consists of penetrating the Gasser ganglion cistern and introducing a mixture of glycerol and CSF into the cistern. In a study assessing 18 patients, 83% showed an improvement after 1-2 injections; after 5 years a recurrence rate of 39% was observed[232].

Gamma-knife surgery

Gamma-knife showed immediate relief of pain, which was maintained for more than 8 months; duration and tolerability of this technique are not known at this moment[233].

3.2 Paroxysmal hemicrania – diagnostic criteria

Paroxysmal hemicrania resembles cluster headache in pain characteristics and associated symptoms; the differences are:

- attacks are of shorter duration
- attacks are more frequent
- occurs more commonly in female
- responds absolutely to indomethacin

A. At least 20 attacks fulfilling criteria B-D
B. Attacks of severe unilateral orbital, supraorbital or temporal pain lasting for 2-30 minutes
C. Headache is accompanied by at least one of the following:
   1. ipsilateral conjunctival injection and/or lacrimation
   2. ipsilateral nasal congestion and/or rhinorrhea
   3. ipsilateral forehead and facial sweating
   4. ipsilateral miosis and/or ptosis
   5. ipsilateral eyelid edema
D. Attacks have a frequency above 5 *per* day for more than half of the time, although periods with lower frequency may occur
E. Attacks are prevented completely by therapeutic doses of indomethacin
F. Not attributed to another disorder

3.2.1 Episodic paroxysmal hemicrania

A. Attacks fulfilling criteria A-F for *3.2. Paroxysmal hemicrania*
B. At least 2 attack periods lasting for 7 days – 1 year and separated by pain-free remission periods of ≥1 month

3.2.2 Chronic paroxysmal hemicrania

A. Attacks fulfilling criteria A-F for *3.2. Paroxysmal hemicrania*
B. Attacks recur over >1 year without remission periods or with remission periods lasting <1 month

Therapy

Acute: Indomethacin in a dose of 150 mg daily orally or rectally, or 100 mg parenterally.

Maintenance: indomethacin, smaller doses are usually sufficient[234].

3.3. Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT) – diagnostic criteria

This syndrome has been very well recognized in the last decade. This syndrome is characterized by short-lasting attacks of unilateral pain that are much briefer than any of those seen in other trigeminal autonomic cephalalgias; attacks are very often accompanied by prominent lacrimation and redness of the ipsilateral eye. Patients may also be seen with other cranial autonomic symptoms such as nasal congestion, rhinorrhea or eyelid edema.

A. At least 20 attacks fulfilling B-D
B. Attacks of unilateral orbital, supraorbital or temporal stabbing or pulsating pain, moderately severe lasting 5-240 seconds.
C. Pain is accompanied by ipsilateral conjunctival injection and lacrimation
D. Attacks occur with a frequency from 3 to 200 *per* day
E. Not attributed to another disorder

Comment: patients have been described in whom there is an overlap between SUNCT and trigeminal neuralgia – such patients should recieve both diagnoses since this differentiation is clinically difficult.

Therapy:

Various treatments have been used, but generally without clinical efficacy

3.4. Probable trigeminal autonomic cephalalgia – diagnostic criteria

Headache attacks that do not quite meet the diagnostic criteria for any of the subtypes described under 3.1, 3.2, or 3.3, becuase the number of typical attacks has been insufficient or any other part of the diagnostic criteria is not fulfilled.

A. Attacks fulfilling all but one of the specific criteria for one of the subtypes of trigeminal autonomic cephalalgia
B. Not attributed to another disorder

4. OTHER PRIMARY HEADACHES

4.1 Primary stabbing headache – diagnostic criteria

Previously used terms: ice-pick pains, ophthalmodynia periodica, cephalgia fugax

Migraine sufferers or patients with cluster headache more often experience stabbing pains; in these patients stabbing pain is felt at the site of migraine or cluster pain. Stabs usually last up to 3 seconds; stabs may move from one area to another in the same or contralateral hemicranium.

A. Head pain occurring as a single stab or series of stabs and fulfilling criteria B-D
B. Exclusively or predominatly felt in distribution of first division of the trigeminal nerve (orbit, temporal, parietal)
C. Stabs last few seconds and recur irregularly (frequency ranging from 1 to many *per* day)
D. No accompanying symptoms
E. Not attributed to another disorder

4.2 Primary cough headache – diagnostic criteria

Primary cough headache predominantly affects patients older than 40, and is usually bilateral. Cough headache is symptomatic in about 40% of cases, the majority of which present Arnold-Chiari malformation type I. Structural cerebral lesions such as a posterior fossa tumor should be excluded by neuroimaging.

A. Headache fulfilling criteria B and C
B. Sudden onset, lasting from one second to 30 minutes
C. Brought on by and occurring only in association with coughing, straining and/or Valsalva maneuver
D. Not attributed to another disorder

Therapy: indomethacin is usually effective

4.3. Primary exertional headache – diagnostic criteria

Primary exertional headache occurs often in warm weather or at high altitude. Any form of exercise precipitates the headache. Subarachnoid hemorrhage and arterial dissection should be excluded.

A. Pulsating headache fulfilling criteria B and C
B. Lasting from 5 minutes to 48 hours
C. Brought on by and occurring only during or after physical exertion
D. Not attributed to another disorder

Therapy: indomethacin is usually effective

4.4. Primary headache associated with sexual activity – diagnostic criteria

Headache precipitated by sexual activity, usually starting as a dull bilateral pain increasing as sexual excitement increases, at orgasm may be very severe. On first onset of orgasmic headache, subarachnoid hemorrhage and arterial dissection should be excluded.

4.4.1 Preorgasmic headache

A. Dull ache in the head and neck associated with awareness of the neck and/or jaw muscle contraction and fulfilling criterion B
B. Occurs during sexual activity and increases with sexual excitement
C. Not attributed to another disorder

4.4.2 Orgasmic headache

A. Sudden severe explosive headache fulfilling criterion B
B. Occurs at orgasm
C. Not attributed to another disorder

Therapy: analgesics, NSARs if necessary

4.5 Hypnic headache – diagnostic criteria

Pain is bilateral in two-thirds of patients. The attack usually lasts from 15 to 180 minutes. The pain is usually mild to moderate.

A. Dull headache, fulfilling criteria B-D
B. Develops only during sleep and awakens the patient
C. At least 2 of the following are present:
   1. occurs >15 times *per* month
   2. lasts ≥15 min after waking
   3. first occurs after age 50

D. No autonomic symptoms and no more than one of nausea, photophobia or phonophobia
E. Not attributed to another disorder

Therapy: aspirin, caffeine in acute treatment and lithium in prophylaxis were effective in several reported cases[235].

4.6 Primary thunderclap headache – diagnostic criteria

"Thunderclap" headache refers to a sudden onset of severe pain that is usually described by patients as "being struck by thunder". Headache may recur within the first week from onset. Normal CSF and brain imaging are required; subarachnoid hemorrhage and arterial dissection should be excluded.

A. Severe head pain fulfilling criteria B and C
B. Both of the following:
   1. sudden onset, reaching maximum severity in <1 min
   2. lasting from 1 hour to 10 days
C. Does not recur regularly over subsequent weeks or months
D. Not attributed to another disorder

Therapy: analgesics if necessary

4.7 Hemicrania continua – diagnostic criteria

Hemicrania continua is a strictly unilateral headache responsive to indomethacin, usually unremitting, rare cases of remission have been reported.

A. Headache present for >3 months fulfilling criteria B-D
B. Pain has all 3 of the following present:
   2. unilateral pain without side-shift
   3. daily and continuous, without pain-free periods
   4. moderate severity, but with exacerbations of severe pain
C. At least one of the following autonomic features occurs during exacerbations and ipsilaterally to the pain side:
   1. conjunctival infection and/or lacrimation
   2. nasal congestion and/or rhinorrhea
   3. ptosis and/or miosis
D. Complete response to therapeutic doses of indomethacin
E. Not attributed to another disorder

Therapy: Indomethacin in a dose of 150 mg daily orally or rectally, or 100 mg parenterally for 3 days

Maintenance: indomethacin, smaller doses are usually sufficient[234].

4.8. New daily persistent headache (NDPH) – diagnostic criteria

NDPH has many similarities to tension-type headache; the main difference is that NDPH is daily, unremitting, continuous from or almost from onset; typically occurring in individuals without a prior headache history. Secondary headaches such as posttraumatic headache, low CSF volume headache, raised CSF pressure headache, medication-overuse headache must be ruled out. Two subforms are recognized:

- self-limiting subform which resolves within several months without therapy
- refractory subform which is resistant to aggressive treatment

A. Headache present for >3 months fulfilling criteria B-D
B. Headache is daily and unremitting from onset or from <3 days from onset
C. At least 2 of the following characteristics:
   1. pressing/tightening quality
   2. mild or moderate severity (may inhibit but does not prohibit activities)
   3. bilateral location
   4. no aggravation by walking stairs or similar routine physical activity
D. Both of the following:
   1. no more than one of photophobia, phonophobia or mild nausea
   2. neither moderate or severe nausea, nor vomiting
E. Not attributed to another disorder

Therapy: See Tension-type headache.

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Sažetak

NA DOKAZIMA ZASNOVANE SMJERNICE ZA LIJEČENJE PRIMARNIH GLAVOBOLJA

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U dijela bolesnika koji pate od glavobolja potreban je neurološki pregled. Smjernice za dijagnostiku i liječenje glavobolja imaju za cilj pomoći liječnicima u svakodnevnom radu s bolesnicima s glavoboljom. U većine bolesnika migrenu nije dijagnosticirao liječnik, te im nije pružena odgovarajuća pomoć za liječenje napadaja. U proteklih petnaestak godina uvedene su nove terapijske metode (za akutno i preventivno liječenje). Bolesnicima koji ne reagiraju na obične analgetike, osobito onima s umjerenim i jakim migrenama, treba ponuditi triptane. Preventivnu terapiju, ovisno o drugim pridruženim bolestima, treba preporučiti osobama s učestalim ili dugotrajnim napadajima migrene. Kod osoba s tenzijskim glavoboljama potrebno je isključiti organsku podlogu glavobolja, a liječenje uključuje farmakološke i nefarmakološke mjere. Premda rijetki, bolesnici s *cluster* glavoboljama imaju jake bolove; u akutnom napadaju preporuča se inhalacija kisika ili triptani, a u pojedinim slučajevima indicirana je i preventivna terapija. Smjernice uključuju klasifikaciju, dijagnostičke kriterije i načela liječenja primarnih glavobolja. Sve preporuke u Smjernicama se temelje na meta-analizama i preporukama iz svjetske literature s osvrtom na terapijske mogućnosti u Hrvatskoj.

Ključne riječi: *migrena, tenzijska glavobolja, cluster glavobolja, liječenje glavobolje, farmakoterapij*a

APPENDIX

Abbreviations:

PO	*per os*
IM	intramuscular
IV	intraveneous
SC	subcutaneous
RPD	rapid disk
OTC	over-the-counter

Classification of published studies according to their scientific validity in evidence levels (according to the criteria issued by the Agency for Health Care Policy and Research; Perfetto and Morris 1996):

Translation of evidence to recommendation:

Level A – requires at least one convincing class I study or at least two consistent, convincing class II studies
Level B – requires at least one convincing class II study or at least three consistent class III studies
Level C – requires at least two convincing and consistent class III studies

Rating of therapeutic article:

Class IA – evidence based on meta-analysis of randomized and controlled studies
Class IB – evidence based on at least one randomized and controlled study
Class II – evidence based on at least one well designed controlled study without randomization
Class III – evidence based on well-designed, non-experimental, descriptive studies, for example, comparison study, correlation study or case-control study
Class IV – evidence based on experience of expert committees or experts; case reports