REPORT OF THE CROATIAN SOCIETY FOR NEUROVASCULAR DISORDERS, CROATIAN MEDICAL ASSOCIATION

EVIDENCE BASED GUIDELINES FOR TREATMENT OF PRIMARY HEADACHES – 2012 UPDATE

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SUMMARY – These guidelines have been developed to assist the physician in making appropriate choices in work-up and treatment of patients with headaches. The specific aim of the Evidence Based Guidelines for Treatment of Primary Headaches – 2012 Update is to provide recommendations for establishing an accurate diagnosis and choose the most appropriate therapy in the group of patients with primary headaches, based on a comprehensive review and meta-analysis of scientific evidence with regard to treatment possibilities in Croatia. These data are based on our previous Evidence Based Guidelines for Treatment of Primary Headaches published in 2005 and other recommendations and guidelines for headache treatment.

Key words: *Migraine; Tension type headache; Cluster headache; Headache treatment; Pharmacotherapy*

International Headache Society classification system (Headache Classification Committee, 2004)

The second edition of the International Headache Society (IHS) classification system was released in 2004[1]. Diagnosis of headache disorders should be made as accurately as possible according to the following classification:

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A. PRIMARY HEADACHE DISORDERS

1	[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 homeostasis
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

Introduction

These Guidelines have been developed to assist the physician in making appropriate choices in the work-up and treatment of patients with headaches. Headache disorders pose a public-health problem with an impact on both individuals and society. The socioeconomic burden includes costs associated with health care utilization and cost due to sick leave or reduced productivity. A large proportion of headache sufferers are never diagnosed or regularly treated.

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

The specific aim of the Guidelines 2012 Update is to provide recommendations for establishing an accurate diagnosis and for choosing the most appropriate therapy in the group of primary headache patients, based on a comprehensive review and meta-analysis of scientific evidence with regard to treatment possibilities in Croatia. These data are based on our previously published Evidence Based Guidelines for Treatment of Primary Headaches from 2005[3] and other recommendations and guidelines for headache treatment.

OVERVIEW, DIAGNOSIS AND CLASSIFICATION

General rules for classification

Classification of a headache disorder requires the following rules to be applied[4]:

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, then code it in 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, lack of ability 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. Preexisting 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[5]:

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 established outpatient treatment plan has failed
5. Diagnostic suspicion of infectious disorder involving central nervous system (CNS) (e.g., brain abscess and meningitis) with initiation of appropriate diagnostic testing.
6. Diagnostic suspicion of acute vascular compromise (e.g., aneurysm, subarachnoid hemorrhage (SAH), 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 (CSF) 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 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 psychological or psychiatric evaluation with sufficient severity of illness such that a 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:
  - Time from onset to peak
  - Usual time of onset (season, month, menstrual cycle, week, hour of day)
  - Frequency
  - Duration
  - 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[6,7]. Neuroimaging may as well relieve the patient's anxiety about having an underlying pathologic condition; therefore neuroimaging may improve patient 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 change in the 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[6,7].

Neurological examination

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

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

Neurological symptoms

Headache worsened by Valsalva maneuver, headache causing awakening from sleep, new headache in elderly 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 neurological 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 positive for human immunodeficiency virus (HIV)
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 in emergency department?

Patients presenting to emergency department with headache and abnormal findings on neurological examination (i.e. focal deficit, altered mental status, and altered cognitive function) should undergo emergent* non-contrast head CT scan. 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 computed tomography scan[5,6] (Level B). Patients who are older than 50 years presenting with a new type of headache without abnormal findings on neurological examination should be considered for an urgent neuroimaging study (Level C).

*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 the emergency department (scan appointment is included in disposition) or performed prior to disposition when follow-up cannot be assured.

III Electroencephalography

Electroencephalography (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[6] (Level C).

IV Lumbar puncture

Lumbar puncture is indicated in the evaluation of:

- meningitis, encephalitis
- meningeal carcinomatosis or lymphomatosis
- 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 lumbar puncture. In the absence of findings suggestive of increased intracranial pressure, lumbar puncture can be performed without obtaining a neuroimaging study[6]. (Note: Lumbar puncture does not assess for all causes of a sudden severe headache) (Level C).

V Angiography

Patients with thunderclap headache who have negative findings on head CT scan, normal opening pressure, and negative findings in CSF analysis do not need emergent angiography and can be discharged from emergency department with follow-up arranged with their primary care provider or neurologist[6] (Level C).

VI Laboratory studies

Routine clinical laboratory studies followed by specific laboratory studies are recommended if indicated[5].

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[5]:

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 is linked to indirect costs[7]. Approximately three fourths of migraine sufferers have a reduced ability to function during attacks with more than half reporting severe disability or need for bed rest. Most migraine sufferers have not been officially diagnosed by a physician; therefore, many patients are

Symptoms	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

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%[8-11]. A prevalence study was carried out in a Croatian population in 2006: the 1-year crude prevalence of migraine without and with aura in this study was 7.5%, of probable migraine 11.3%, and of TTH 21.2%. The 1-year age- and sex-adjusted prevalence of migraine was 6.2%, of probable migraine 8.8%, and of TTH 20.7%; the prevalence of migraine combined with probable migraine was 15.0%. Total crude prevalence of headache (combination of migraine, probable migraine and TTH) was 39.9%[12].

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. A similar trend is seen in males, although the peak prevalence occurs earlier. Thereafter, the prevalence decreases for both genders but remains higher in women than in men.

Migraine prevalence is significantly higher in Caucasians (20.4%) than in African Americans (16.2%) or Asian Americans (9.2%)[13].

The mechanism of migraine pain development is not fully understood. Migraine was initially considered a cerebrovascular condition, then a neuroinflammatory process, and now primarily a neurogenic disorder. 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. The genetic discoveries are the latest step in the evolution of our understanding of migraine revealing that ion channels and transporter mutations may be causative of migraine. 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[14]. Genetic and epidemiological evidence suggest that changes in blood vessels, hypoperfusion disorders and microembolization can cause neurovascular dysfunction and evoke cortical spreading depression[15-18].

Diagnostic testing

There are, as yet, no tests that confirm the diagnosis of migraine[5,19-21]. The headache diary is the most important diagnostic tool and should be filled in for at least 3 months, in which the frequency, duration and intensity of migraine attacks are recorded. The total number of hours with headache *per* month, presence of accompanying symptoms, and use of symptomatic therapy should be listed[22]. Selective testing, including neuroimaging (CT or MRI), EEG, lumbar puncture, CSF and blood studies may be indicated to evaluate for secondary headache if the causes of concern have been identified in patient history or 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 neurological examination[6,20,21]. Neuroimaging is not usually warranted for patients with migraine and normal neurological 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).

Migraine types

1.1 Migraine without aura – diagnostic criteria

Previously used terms: 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** accompagnée*

The migraine headache may be preceded by aura; approximately 10%-25% of migraine sufferers report aura[5,11]. 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 for 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

A. 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:
   l. 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 the 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 visual symptoms or follows them within 60 minutes

D. Normal ophthalmological 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 for 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 the 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

Proposed new subclassification
*A 1.1 Migraine without aura:

A1.1.1 Pure menstrual migraine without aura

Diagnostic criteria:
Attacks, in a menstruating woman, fulfilling criteria for 1.1 Migraine without aura
Attacks occur exclusively on day 1±2 (i.e. days -2 to +3) of menstruation in at least two of three menstrual cycles and at no other times of the cycle

Notes:

The first day of menstruation is day 1 and the preceding day is day -1; there is no day 0.

For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either normal menstrual cycle or from withdrawal of exogenous progestagens, as in case of combined oral contraceptives and cyclic hormone replacement therapy.

A1.1.2 Menstrually-related migraine without aura

Diagnostic criteria:

Attacks, in a menstruating woman, fulfilling criteria for 1.1 Migraine without aura
Attacks occur on day 1±2 (i.e. days -2 to +3) of menstruation in at least two out of three menstrual cycles and additionally at other times of the cycle

Notes:

The first day of menstruation is day 1 and the preceding day is day -1; there is no day 0.

For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either normal menstrual cycle or from withdrawal of exogenous progestagens, as in case of combined oral contraceptives and cyclic hormone replacement therapy.

A1.1.3 Non-menstrual migraine without aura

Diagnostic criteria:

Attacks, in a menstruating woman, fulfilling criteria for 1.1 Migraine without aura
Attacks have no menstrual relationship

Note:

That is, they do not fulfill criterion B for A1.1.1 Pure menstrual migraine without aura or A1.1.2 Menstrually-related migraine without aura.

Comments:

This subclassification of 1.1 Migraine without aura is applicable only to menstruating women.

The importance of distinguishing between A1.1.1 Pure menstrual migraine and A1.1.2 Menstrually-related migraine is that hormone prophylaxis is more likely to be effective for pure menstrual migraine. Documented prospectively recorded evidence, kept for a minimum of three cycles, is necessary to confirm the diagnosis, as many women over-report an association between attacks and menstruation. Menstrual attacks are mostly migraine without aura. In a woman who has migraine both with and without aura, migraine with aura does not appear to be associated with menstruation[23].

Migrainous vertigo was not included into the IHS criteria for migraine, although epidemiological data show a relatively high prevalence among migraineurs[24-26].

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[27]. A community based study in Croatia revealed similar results: only 16.8% of patients with migraine pay regular visits to physicians, while 36.3% never visited a physician. The same study revealed that specific antimigraine therapy was taken by half of patients with migraine: 35.7% of patients used triptans and 21.7% ergotamines. Prophylactic treatment was used by 13.9% of migraine patients, 1.2% of TTH, and 6.9% of probable migraine patients[28].

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 pro 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 the possible triggers, days of disability or missed work, school or social activities.
5. Educate the patient to identify and avoid the 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 practitioner must always remain alert to the possibility of secondary causes for 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 – the 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 lasted for more than 72 hours.

This categorization influences the 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[5,29-43]:

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 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 emergency department).
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.

A wide array of data regarding acute migraine treatment are available, but few trials strictly adhere to IHS guidelines for patient inclusion criteria.

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, the potential for overuse and adverse events.

Triptans or DHE are first-line drugs for severe attacks and for less severe attacks that do not adequately respond to analgesics. Triptans appear to have similar efficacy profiles, but among newer triptans, almotriptan offers improved tolerability over sumatriptan. Thus NSAIDs, particularly effervescent aspirin, should be considered the first-line treatment of migraine attacks. Multi-targeted combination therapy with a triptan plus a NSAID such as sumatriptan/naproxen sodium is more effective in acute migraine treatment than monotherapy with either agent alone. A non-oral route of administration combined with an antiemetic should be applied in cases of severe nausea and vomiting. A recent study regarding prescription patterns in acute treatment of migraine showed that NSAIDs were used more often than triptans[35,36,39,41,42].

Nonspecific medications

NSAIDs and non-opioid analgesics

Analgesics, NSAIDs and acetylsalicylic 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.

Aspirin 1000 mg is an effective treatment for acute migraine headaches, similar to sumatriptan 50 mg or 100 mg. Addition of metoclopramide 10 mg improves relief of nausea and vomiting[44]. Ibuprofen is an effective treatment for acute migraine headaches, providing pain relief in about half of sufferers, but complete relief from pain and associated symptoms for only a minority; number needed to treat for all efficacy outcomes were better with 400 mg than 200 mg in comparison with placebo, and soluble formulations provided more rapid relief[45].

NSAIDs and combination analgesics containing caffeine, paracetamol, ASA are a reasonable first-line treatment for mild to moderate migraine attacks or severe attacks that have been responsive in the past to similar NSAIDs or non-opiate analgesics (Level A)[29].

The combination of aspirin and metoclopramide is almost as effective as sumatriptan[46].

Paracetamol (acetaminophen) alone is not recommended for migraine, except for 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[3].

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 the potential risk 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.

* Most NSAIDs and non-opioid analgesics are available in Croatia; only ibuprofen 200 mg and 400 mg can be bought as OTC drugs and a prescription is needed for the others. Some of them are partially covered by the Croatian Institute of Health Insurance, a prescription is 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[47].

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[29,48]. Parenteral and oral combination use should be considered only when the risk of abuse has been addressed and sedation will not put the patient at risk. Weak opioids are tramadol, dihydrocodeine, codeine; strong opioids are oxycodone, sevredol, buprenorphine, fentanyl, hydromorphone.

* opioids are available in Croatia, a prescription is needed

Combination drugs

Combination of mild opioid (such as codeine) enhances analgesic effectiveness up to 40%. Propyphenazone 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. However, combinations such as simple analgesics and antiemetics have been proven to be efficient in acute migraine attack: paracetamol 1000 mg alone is an effective treatment for acute migraine headaches, and the addition of 10 mg metoclopramide gives short-term efficacy equivalent to oral sumatriptan 100 mg[49].

Combination drugs common on the market:

ASA 200 mg + paracetamol 200 mg + caffeine 60 mg

Paracetamol 210 mg + propyphenazone 250 mg + caffeine 50 mg + codeine 10 mg

Paracetamol 200 + propyphenazone 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 the treatment choice for rescue therapy for patients with status migrainosus. Dexamethasone is efficacious in preventing headache recurrence and safe when added to standard treatment for the management of acute migraine headache in emergency department. When added to standard abortive therapy for migraine headache, single dose parenteral dexamethasone is associated with a 26% relative reduction in headache recurrence within 72 hours[50,51].

Antiemetics

Relatively few studies have investigated their effectiveness in migraine attacks; in the majority of cases, such studies concern combination of analgesics or NSAIDs with antiemetics. These associations have been proposed to improve the absorption of symptomatic drugs and to act as adjuvant 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[41].

Thiethylperazine and prochlorperazine are adjuncts in the treatment of acute migraine with nausea and vomiting[29,35,37]. Chlorpromazine iv. may be 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 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 which it can 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, thiethylperazine – acute extrapyramidal side effects such as dystonia, akathisia, and oculogyric crisis may occur. Prochlorperazine, chlorpromazine – drowsiness, sedation, postural hypotension.

* Metoclopramide is available as tablets and thiethylperazine as suppository, and are fully covered by the Croatian Institute of Health Insurance, a prescription is needed.

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 on headache but also on accompanying symptoms (photophobia, phonophobia, nausea and vomiting) and on functional disability[5,54-89].

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. Triptans should be used as soon as possible after headache onset. To date, no evidence supports their use during the 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. An economic analysis of a prospective observational 6-month outcomes 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 patient disability and thus improving their ability to function at work and non-work activities[75].

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, selective serotonin reuptake inhibitors (SSRIs) and lithium. Rizatriptan and zolmitriptan are contraindicated in patients with liver dysfunction.

Cautions: $5HT_1$ agonists should be used with caution in conditions which predispose to coronary artery disease (pre-existing 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 applied in patients over 65 years. Sumatriptan and naratriptan contain the sulfonamide component, which can 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[71]. 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[72]. However, so far in the literature, sumatriptan, zolmitriptan, naratriptan and frovatriptan have been described to cause acute coronary syndromes. Therefore, triptans should not be prescribed in patients with pre-existing coronary heart disease. Severe or persistent thoracic pain after taking triptans should therefore be investigated accordingly[90-92].

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 nasal spray, 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 nasal spray
- 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 20mg, 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.

* Sumatriptan 50 mg po. (tablet), sumatriptan 20 mg nasal spray, zolmitriptan 2.5 mg rapid melting disk and rizatriptan 10 mg rapid melting disk are available in Croatia; sumatriptan 50 mg po. is fully covered by the Croatian Institute of Health Insurance and the rest are partially covered, a prescription is needed.

Despite the similarities of the available triptans, pharmacological heterogeneity offers slightly different efficacy profiles, pharmacokinetics, pain response, recurrence and adverse events.

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; physicians thus 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[29,54]. Controlled clinical studies reveal that most of oral triptans have broadly similar efficacy profiles. Switching triptans can therefore only be recommended if the patient experiences problems such as the lack of efficacy or intolerable side effects following repeated use of the initial triptan[93]. 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 the pain and associated symptoms quickly with minimum adverse events and without recurrence of symptoms.

All triptans are superior to placebo in clinical trials, and some, such as rizatriptan 10 mg, eletriptan 40 mg, almotriptan 12.5 mg, and zolmitriptan 2.5 and 5 mg are very similar to each other and to the prototype triptan, sumatriptan 100 mg. These five are known as the fast-acting triptans. Increased dosing can offer increased efficacy but may confer a higher risk of adverse events, which are usually mild to moderate and transient in nature.

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. A 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 adverse events and the need of self-injection. Several placebo controlled trials support the efficacy of sumatriptan nasal spray for headache relief at 1 and 2 hours; a dose-response relationship was demonstrated, with superiority to placebo at the 10, 20 and 40 mg doses. Sumatriptan is metabolized mainly by the monoamine oxidase (MAO-A) and is contraindicated in patients using MAO inhibitors. Substantial drug interactions with other traditional migraine-preventive medications, including beta blockers, calcium channel antagonists, SSRIs and tricyclic antidepressants were not found.

Zolmitriptan has oral bioavailability of 40%, half life about 2.5 hours and is metabolized by the cytochrome P450 system. No significant difference was found between 2.5 mg and 5 mg doses. 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 have been 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 to a slower onset of improvement, thus naratriptan can be offered in patients with mild to moderate migraine.

Rizatriptan has rapid oral absorption and high oral bioavailability (45%) at 10 mg dose. There is no significant difference at 2 hours between sumatriptan and 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); interaction with other beta-blockers has not been observed.

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

Frovatriptan was effective and well tolerated across a wide range of doses (2.5, 5, 10, 20 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 a long half-life (5 hours); it 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.

Tables 1 and 2 show pharmacokinetic variables for 5-$HT_{1B/1D}$ agonists[56].

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

	T max (h)	T ½	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

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

	Dose	Pain response mg	Pain response 2 h (%)	Pain free 4 h (%)	Recurrence 2 h (%)
Sumatriptan po.	50	63	77	28	28
Sumatriptan po.	100	59	–	29	30
Sumatriptan nasal spray	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	–	–

Ergot alkaloids and derivatives

Ergot alkaloids were the first specific antimigraine therapy available. However, with the advent of triptans, their use in the treatment of migraine has declined and their role has become less clear. In randomized clinical trials, oral ergotamine was found to be superior to placebo, but inferior to 100 mg of oral sumatriptan. In contrast, rectal ergotamine was found to have higher efficacy (73% headache relief) than rectal sumatriptan (63% headache relief). Intranasal DHE was found to be superior to placebo, but less effective than subcutaneous and intranasal sumatriptan[94]. Ergotamine is still widely used in some countries for the treatment of severe migraine attacks. It is generally regarded as a safe and useful drug if prescribed for infrequent use, in a correct dose, and in the absence of contraindications.

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[95]. The value of ergotamine in the treatment of migraine is limited by difficulties in absorption and by its side effects. Ergots have much greater receptor affinity at 5-HT$_1$a, 5-HT$_2$, adrenergic and dopaminergic receptors than triptans, leading to more adverse events. Ergot derivatives may worsen nausea and 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.

Ddihydroergotamine (DHE) administered by parenteral route was the treatment of choice 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[96]. DHE sc. And nasal spray 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[97]. 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 interval of less than 4 days. Triptans and ergot derivatives are associated with an increased risk of drug dependence; patients who regularly use ergot derivatives for more than 2-3 days/week can develop rebound headache[98,99]. 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 best be avoided if possible (consider other therapies such as triptans). Oral triptans are superior to oral ergotamine most likely because the bioavailability of oral ergotamine is extremely low (<1%).

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[100].

Cautions: 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 after 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 dose may cause ergotism with gangrene and confusion, ischemic neuropathies, pericardial, pleural and peritoneal fibrosis[101].

*** Ergotamine and DHE are not registered in Croatia.**

Evidence summary for treatment of acute attacks of migraine are listed in Table 3.

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

Migraine status

The principles of treatment for status migrainosus include the following:

1. Consider brain imaging
2. Fluid replacement and correction of metabolic parameters (if indicated) for 24-48 hours

Table 3. Evidence summary for treatment of acute migraine attacks

Drug	Level of evidence	Clinical effectiveness
Triptans		
Sumatriptan sc.	A	+++
Sumatriptan nasal spray	A	+++
Sumatriptan oral	A	+++
Zomitriptan 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 nasal spray	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	?

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) Thiethylperazine	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 nasal spray	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 nasal spray	2 mg
5. Very rapidly developing symptoms		
1) Sumatriptan 6 mg sc.		
2) Sumatriptan 20 mg nasal spray		
6. Tolerating triptans poorly		
DHE	0.5-2 mg nasal spray	2 mg

*MLT = melting wafer

3. Drug detoxification
4. Parenteral pharmacotherapy
   a) analgesics, NSAID 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

1. Concurrent implementation of migraine prophylaxis (if indicated)
2. Consider admission in cases 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

Consistent evidence exists, from several randomized, controlled studies, for the efficacy of various medications in migraine prophylaxis. The various effective preventive agents used in migraine prophylaxis, such as topiramate, valproate, β-blockers, and tricyclic antidepressants, appear to have a common effect of suppressing cortical excitability[102]. Considering resource utilization, various studies suggest that migraine prophylaxis with antiepileptics, antidepressants, beta-blockers or calcium channel antagonists markedly reduces triptan use and visits to physician offices and emergency departments. Prophylactic therapy appears to be an effective option, particularly with respect to decreasing resource use and improving productivity[103,104].

The principles and recommendations for preventive treatment of migraine attacks are as follows[5,88,101,105-119].

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

1. reduce attack frequency, severity and duration; it is generally accepted that a 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
3. improve function and quality of life

Who should be offered 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
   - initiate 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 treatment being used for coexisting condition does not exacerbate migraine attacks
- beware of all drug interactions

4. Special attention is warranted in 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. Nonpharmacological treatment

Over the past two decades, several behavioral treatments for migraine prevention have been used widely as independent therapies or combined with pharmacological 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 nonpharmacological treatment
- poor tolerance to specific pharmacological treatments
- medical contraindications for specific pharmacological treatments
- insufficient or no response to pharmacological 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

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

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 medications or different drugs of the same class.

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	++
Gabapentin	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	++

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 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 the levels of evidence and clinical effectiveness are listed in Table 5[101].

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. On the other hand, some comorbid illnesses affect prophylactic choices. Prophylactic treatment should be started at low doses, possibly as monotherapy; doses can be slowly increased until therapeutic goals are achieved and the 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 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 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 are recorded as well as taken drugs and possible adverse events.

Pharmacological 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. Beta blockers considered to be effective in migraine prophylaxis are propranolol, atenolol, metoprolol and timolol[30,101,105,120]. A meta-analysis which included 74 controlled studies has shown that propranolol was consistently effective for migraine prevention in a daily dose of 120-240 mg. No absolute correlation has been found between propranolol dose and its clinical efficacy. On average, propranolol yielded a 44% reduction in migraine activity compared with a 14% reduction with placebo[105,121,122].

Therapy should be started with low doses and then slowly increased if necessary. When migraine attacks are controlled, doses can be reduced slowly. Abrupt cessation of therapy with beta blockers might 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 a 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.

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

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

Metoprolol has a 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.

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

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

Cautions: abrupt stopping of therapy with beta blockers can cause increased headache, withdrawal symptoms of tachycardia and tremulousness.

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

* most beta-blockers are available in Croatia, covered by the Croatian Institute of Health Insurance (100%), a prescription is needed.

Antidepressants

Only tricyclic antidepressants have proven efficacy in migraine. The mechanism by which antidepressants

exert headache prophylaxis is uncertain, but does not result from treating masked depression. Amitriptyline modulates monoaminergic pathways by inhibiting the reuptake of both adrenaline and serotonin. Tricyclic antidepressants are effective in preventing migraine and tension-type headaches and are more effective than SSRIs, although with greater adverse effects. The effectiveness of tricyclics seems to increase over time[123].

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[124].

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 to up to a maximum of 50 mg *per* day[101,124]. High doses could be necessary in the presence of depression.

One trial comparing propranolol and amitriptyline has suggested that propranolol is more efficacious in patients with migraine alone and amitriptyline is superior for patients with the phenotypes of migraine and tension type headache[125].

Contraindications: severe cardiac, liver, renal, prostatic and 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 the Croatian Institute of Health Insurance (100%), a prescription is needed.

SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) and SSRIs/selective noradrenaline-reuptake inhibitors (SNRIs) (venlafaxine, duloxetine)

Recent studies have shown that venlafaxine and escitalopram are both effective in the prophylaxis of migraine headache without depression and anxiety; this effect was independent of mood disorder. Escitalopram should be the first choice because of its fewer side effects, but venlafaxine may be used if escitalopram is found to be insufficient[126,127].

Most studies, however, show that over 2 months of treatment, SSRIs are no more efficacious than placebo in patients with migraine[128]. At the moment, there is no definitive evidence supporting the use of these drugs in preventing migraine attacks[129,130].

With only Class IV evidence available in the literature, inadequate data are available to determine the risk of serotonin syndrome with the addition of a triptan to SSRIs/SNRIs or with triptan monotherapy. The currently available evidence does not support limiting the use of triptans with SSRIs or SNRIs, or the use of triptan monotherapy, due to concerns for serotonin syndrome (Level U). However, given the seriousness of serotonin syndrome, caution is certainly warranted and clinicians should be vigilant to serotonin toxicity symptoms and signs to insure prompt treatment[131].

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

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, while verapamil has shown to be marginally effective; there is no randomized controlled trial evidence to support the use of verapamil in migraine105,107. Cyclandelate has comparable efficacy with that of beta blockers and only a few side effects132.

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 blockers105,133-135. 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, nifedipine and nimodipine are available in Croatia, covered by the Croatian Institute of Health Insurance (100%), 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. Neither is available in Croatia.

Pizotifen. Controlled and uncontrolled studies have shown that pizotifen is of benefit in 40%-79% of patients[136,137]. 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[138-140]. However, in 26 trials reviewed, pizotifen was generally poorly tolerated.

The dose recommendation is 0.5-1 mg 1-3 times daily by titration[105].

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; no difference was shown in comparison with propranolol and pizotifen[139,141]. 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 doses given in 3 times; starting dose is 1 mg and 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 in 5000 treated patients)[137]. 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 because of placebo-controlled, double blind trials that proved it to be effective. The majority of these trials refer to valproate and topiramate, having shown these drugs to be effective and well tolerated in migraine prevention and suitable for first-line clinical use. On the other hand, lamotrigine, oxcarbazepine and vigabatrin have been shown ineffective and gabapentin requires further evaluation. For the rest of the antiepileptic drugs, no data from controlled trials are available[113].

Studies with divalproex sodium and sodium valproate provided strong and consistent support for their efficacy[142-144]. 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[145]. Starting dose is 250-500 mg in divided doses; the dose is slightly increased usually up to 1000 mg daily. Baseline liver function studies should be obtained.

Contraindications: pregnancy – 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.

Topiramate is generally safe and reasonably well tolerated for the prevention of migraine in adults[114-117]. 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 had 47% of patients in topiramate group (dose 200 mg in divided doses in 6 weeks) as compared with 6.7% in placebo group[146-149]. 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.

Gabapentin was effective in several trials. Gabapentin 600-1800 mg was effective in a 12-week open

label study, and in dose 1800-2400 gabapentin was superior to placebo in reducing the frequency of migraine attacks by 50% in about 1/3 of patients. Gabapentin was not effective in one placebo-controlled, double blind study[150,151]. In an open-label study, the mean number of migraine days/4 weeks was reduced from 15.8 to 8.6; furthermore, pain intensity was reduced by 25% in 14 (26.9%), by 50% in 29 (55.7%), by 75% in 3 (5.7%) patients, and no improvement was seen in 6 (11.5%) patients. A significant reduction of acute medication use was reported[152].

Adverse effects: dizziness, drowsiness.

Pregabalin: recent data suggest that pregabalin may be a useful alternative prophylaxis for chronic migraine[153,154]. These promising results from open-label studies should be confirmed in randomized clinical trials.

Lamotrigine showed lower efficacy in comparison to topiramate and in preventing migraine without aura, whereas it was efficacious in the prevention of high frequency migraine attacks with aura[155-157].

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

Levetiracetam seems to be a safe and effective treatment for migraine with aura at a dosage of 1000 mg/d for 6 months and in elderly patients; however, in the prevention of chronic daily headache levetiracetem was not as effective[158-160]. Controlled trials are needed to confirm the observed results.

*All listed medications are available in Croatia but are NOT covered by the Croatian Institute of Health Insurance for migraine prophylaxis and can be purchased with a prescription.

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, whereas, even in the absence of inflammation, NSAIDs are active in reduction of migraine pain. Some NSAIDs show discrete effectiveness in migraine prophylaxis; these include acetylsalicylic acid, flurbiprofen, ketoprofen; naproxen and naproxen sodium are, however, useful in the prevention of menstrual migraine[161-165]. NSAIDs should be used for intermittent prophylaxis in menstrual migraine, not for prolonged periods of time because of their gastric side effects.

Placebo response in prophylactic therapy

A meta-analysis to evaluate the placebo response rate in migraine prophylaxis in all clinical trials published since 1988 was performed; the pooled estimate of the placebo response (patients who improved) was 21%. The placebo response rates were significantly higher in studies with a parallel design than those in cross-over studies ($p<0.01$). This response was also higher in European studies than in those performed in North America ($p<0.001$). Adverse events occurred in 30% of the patients who took a placebo, and the percentage of patients with adverse events was significantly higher in the North American studies than in those conducted in Europe ($p<0.01$). These data reinforce the need to consider the placebo effect when ascertaining the true therapeutic effect of any drug, as well as to design any clinical trial in the prophylaxis of migraine[166].

Complementary drugs

Although a wide range of acute and preventive medications are now available for the treatment of migraine headaches, many patients will not have significant improvement in the frequency and severity of their headaches unless lifestyle modifications are made. Also, given the number of side effects of traditional prescription medications, there is an increasing demand for "natural" treatment like vitamins and supplements for the treatment of headaches. The identification of food triggers, with the help of food diaries, is an inexpensive way to reduce migraine headaches. The following supplements in the preventive treatment of migraine have been evaluated: magnesium, *Petasites hybridus*, feverfew, coenzyme Q10, riboflavin, and ginkgolide[167-169].

Vitamin B2 (riboflavin)

A recent open-label and a randomized, placebo-controlled study have found daily supplements of riboflavin 400 mg to be moderately effective in reducing the frequency and severity of migraine[170,171]. However, riboflavin is not available in most countries in such high doses.

Riboflavin 25 mg showed an effect comparable to a combination of riboflavin 400 mg, magnesium 300 mg and feverfew 100 mg; the placebo response exceeded that reported for any other placebo in trials of

migraine prophylaxis, and suggests that riboflavin 25 mg may be an active comparator[172]. However, there is at present conflicting scientific evidence with regard to the efficacy of these compounds for migraine prophylaxis.

Adverse effects: mild abdominal pain and diarrhea.

Feverfew

This herbal therapy is made from crushed chrysanthemum leaves; 250 micrograms of the active ingredient, parthenolide, is considered necessary for therapeutic effectiveness. Feverfew is considered an anti-inflammatory medication with serotonin effects. The role of feverfew in migraine prophylaxis is not well established. Despite studies showing superiority to placebo, there is insufficient evidence from randomized, double-blind trials to suggest an effect of feverfew over and above placebo for preventing migraine[173-175].

A recent study has shown that feverfew is efficient in acute treatment of migraine attacks; sublingual feverfew/ginger appears safe and effective as a first-line abortive treatment for a population of migraineurs who frequently experience mild headache prior to the onset of moderate to severe headache[176]. The efficacy of feverfew was not confirmed in a Cochrane review, probably because of the 400% variations in the dosage of its active principle.

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[177-180].

Magnesium sulfate has been shown to be efficient in acute migraine treatment: in the migraine with aura group patients receiving magnesium sulfate presented a statistically significant improvement of pain and of all associated symptoms compared with controls[181].

Coenzyme Q-10

Magnetic resonance spectroscopy 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 (CoQ10) could be used as a preventive treatment for migraine.

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[182]. In a randomized, double-blind controlled trial, CoQ10 (3x100 mg/day) was compared to placebo in 42 migraine patients and CoQ10 was superior to placebo for attack frequency, headache days and days-with-nausea in the third treatment month and was well tolerated[183].

Ginkgolide B, a herbal constituent extract from *Ginkgo biloba* tree leaves, was evaluated in a multicenter, open, preliminary trial in the prophylactic treatment of migraine with aura; ginkgolide B was shown to be effective in reducing migraine with aura frequency and duration[184].

*All complementary drugs are available in Croatia and can be purchased as OTC drugs

Other therapy

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

Botulinum toxin

Botulinum toxin significantly reduces the frequency, severity and disability associated with migraine headaches; efficacy was good and consistent through studies[185-189]. Several retrospective open label chart reviews and double-blind, placebo-controlled studies have demonstrated the efficacy of botulinum toxin type A in migraine prophylaxis. The results of PREEMPT 2 demonstrate that onabotulinumtoxinA is effective for prophylaxis of headache in adults with chronic migraine. Repeated onabotulinumtoxinA treatments were safe and well tolerated[190]. OnabotulinumtoxinA was effective for chronic migraine and well tolerated, but the therapeutic gain over placebo was modest; the clinical profile of responders remains to be determined before widespread use[40].

OnabotulinumtoxinA and topiramate demonstrated similar efficacy for subjects with chronic migraine; overall, the results were statistically significant within groups but not between groups[191].

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, 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[192].

Adverse effects: to date, neither organic damage nor allergic complications have been reported and no CNS side effects have been noticed.

The tolerability and safety of botulinum toxin type A seem to be high. There are 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.

Occipital nerve stimulation

Occipital nerve stimulation was effective in intractable chronic migraine with 39% of responders compared to 6% after sham stimulation[40].

Hyperbaric and normobaric oxygen therapy (HBOT, NBOT)

A double-blind, placebo-controlled study in which the treatment group received 100% oxygen during 30 minutes on 3 consecutive days (the control group received air) showed a nonsignificant reduction in hours of headache *per* week; the authors concluded that the tested protocol did not show a prophylactic effect on migraine[193]. However, HBO showed significant effect in acute migraine attacks[194,195].

Randomized trials comparing HBOT or NBOT with one another, other active therapies, placebo (sham) interventions or no treatment in patients with migraine or cluster headache showed that there was some evidence that HBOT was effective for termination of acute migraine in an unselected population, and weak evidence that NBOT was similarly effective in cluster headache. Given the cost and poor availability of HBOT, more research should be done in patients unresponsive to standard therapy. NBOT is inexpensive, safe and easy to apply, so it will probably continue to be used despite the limited evidence in this review[196].

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 of 2.5 mg to 35 mg during 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[197].

Haloperidol iv. is very effective in relieving migraine-associated pain; significant pain relief was achieved in 80% of patients treated with haloperidol, whereas only 3 (15%) patients responded to placebo ($p<0.0001$)[198].

Why treatment fails

Treatment of acute attacks or prophylactic treatment of migraine may fail because of the following[199]:

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)
   b) caffeine overuse
3. Dietary or lifestyle triggers
4. Hormonal triggers
5. Psychosocial factors
6. Other medications that trigger headaches (pharmacotherapy has been inappropriate)
7. Ineffective drug; at least 3 attacks should be treated before deciding that a drug is ineffective
8. Inadequate initial doses (low, excessive)

9. Inadequate duration of treatment
10. Unrealistic expectations
11. Comorbid conditions complicate therapy
12. Inpatient treatment required
13. Inadequate formulation or route of administration
14. There is an analgesic abuse

Non-pharmacologic treatments include:

Behavioral treatments

It is extremely difficult to design studies with matching placebo, since double blind is impossible, thus the majority of studies compared active treatments *vs*. control group including patients in an outpatient setting (mostly prospective, controlled "randomized" studies)[200,201].

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 pharmacological treatment[202,203].

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 headache. Cognitive-behavioral training (stress management training) teaches skills for identifying and controlling stress and minimizing the effects of stress[204].

C) Biofeedback therapy

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

The results obtained with EMG biofeedback and TBR have shown 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, a combination of TBR and EMG biofeedback yielded the best results[205,206]. Thermal biofeedback associated with relaxation techniques has been recommended as a first-choice nonpharmacological treatment for migraine, and physical therapy has been indicated as a second-choice treatment for migraineurs who do not sufficiently improve with TBR[207]. A study where patients were randomly assigned to receive biofeedback in addition to the basic relaxation instruction or relaxation techniques alone and received instruction in pain theory showed that biofeedback provided no additional benefit when compared to simple relaxation techniques alone, in the treatment of migraine and tension type headaches in adults[208]. However, a meta-analysis of papers on biofeedback showed that the main results were medium-to-large mean effect sizes for biofeedback in adult migraine and tension-type headache patients. Treatment effects remained stable over an average follow-up period of 14 months, both in completer and intention-to-treat analyses. Headache frequency was the primary outcome variable and showed the largest improvements. Further significant effects were shown for perceived self-efficacy, symptoms of anxiety and depression, and medication consumption. Reduced muscle tension in pain related areas was observed in EMG feedback for tension-type headache. Biofeedback was more effective than waiting list and headache monitoring conditions in all cases, while EMG feedback for tension-type headache showed additional significant effects over placebo and relaxation therapies. Levels of efficacy (migraine: efficacious, level 4; tension-type headache: efficacious and specific, level 5)[209].

D) Hypnosis

Hypnosis has a long tradition but a few controlled studies are available regarding its effectiveness in migraine treatment. In considering the possibility of combining hypnosis with other nonpharmacological 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[210].

Physical treatment

A few noninvasive physical treatments may be effective as prophylactic treatments for chronic/recurrent headaches. The randomized controlled trials suggest that massage therapy, physiotherapy, relaxation and chiropractic spinal manipulative therapy might be as effective as propranolol and topiramate in the prophylactic management of migraine. For the prophylactic treatment of migraine headache, there is evidence that spinal manipulation may be an effective treatment option with a short-term effect similar to that of a commonly used, effective drug (amitriptyline). Other possible treatment options with weaker evidence of effectiveness are pulsating electromagnetic fields and a combination of transcutaneous electrical nerve stimulation (TENS) and electrical neurotransmitter modulation. For the prophylactic treatment of chronic tension-type headache, amitriptyline is more effective than spinal manipulation during treatment. However, spinal manipulation is superior in the short term after cessation of both treatments. Other possible treatment options with weaker evidence of effectiveness are therapeutic touch; cranial electrotherapy; a combination of TENS and electrical neurotransmitter modulation; and a regimen of auto-massage, TENS, and stretching. For episodic tension-type headache, there is evidence that adding spinal manipulation to massage is not effective. Based on trial results, these treatments appear to be associated with a little risk of serious adverse effects. However, the evaluated randomized controlled trials had many methodological shortcomings.

The clinical effectiveness and cost-effectiveness of noninvasive physical treatments require well-conducted randomized controlled trials of manual therapies for migraine[211,212].

A) Acupuncture

Acupuncture has been used both to prevent and treat diseases for over 3000 years. Controlled studies specifically applied to migraine have produced mixed findings and positive studies had some methodological doubts[213]. Treatment outcomes for migraine do not differ between patients treated with sham acupuncture, *verum* acupuncture, or standard therapy[214,215]. However, a Cochrane review on its use in migraine concludes that acupuncture is effective and should be considered as a prophylactic measure for patients with frequent or insufficiently controlled migraine attacks[216].

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 for cerebral infarction and death from cervical manipulation. The scientific evidence is not convincing to show significant benefits[217,218].

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 nonpharmacological treatment:

1. Relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback and cognitive-behavioral therapy may be considered as treatment options for prevention of migraine (Level A). Specific recommendations regarding which of these to use in 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 possible for hyponosis, acupuncture, tran-

scutaneous electrical nerve stimulation, chiropractic or osteopathic cervical manipulation, and hyperbaric oxygen (Level C).

Menstrual migraine

The definition of menstrual migraine has been proposed in the appendix of IHS: pure menstrual migraine without aura, menstrually-related migraine without aura and non-menstrual migraine without aura[23]. Menstrually related migraine (MRM) headache is common in women and associated with substantial disability. 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[219, 220]. Iron deficiency anemia may play a role in the severity of migraine, particularly menstrual migraine[220].

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 record 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[221].

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 intensity
- development of unusual aura symptoms, particularly prolonged aura

Treatment of menstrual migraine – cyclic prophylaxis

Acute attacks of menstrual migraine should be treated as usual. Prophylactic treatment includes NSAIDs, triptans and hormonal prophylaxis[222-228]:

NSAIDs should be considered 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 through the at-risk period. Based on the evidence, grade B recommendations can be made for the use of sumatriptan 50 and 100 mg, mefenamic acid 500 mg, frovatriptan 2.5 mg twice daily, naratriptan 1 mg twice daily and rizatriptan 10 mg for the acute treatment of MRM.

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. Estrogen levels decrease during the late luteal phase of the menstrual cycle, 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 (grade B recommendations).

Choosing among treatment strategies must be based on clinical considerations. Contraceptive strategies offer the opportunity for treating menstrual migraine in women who also require effective contraception.

Migraine and menopause

During perimenopause, it is likely to observe worsening of migraine, and tailored hormonal replacement therapy (HRT) to minimize estrogen/progesterone imbalance may be effective. Although migraine prevalence decreases with advancing age, migraine can either regress or worsen at menopause. Women with prior migraine generally improve with physiological menopause; in contrast, surgical menopause usually results in worsening of migraine[229-231].

Treatment of hormonal replacement headache

In the treatment of hormonal replacement headache try the following:

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 HRT

A systematic review and meta-analysis of migraine and cardiovascular disease has shown that migraine is associated with a twofold increased risk of ischemic stroke, which is only apparent among people who have migraine with aura. The results also suggest a higher risk among women and the risk was further magnified in people with migraine who were aged less than 45, smokers, and women who used oral contraceptives. There has not been found an overall association between any migraine and myocardial infarction or death due to cardiovascular disease. Too few studies are available to reliably evaluate the impact of modifying factors, such as migraine aura, on these associations[232]. Studies also show that COC users with a history of migraine are two to four times as likely to have an ischemic stroke as nonusers with a history of migraine. The odds ratios for ischemic stroke ranged from 6 to almost 14 for COC users with migraine compared with nonusers without migraine[233].

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 counseled and regularly assessed for the development of additional risk factors. Currently, the usual indications and contraindications for HRT should be applied. In certain cases, COCs may be contraindicated. 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 oral contraceptives (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). The decision should be individualized and should be made with the patient.

A quantitative systematic review on patent foramen ovale (PFO) and migraine showed that the association between migraine and PFO was OR 2.54 (95% CI 2.01, 3.08). Although PFO closure seemed to affect migraine patterns favorably, the very low grade of available evidence to support this association precludes definitive conclusions[234].

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-ethinyl estradiol methods in women who are at an increased risk of ischemic stroke, particularly those who have multiple risk factors. Observational studies suggest that progesterone-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
- diabetes 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

A recent study has shown that there is no clear evidence for the increased risks of preterm delivery and its subtypes with isolated migraine disorder. Women with mood disorder had elevated risks of pre-eclampsia (adjusted RR=3.57, 95% CI 1.83, 6.99). Our results suggest an association between isolated migraine disorder and pregnancy-induced hypertension (adjusted RR=1.42, 95% CI 1.00, 2.01)[235].

Most women with migraine improve during pregnancy; however, some women have their first attack during pregnancy[236-238]. Migraine often recurs during postpartum and can begin for the first time in general. Migraine treatment is often necessary because maternal and fetal risks related to acute attacks may be more harmful than the therapy itself, especially if they are frequent, severe and associated with nausea, anorexia, vomiting, hypotension or dehydration. The major concern in managing the pregnant migraineur is the effect of both medication and migraine on the fetus. Since migraine usually improves after the first trimester, many women can manage their headaches with this reassurance along with nonpharmacological means and it should be preferred. 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. Because of the possible risk of injury to the fetus, medication use should be limited; however, it is not contraindicated during pregnancy.

Among nonpharmacological migraine prophylaxis, only relaxation techniques, biofeedback in particular, and acupuncture have accumulated sufficient evidence in support of their efficacy and safety. Some vitamins and dietary supplements have been proposed: the prophylactic properties of magnesium, riboflavin and coenzyme Q10 are probably low, but their lack of severe adverse effects makes them good treatment options[239].

Paracetamol and NSAIDs should be preferred for the treatment of acute migraine attacks in pregnant women. Migraine prophylaxis should be undertaken when patients experience at least three prolonged severe attacks a month that are particularly incapacitating or unresponsive to symptomatic therapy and likely to result in complications. If nonpharmacological approaches are not effective, preventive treatment should include low doses of β-blockers and amitriptyline[240].

Caution – aspirin in low intermittent doses is not associated with a significant teratogenic risk, although 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 limited need for 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) the earliest possible in the attack. Adequate dosage should be administered; keep in mind that the dosage is higher than the usual analgesic/antipyretic dose. Appropriate pharmacological 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 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 (TTH)

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%[241]. A population-based study in Croatia has estimated the 1-year age- and sex-adjusted prevalence of TTH to be 20.7%[12].

In the general population, 4%-5% of individuals suffer from chronic daily headache and about half of them have chronic tension-type headache (CTTH) with more than 15 headaches *per* month[242].

Frequent episodic and chronic TTH is caused by a combination of genetic and environmental factors, while infrequent episodic TTH is caused primarily by environmental factors[243]. 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[244-246]. Increased pericranial tenderness recorded by manual palpation is the most significant abnormal finding in patients with TTH. The tenderness increases with the intensity and frequency of headache. Studies on the exteroceptive suppression of temporal muscle contraction have detected a dysfunction of the brainstem excitability and of its suprasegmental control. A similar conclusion has been reached by using the trigeminocervical reflexes, whose abnormalities in TTH have suggested a reduced inhibitory activity of brainstem interneurons, reflecting abnormal endogenous pain control mechanisms. It is interesting that the neural excitability abnormality in TTH seems to be a generalized phenomenon, not limited to the cranial districts. It has been demonstrated that continuous nociceptive input from peripheral myofascial structures may induce central sensitization and thereby chronification of the headache. Measurements of pain tolerance thresholds and suprathreshold stimulation have shown the presence of generalized hyperalgesia in CTTH patients[247,248].

Diagnostic 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 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:

Pressing/tightening (nonpulsating) quality
Mild or moderate intensity (may inhibit but does not prohibit activities)
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 from 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 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 nor severe nausea or 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 of TTH.

Neuroimaging is unlikely to reveal an abnormality on MRI or CT scanning in patients with tension-type headache and normal neurological examination[6].

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 antidepressant drugs[247,248]. The vast majority of people with tension-type headache take simple analgesics or no medicine at all; people may seek help if TTH episodes occur with unusual frequency or intensity.

I Acute treatment

Simple analgesics and NSAIDs are recommended for the treatment of episodic TTH. Combination analgesics containing caffeine are drugs of second choice. Triptans, muscle relaxants and opioids should not be used. It is crucial to avoid frequent and excessive use of analgesics to prevent the development of medication-overuse headache[249].

As a general rule, medications used for an acute headache should be taken at a relatively high dose and as early as possible[5].

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 the Croatian Institute of Health Insurance, a prescription is usually needed.

II Preventive treatment

Although TTH typically is not as disabling as migraine, its chronic form may significantly impair the patients' functional ability. Most preventive agents used for primary TTH have not been examined in well-designed double-blind studies. The tricyclic antidepressant amitriptyline is the drug of first choice for prophylactic treatment of chronic TTH. Mirtazapine and venlafaxine are drugs of second choice. Overall, evidence for the efficacy of different antiepileptic drugs in chronic headache forms and in chronic headache is still lacking, most studies being open-label, small-sample trials[123,128,249,250].

Pharmacological treatment

Antidepressants

Antidepressants are most commonly used since many patients have comorbid depression and anxiety. In an open label study in non-depressed 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[251]. The tricyclic antidepressant amitriptyline is the drug of first choice for prophylactic treatment of chronic TTH. Mirtazapine and venlafaxine are second-choice drugs[249,252].

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

Anticonvulsants

Anticonvulsants represent a therapeutic option for chronic daily headache; studies evaluating gabapentin, topiramate, sodium valproate and levetiracetam have been conducted[160,253-256].

Botulinum toxin

Botulinum toxin was shown to affect the release of neurotransmitters that are important in pain transmission and in migraine pathogenesis. Data from both animal and clinical studies suggest that the toxin may have an analgesic effect that is independent from its effect on muscle tone. T he high tolerability and long duration of action of the drug make it appealing as a potential prophylactic treatment for headache patients. Results of controlled trials on the efficacy of botulinum toxin in the treatment of episodic migraine are mostly negative, although some subgroups of patients (e.g., those with high attack frequency) may respond to the drug. Studies of patients with chronic daily headache have been inconclusive, although (as with the episodic migraine studies) specific subgroups of patients appear to benefit from the drug. Botulinum toxin is probably ineffective for the treatment of chronic TTH[257,258].

Most of the initial reports on botulinum toxin in TTH and in migraine were positive. Unfortunately, these results were not reproduced in well-designed,

randomized controlled trials. So far, doses from 20 U (Botox) to 500 U (Dysport) have been studied in patients with chronic TTH, and doses from 16 to 200 U (Botox) in patients with migraine. Overall, there is no evidence for a beneficial effect of botulinum toxin, although trends favoring botulinum toxin have been reported. Experience with botulinum toxin type B (Myobloc/NeuroBloc) is limited and similar to the experience with type A. Thus, a widespread use of botulinum toxin therapy in headache can currently not be recommended[259-264].

* Botulinum toxin is available in Croatia, NOT covered by the Croatian Institute of Health Insurance for the treatment of tension type headaches and should not be given in the preventive approach for headache management.

Nonpharmacological treatment

Non-drug management should always be considered, although the scientific basis is limited. Information, reassurance and identification of trigger factors may be rewarding. Electromyography (EMG) biofeedback has a documented effect in TTH, whilst cognitive-behavioral therapy and relaxation training most likely are effective. Physical therapy and acupuncture may be valuable options for patients with frequent TTH, but there is no scientific evidence for efficacy[249]. Cochrane review on the use of acupuncture in TTH concludes that it could be a valuable nonpharmacological tool in patients with frequent episodic or chronic TTHs[265].

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 nonpharmacological treatment)

3. CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

Trigeminal-autonomic cephalalgias (TACs) are primary headaches characterized by short-lasting, unilateral, severe attacks of headache and accompanying typical cranial autonomic symptoms.

According to the second edition of the HIS classification, the following syndromes belong to TACs: 3.1 Episodic and chronic cluster headache; 3.2 Episodic and chronic paroxysmal hemicrania; 3.3 SUNCT; and 3.4 Probable TACs[3].

3.1 Cluster headache

Previously used terms: Horton's headache, Horton's neuralgia, migrainous neuralgia, hemicrania neuralgiformis chronica, ciliary neuralgia, histaminic cephalalgia, 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 and months or years. Pain almost invariably recurs on the same side during an individual cluster period. About 15% of patients have chronic symptoms without remissions longer than 30 days. Conversion to a chronic form seems to be related to the occurrence of more than one cluster period a year and the short-lived duration of remission periods, longer duration of the disease and to a late age at onset[266]. A single cluster period has been described in 27% of patients[267]. During the cluster period, attacks may be provoked by alcohol (not during remision periods), histamine or nitroglycerine, or sudden variation in temeperature. 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 to 120 minutes (minimum 15, maximum 180 minutes). The individual attacks show a defined temporal profile, they often occur with 'clock-like' regularity; cluster periods often begin in spring and autumn (268). The usual age at onset is in the 20s to 40s, and is older in chronic than in episodic CH; the prevalence is 5-6 times higher in men than in women. The pooled data showed a lifetime prevalence of 124 *per* 100,000 and a 1-year prevalence of 53 *per* 100,000[269].

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 inheritence). Epidemio-

logical 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. Acute attacks involve activation of the posterior hypothalamic grey matter.

The diagnosis of CH is mainly based on accurate description of the headache and associated headache symptoms; neurophysiological tests are not warranted in the routine work-up of such patients. Diagnostic criteria for cluster headache are as follows:

A. At least 5 attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting for 15-180 minutes if untreated[x]
C. Headache is accompanied by at least one of the following:
   ipsilateral conjunctival injection and/or lacrimation
   ipsilateral nasal congestion and/or rhinorrhea
   ipsilateral eyelid edema
   ipsilateral forehead and facial sweating
   ipsilateral miosis and/or ptosis
   a sense of restlessness or agitation
D. Attacks have a frequency from one every other day to 8 *per* day[xx]
E. Not attributed to another disorder[xxx]

Note:

[x]During part (but less than half) of the time-course of cluster headache, attacks may be less severe and/or of shorter or longer duration.

[xx]During part (but less than half) of the time-course of cluster headache, attacks may be less frequent.

[xxx]History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such a disorder but it is ruled out by appropriate investigations, or such a disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

3.1.1 Episodic cluster headache

Diagnostic criteria:

A. Attacks fulfilling criteria A-E for 3.1 **Cluster headache**
B. At least two cluster periods lasting for 7-365 days[x] and separated by pain-free remission periods of ≥1 month

Note:

[x]Cluster periods usually last between 2 weeks and 3 months.

3.1.2 Chronic cluster headache

Diagnostic criteria:

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

Comment:

Chronic cluster headache may arise *de novo* (previously referred to as **primary chronic cluster headache**) or evolve from the episodic subtype (previously referred to as **secondary chronic cluster headache**). Some patients may switch from chronic to episodic cluster headache.

THERAPY

I Acute treatment

In all cases, patients should be instructed to avoid afternoon naps and alcohol drinks, 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 cluster 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.

Triptans

Sumatriptan. Three clinical trials, controlled *versus* placebo, were investigating the efficacy of sumatriptan in acute cluster headache attacks. Subcutaneous sumatriptan 6 mg was tested in two studies[270, 271], sub-

cutaneous sumatriptan 12 mg in one[271], and intranasal sumatriptan 20 mg in one study[272].

Subcutaneous sumatriptan is well tolerated and effective even when taken frequently during a cluster period. The recommended dose is 6 mg (Level A). Intranasal sumatriptan in a dosage of 20 mg appears to be less effective than subctaneous formulation, and not to have rapid onset of action as the latter one (Level B).

Zolmitriptan. The efficacy of zolmitriptan in cluster headache was investaigated in three controlled *versus* placebo studies. Oral zolmitriptan 5 mg and 10 mg doses were tested in one study[273], and intranasal zolmitriptan 5 mg and 10 mg doses in two studies[274,275].

Oral zolmitriptan in a single dosage of 10 mg has proved its efficacy only in episodic cluster headache attacks (Level B). Intranasal zolmitriptan may have comparable clinical efficacy to that of sumatriptan (Level A).

Oxygen

Two randomized controlled studies have investigated 100% oxygen *versus* placebo for the acute treatment of cluster headache[276,277]. The results showed the inhalation ofoxygen at a rate of 6-12 L/min in sitting position for at least 15 minutes was effective treatment for acute cluster headache attacks in the majority of patients (Level A). Unlike triptans, oxygen does not have major adverse events, is well tolerated and there is no limitation to the number of times *per* day it can be used. Oxygen therapy for cluster headache should be used with caution in patients with chronic obstructive pulmonary disease.

There was a trend to better outcome in a single trial evaluating hyperbaric oxygen therapy (HBOT) for termination of cluster headache. HBOT may be considered for breaking the cluster cycle in refractory cluster headache patients, although the majority of cluster headache patients would not benefit any sustained effect (Level C).

Dihydroergotamine and ergot derivatives

The role of ergot alcaloids in the acute treatment of cluster headache is limited. Combinations of ergotamine and caffeine failed do demonstrate clinical efficiency in acute cluster headache attacks. Only one placebo controlled study showed clinical benefit of intranasal DHE (0.5 mg *per* spray *per* nostril) in the treatment of acute cluster headache. Intranasal DHE decreased the intensity but not the duration of the attacks, and was well tolerated (Level B) (278). In an open retrospective trial, the intravenous application of 1 mg DHE over 3 days has been shown to be effective for termination of refractory cluster attacks (Level C)[279]. Ergots may have serious adverse effects and are contraindicated in patients with cardiovascular diseases; they cannot be used simuntaneously with triptans.

Lidocaine

Based on the results from several noncontrolled studies and 1 randomized controlled trial, intranasal lidocaine (1 mL solution with a concentration of 4%) is moderately effective in the treatment of acute cluster headache attacks (Level B)[280,281]. It should be used as adjunctive therapy when patients do not respond to more effective therapies.

Octreotide

In a placebo controlled trial, octreotide, a somatostatin analog, in a dose of 100 μg sc. has been shown to be effective in the treatment of acute cluster headache attacks (Level B)[282]. It has no vasocnostrictor effect and could be used in patients with contraindications to triptans.

Table 6. Evidence for acute medication in cluster headache attacks

Drugs	Level of evidence	Clinical effectiveness
Triptans	A	+++
Sumatriptan sc.	B	+
Sumatriptan IN*	A	+
Zolmitriptan IN*	B	?
Zolmitriptan po.	A	++
Oxygen inhalation	A	++
Ergots		
DHE IN*	B	?
DHE iv.	C	++
Lidocaine IN*	B	+
Octreotide sc.	B	+

* IN = intranasal

Olanzapine

Olanzapine was given as an abortive agent (2.5 to 10 mg) to five patients with cluster headache in only one open-label trial[283].

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

To treat acute attacks, try the following:

1. Oxygen inhalation at a flow rate of 6-7 L/min for at least 15 minutes
2. Sumatriptan 6 mg sc. (if available) or 20 mg nasal spray
3. Zolmitriptan 5-10 mg nasal spray (if available) or 5-10 mg po.*
4. DHE 1 mg nasal spray (if available) or 1 mg iv.
5. Lidocaine 4% sol intranasal

Alternatively

6. Octreotide 100 μg sc.**

*po. only for episodic cluster
**only if steps 2-5 are contraindicated

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 phrophylactic therapy are:

- Begin treatment early, particularly in the episodic forms
- Continue treatment for at least 10 to 14 days after the disapperance of the crisis
- Gradually suspend treatment
- If the crisis reappears, 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 cluster headache (episodic or chronic)
- Response to previous treatments
- Possible reported side effects
- Contraindications to the use of the drug
- Comorbid pathologies

Pharmacological treatment

Calcium channel blockers

Verapamil is considered the first-choice drug for prophylactic treatment of cluster headache, both the episodic and chronic forms. There are 2 placebo controlled trials investigating the use of verapamil as a prophylactic drug for cluster headache (Level B). During 2 weeks of treatment, 80% of patients receiving verapamil had a greater than 50% reduction in headache frequency[284]. Most patients will respond to doses of 240 mg to 480 mg *per* day divided in three doses. Both immediate and extended release formulations may be used. To reduce side effects (hypotension, constipation, and peripheral edema), start with low initial dose (120 mg daily) and slowly taper up to the target dose. ECG monitoring is recomended during verapamil therapy because of the risk of heart block and bradycardia. Verapamil may be combined with corticosteroids, triptans and other prophylactic agents.

Corticosteroids

Corticosteroids are often prescribed as initial prophylactic drug, in order to obtain rapid relief of cluster attacks. They induce remission in most severe cases with high attack frequency and pain intensity, particularly in the central phase of the cluster period. In several open studies, both oral and parenteral corticosteroids provided benefit in cluster headache patients.

Prednisone is used at doses of 50-60 mg *per* day for 2-3 days, then decresasing the dose by 10 mg *per* 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 long-acting prophylactic drug may be added along with prednisone. Despite the fact that there are no adequate randomized, placebo-controlled trials available on the use of prednisone in cluster headache, prednisone is considered as a clinically effective prophylactic agent (Level C).

A single high dose of intravenous methyl prednisolone in most patients with episodic cluster headache may interrupt attack recurrence for a few days, but is ineffective in maintaining complete clinical remission. It does not provide any advantage above prednisone in cluster headache treatment[285].

In an open study, dexamethasone administered parenterally at a dose of 4 mg bid for 2 weeks followed by 4 mg a day in the 3rd week was able to interrupt the cluster period[286].

Suboccipital corticosteroid injection. There are two placebo controlled studies investigating suboccipital corticosteroid injections in cluster headache (Level B). A total of 85% of patients in the study group had relief of cluster headache attacks by 72 hours after single application of betamethasone dipropionate and betamethasone disodium phosphate with Xylocaine 2%, compared to 0% of patients in the placebo group. This effect was maintained for at least 4 weeks in the majority of them[287]. In another study, patients who received cortivazol also had fewer attacks in the first 15 days of the study than controls irrespective of the cluster headache type (chronic or episodic)[288].

Lithium

Lithium carbonate is considered to be effective in the prophylaxis of both episodic and chronic cluster as much as verapamil[289]. However, lithium should be administered as a second choice of prophylactic therapy for chronic cluster (Level C) because of its side effects (tremor, diarrhea, mental confusion), the need for blood test monitoring during therapy, and its potential for drug interactions with SSRIs, thiazide diuretics, indomethacin and diclofenac.

The initial dose is 300 mg, which should be increased to 900 mg *per* day (maximum dose is 1200 mg *per* day). Serum doses should be measured 12 hours after the last dosage and should not exceed 1.2 mmol/L (effective serum concentration 0.6 to 0.8 mmol/L). Thyroid and renal functional parameters should be checked before and during treatment.

Serotonin antagonists

Methysergide. A review of observational studies published in 1967 found that methysergide was an effective preventive drug for 73% of people with episodic cluster headache[290]. However, later studies found that effieciency ranged from 20% to 30%[291]. Prolonged treatment with methysergide has been associated with rare fibrotic reactions (retroperitoneal, pulmonary, pleural, and cardiac). Therefore, methysergide should be administired for the prophylaxis of episodic cluster headache no longer the 3 months in a dosage of 8-12 mg *per* day (Level C).

Pizotifen. In a small, single-blind, non-randomized, crossover-design controlled trial in patients with episodic cluster headache, pizotifen significantly reduced the number of headache attacks, duration and severity compared with placebo[292]. It should be administered only in case of refractory episodic cluster, when other therapies fail (Level C). The recommended daily dosage is 1.5 mg, taken in 3 divided doses or as a single dose before sleep.

Anticonvulsants

Valproate. In open and retrospective studies, valproate has been shown to be effective for prophylaxis of cluster headache[293,294]. However, one double-blind placebo-controlled study of sodium valproate did not support its efficacy due to an unexpectedly high response rate in the placebo group[295]. The recommended daily dosage ranges from 500 to 2000 mg in 2 divided doses.

Topiramate. Observational studies have found that topiramate may be effective in about 50% of people with cluster headache[296,297]. Placebo controlled studies with longer treatment periods are required to establish the efficacy of topiramate for the prevention of cluster headache. The recommended daily dosage is 50 to 200 mg in 2 divided doses. The adverse effects associated with topiramate use include paresthesia, fatigue, anorexia, nausea, and cognitive impairment.

Gabapentin. Open studies showed clinical benefit of gabapentin in patients treated for chronic or refractory cluster headache[298,299]. The recommended doses range from 800 mg to 3600 mg *per* day. Common adverse events include somnolence and fatigue, dizziness, weight gain, peripheral edema, and ataxia.

Other agents

Melatonin. There is 1 placebo-controlled trial that investigated melatonin 10 mg daily in prophylaxis of cluster headache (Level C).There was a reduction in daily headache frequency in the melatonin group but not in the placebo group[300]. However, melatonin failed to produce any additional benefit as adjunctive therapy in patients with refractory cluster headache[301].

Dihydroergotamine. DHE administered intravenously was demonstrated to induce rapid dissa-

pearence of cluster attacks when administered daily (0.5-0.8 mg in 8 h)[302]. It is useful for refractory cluster headache, is more effective for the episodic form than the chronic form, and has a rapid onset of action. It did not change the evolution of the episodic form, but it did appear to induce remission in the chronic form or transform it to the episodic form[303].

Ergotamine tartrate. Oral ergotamine tartrate is recommended for short-term prophylaxis (up to 4 weeks) of nocturnal attacks. The recommended dose is 1-2 mg taken before sleep.

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 effective than placebo in reducing the frequency and severity of the crises[304]. Long-term use of capsaicin is inappropriate because of the unpleasant local reactions induced by the drug.

Civamide. In a small double blind study, intranasal civamide solution at a dose of 50 μg may be modestly effective in the preventive treatment of episodic cluster headache[305].

Clonidine applied as 7.5 mg transdermal patch was studied in 2 small open-label studies[306,307]. In the first one, there were significant reductions in the attack frequency, pain intensity, and attack duration of cluster headache. On the other hand, the second study failed to confirm its clinical benefit.

In the prophylactic therapy of cluster headache try the following:

1. Verapamil 3x80 mg *per* day to 3x120 mg, max. 480 mg *per* day.
2. Prednisone 50-60 mg for 3-5 days, followed by 10 mg decrements over 3 days up to 3 weeks or dexamethasone 4 mg bid for 2 weeks followed by 4 mg *per* day for 1 week.
3. Lithium carbonate 300 mg tid or 450 mg sustained release if chronic cluster headache. Note: litium has narrow therapeutic window. The serum concentration should be measured 12 hours after the last dose and should not exceed 1.0 mmol/L.
4. Topiramate 50 mg to 200 mg *per* day divided in 2 doses.
5. DHE administered intravenously for refractory cluster headache or ergotamine tartrate 1-2 mg *per os* before sleep for nocturnal attacks.

Evidence for prophylactic medication in cluster headache is listed in Table 7.

Nonpharmacological treatment

Refractory patients

Approximately 10% of patients develop chronic cluster headache which does not respond to monotherapy. In patients with chronic headache, surgical treatment may be the only alternative therapy when medical therapy is ineffective, is limited by contraindications, or is poorly tolerated[308].

The following criteria should be applied in carefully selected patients:

1) Total resistance to pharmacolagical treatment (severe side effects and contraindicitaions 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:

Neuromodulation

Chronic occipital nerve stimulation through a subcutaneous occipital electrode connected to an im-

Table 7. Evidence for prophylactic medication in cluster headache (CH)

Drugs	Level of evidence	Clinical effectiveness	Comment
Verapamil po.	B	+++	First choice for both episodic and chronic CH
Prednisone po.	C	+++	Initial prophylaxis th. combined with maintenance drugs
Lithium po.	C	+++	Chronic CH
Suboccipital corticosteroid	B	++	Both episodic and chronic CH
Methysergide po.	C	+	Episodic CH up to 3 months
Pizotifen po.	C	?	Refractory episodic CH
Melatonin po.	C	?	

planted generator, in order to induce paresthesias perceived locally in the lower occipital region. The mean attack frequency and intensity decreased by 68% and 49%, respectively[309].

In observational studies, hypothalamic deep brain stimulation has been proved to successfully prevent attacks in more than 60% of 58 hypothalamic implanted drug-resistant chronic cluster headache patients. The implantation procedure has generally been proved to be safe, although it carries a small risk of brain hemorrhage[310]. Randomized phase findings of a randomized placebo-controlled double-blind trial did not support the efficacy of deep brain stimulation in refractory chronic cluster headache[311].

Stereotactic radiosurgery

Gamma knife surgery for intractable, medically refractory cluster headache provided lasting pain reduction in approximately 60% of patients, but was associated with a significantly greater chance of facial sensory disturbances than gamma knife surgery used for trigeminal neuralgia[312].

Ablative surgical procedures in trigeminal region

The procedures that appear to be more effective in the long-term management of the disease are radiofrequency trigeminal ganglion ablation and trigeminal rhizotomy[313,314]. There is strong evidence that even complete trigeminal denervation is not effective in preventing attacks or autonomic symptoms of refractory chronic cluster headache[315].

3.2 Paroxysmal hemicrania

Some features of paroxysmal headache attacks, the pain character and associated autonomic symptoms may resemble those observed in cluster headache. However, the attacks are of shorter duration and more frequent, more related to female sex and terminated by use of indomethacin. There is an episodic and a chronic form of paroxysmal hemicrania with the following diagnostic criteria:

A. At least 20 attacks fulfilling criteria B-D
B. Attacks of severe unilateral orbital, supraorbital or temporal pain lasting for 2-30 min
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 eyelid edema
   4. ipsilateral forehead and facial sweating
   5. ipsilateral miosis and/or ptosis
D. Attacks have a frequency above 5 *per* day for more than half 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 form

Diagnostic criteria:

A. Attacks fulfilling criteria A-F for 3.2 **Paroxysmal hemicrania**
B. At least two attack periods lasting for 7-365 days and separated by pain-free remission periods of ≥1 month

3.2.2 Chronic form

Diagnostic criteria:

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

Indomethacin in daily doses of 150 mg up to 200 mg is the first choice for the treatment of paroxysmal hemicrania (Level A). If not tolerated, verapamil or other NSAIDs may be substituted.

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

SUNCT syndrome is very rare in the general population and its real prevalence is unclear. It is more frequent in female sex (male/female ratio is 1:4). 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 autonomic symptoms of the ipsilateral eye (lacrimation and redness);

although other cranial autonomic symptoms such as nasal congestion, rhinorrhea or eyelid edema may occur (in the latter cases, the proper description term is short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)).

The differential diagnosis to the classical trigeminal neuralgia may be difficult, but autonomic symptoms are not prominent and triggered attacks have a clear refractory period

Diagnostic criteria:

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

Until recently, there was no consistently effective treatment known for SUNCT syndrome Lamotrigine in initial dose of 25 mg/day and gradually titrated to higher daily dose is the treatment of choice for SUNCT (Level C). Lamotrigine appears to decrease the frequency and severity of SUNCT attacks, leading to complete resolution in some patients[316]. There is a lack of randomized placebo-controlled clinical trials evaluating lamotrigine in SUNCT syndrome therapy.

Alternative medication options include other anticonvulsive agents (gabapentin, topiramate or oxcarbazepine) or intravenous lidocaine[317]. In refractory cases, these drugs may be applied in combination.

3.4 Probable trigeminal autonomic cephalalgia

Headache attacks that are believed to be a subtype of trigeminal autonomic cephalalgia but which do not quite meet the diagnostic criteria for any of the subtypes described under 3.1., 3.2., 3.3.
Diagnostic criteria:

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.

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Appendix

Classification of published studies according to their scientific validity in evidence levels (according to the criteria of 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

Sažetak

Ove su smjernice izrađene kako bi pomogle liječniku u ispravnom odabiru dijagnostičkih i terapijskih postupaka kod bolesnika s glavoboljom. Glavni cilj ovih Smjernica zasnovanih na dokazima za liječenje primarnih glavobolja – Dopunjeno izdanje 2012. jest dati preporuke za postavljanje točne dijagnoze i za odabir odgovarajuće terapije u skupini bolesnika s primarnim glavoboljama, zasnovane na sveobuhvatnom pregledu i meta-analizi znanstvenih dokaza u odnosu na terapijske mogućnosti u Hrvatskoj. Ovi su podaci utemeljeni na našim prethodnim Smjernicama zasnovanim na dokazima za liječenje primarnih glavobolja objavljenim 2005. godine te na drugim preporukama i smjernicama za liječenje glavobolje.

Ključne riječi: *Migrena;* Cluster *glavobolja; Liječenje glavobolje; Farmakoterapija*