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Revised guidelines of the French Headache Society for the diagnosis and management of migraine in adults. Part 1: Diagnosis and assessment

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ABSTRACT

The French Headache Society proposes updated French guidelines for the management of migraine. The first part of these recommendations is focused on the diagnosis and assessment of migraine. First, migraine needs to be precisely diagnosed according to the currently validated criteria of the International Classification of Headache Disorders, 3d version (ICHD-3). Migraine-related disability has to be assessed and we suggest to use the 6 questions of the headache impact test (HIT-6). Then, it is important to check for risk factors and comorbidities increasing the risk to develop chronic migraine, especially frequency of headaches, acute medication overuse and presence of depression. We suggest to use a migraine calendar and the Hospital Anxiety and Depression scale (HAD). It is also necessary to evaluate the efficacy and tolerability of current migraine treatments and we suggest to systematically use the self-administered Migraine Treatment Optimization Questionnaire (M-TOQ) for acute migraine treatment. Finally, a treatment strategy and a follow-up plan have to be proposed. Guidelines for pharmacological and non-pharmacological treatments are presented in the second and third part of the recommendations.

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1. Introduction: Why should we be concerned by migraine?

Migraine is the second most common neurological disease after tension type headache, but many affected patients remain undiagnosed and undertreated. The prevalence of migraine is 14,4% with a peak between 35 and 39 years, 30% of women and 15% of men being affected in this age group [1]. In France, one in every five persons aged $\geq$ 18 years (21.3%) has migraine satisfying the diagnostic criteria of the International Classification of Headache Disorders, 3d version (ICHD-3) [2,3].

Migraine is a primary headache disorder that should no longer be considered as benign because it is the second cause of years lived with chronic disability after low back pain, and even the leading cause in individuals aged $<$ 50 years [1]. Patients with migraine have a markedly reduced health-related quality of life as compared to healthy persons, both during and between attacks, because the disorder has negative impacts on patients' work performance, household tasks, leisure time activity [4] and family relationships [5]. In addition, migraine leads to considerable costs, including direct costs of health care and treatments, and indirect costs of absenteeism and reduced work productivity. The burden of migraine culminates in patients with chronic migraine, formerly called ''chronic daily headache'' or ''transformed migraine'' [6]. Migraine is an independent vascular risk factor [7], and patients with migraine with aura have a two-fold increased risk of ischemic stroke [8]. Although its exact mechanisms are incompletely deciphered, migraine is a neurovascular condition due to the interplay of complex genetic factors with multiple environmental factors.

2. Methods

The French Headache Society has prepared, revised guidelines to provide healthcare professionals with practical and up to date recommendations to optimize diagnosis and treatment of migraine, with the aim of improving the quality of life of affected patients and their relatives. The first part presents guidelines about the diagnosis and assessment of migraine. The second and third parts respectively present guidelines about pharmacological and non-pharmacological treatments of migraine [9] [10].

2.1. Objectives

These recommendations were elaborated under the auspices of the French Headache Society (*Société Française d'Etude des Migraines et Céphalées, SFEMC*) and update the previous guidelines [11,12]. They summarize and evaluate available evidence with the aim of assisting all health care professionals supporting patients with migraine in selecting the best management strategies. These recommendations concern adult patients with migraine.

2.2. Guideline development

The development process consisted in five stages:

- literature review within each writing sub-groups (writing group members and invited experts), ii) draft update within each sub-groups;
- review of the whole draft by the writing group;
- review by the reading group;
- final editing by the writing group in the light of all comments.

Each sub-group was responsible for the literature review focusing on five key topics: ''Diagnosis and assessment of migraine,'' ''Acute migraine treatment'', ''Prophylactic treatment'', ''Specific situations in women with migraine'' and ''Non-pharmacological approaches''. The literature review on ''Diagnosis and assessment of migraine'' and ''Pharmacological treatment'' was conducted since previous French guidelines, as several authors (ADo, CL, MLM) were involved in both works and as the same methodology was used. For topics that were not covered by the previous recommendations (e.g. neuromodulation, other non-pharmacological approaches), we searched for articles published since MEDLINE was launched in 1966.

We first graded the levels of evidence in three categories ''High = We are confident that the true effect lies close to the estimate given by the evidence available'', ''Moderate = We are moderately confident in the effect estimate, but there is a possibility it is substantially different'', ''Low = Our confidence in the effect estimate is limited. The true effect may be substantially different''. Secondly, we provided the strength of recommendation grades for clinical implication [13]: ''Strong = Benefits clearly outweigh risks and burdens for most patients = Can apply to most patients in most circumstances'', ''Moderate = Benefits clearly outweigh risks and burdens for most patients = Can apply to most patients, but there is a chance the recommendation may change with more research'', ''Weak = Benefits clearly outweigh risks and burdens for most patients = Can apply to most patients, but there is a good chance the recommendation could change with more research'' or ''Not recommended''. A reading committee scored the proposals by attributing a score ranging from 1 to 9 (best score). Any score below 5 had to be justified. All the proposals were finally deemed appropriate by the reading group (median $\geq$ 7). Relative (range: 5 to 9) or strong (range: 7 to 9) agreement of at least 90% of reading group members [14] was obtained for all recommendations.

2.3. Guideline panel composition

During the first stage, an expert writing group (CL, CR, ADo, ADu, GD, SDG, EGM, JM, XM MLM, PG, DV) and 14 invited experts were assembled to summarize the existing literature. Each sub-group was responsible for the literature review for its topic. A group of 24 interprofessional external reviewers and patients who were not involved in any aspects of the guideline development, was convened to conduct a final review of the guidelines. All active contributors to the review are named in the acknowledgments at the end of the article.

3. Diagnosis and assessment of migraine

The management of migraine aims to precisely diagnose migraine according to ICHD-3 criteria, check for risk factors for

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Box 1. Relevant information to collect in a patient with migraine.

Headache history

- First consultation: diagnosis of the type of migraine
  - age at onset
  - location, type and intensity of pain
  - associated signs and symptoms before (prodromal phase), during, and between attacks
  - presence of aura symptoms and signs
  - duration of attacks
  - migraine triggers (true or supposed)
- Follow-up: check for the absence of a new type of headache
- Frequency of attacks (migraine calendar): number of monthly migraine days and headache days
- Risk factors for chronic migraine, comorbidities and emotional burden (HAD scale)
- Migraine impact and disability: HIT-6 scale, assess avoidance behavior against triggers
- Migraine medications
  - previous treatment: acute and preventative drugs used, efficacy, observance, tolerance, dose, duration of administration, reasons for stopping
  - current treatment (review the migraine calendar)
  - acute treatment: efficacy, number of days with intake, tolerance, dose, timing and route of administration, respect of contraindications
  - prophylactic medication: efficacy, observance, tolerance, dose, respect of contraindications
  - non-drug treatment: type, efficacy

Medical history

- other cephalic or non-cephalic pain diseases
- other conditions and their medications
- women: desire of pregnancy, pregnancy, breast-feeding, contraception, menopause

Physical exam

- Blood pressure, heart-rate, weight and height (BMI), neurological exam

chronic migraine and comorbidities, assess migraine-related disability and severity, evaluate the efficacy and tolerability of current migraine treatments, and propose a treatment strategy and a follow-up plan (Box 1). The efficacy of the management is driven by the precision of the initial diagnosis, which relies on a careful and detailed initial assessment.

3.1. *Diagnose migraine attacks according to ICHD-3 criteria*

Patients can have attacks of migraine without aura and/or with aura. When patients have both types of attacks, both the diagnosis of migraine with and without aura must be given [2]. The pattern can change over the years.

3.1.1. *Migraine without aura*

Migraine without aura, the commonest type of migraine, is diagnosed when patients have had at least five attacks of migraine without aura and no any aura [2]. Attacks typically comprise an incapacitating headache associated with light and sound hypersensitivity and/or digestive symptoms, lasting 4 to 72 h when untreated (Box 2). Osmophobia is not included in the ICHD-3 criteria, but is considered as a highly specific symptom of migraine [15].

Typical pain is located in the frontal, orbital, temporal and occipital regions [16]. Migraine pain frequently involves the neck and the face [17–20] and is commonly misdiagnosed as occipital neuralgia (Arnold's neuralgia) or sinus headache respectively. Other non-painful symptoms comprise osmophobia, cutaneous allodynia, fatigue, yawning, concentration difficulties, mood changes, neck stiffness, pallor and dizziness [15]. In a subset of patients, pain is accompanied by cranial dysautonomic features such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid oedema, miosis and ptosis [21,22]. In the presence of dysautonomic symptoms, migraine attacks must carefully be distinguished from cluster headache attacks. All the non-painful symptoms, which can be very bothersome, may begin up to two days before the headache during the ''prodromal phase'' and may last following pain resolution during the so-called ''postdrome phase'' for up to two days. They might even persist in some patients between the migraine attacks.

Probable migraine without aura is diagnosed in patients with attacks fulfilling all but one criteria A-D for migraine without aura and not fulfilling ICHD-3 criteria for another headache disorder [2].

3.1.2. *Migraine with aura*

Migraine with aura is diagnosed when patients have had at least two attacks of migraine with aura, irrespective of the number of attacks of migraine without aura [2]. About one-third of patients with migraine have migraine with aura [23].

Box 2. ICHD-3 diagnostic criteria for migraine without aura [2].

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
a. unilateral location
b. pulsating quality
c. moderate or severe pain intensity
d. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D. During headache at least one of the following:
e. nausea and/or vomiting
f. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

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Box 3. ICHD-3 diagnostic criteria for migraine with aura [2].

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
a. visual
b. sensory
c. speech and/or language
d. motor
e. brainstem
f. retinal

C. At least three of the following six characteristics:
g. at least one aura symptom spreads gradually over ≥ 5 minutes
h. two or more aura symptoms occur in succession
i. each individual aura symptom lasts 5–60 minutes
j. at least one aura symptom is unilateral
k. at least one aura symptom is positive
l. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis.

Typical aura comprises visual (> 90%), sensitive (30%), and more rarely, speech/language symptoms (Box 3). Each individual symptom usually lasts less than one hour. On the contrary of transient ischemic attacks, which symptoms start suddenly and concomitantly, aura symptoms spread gradually over ≥ 5 min, and occur in succession. Visual symptoms affect both eyes and include positive (flashing lights, zig-zag lines), and/or negative (blind spots) disturbances. Sensitive symptoms often comprise unilateral negative (numbness), or positive (tingling, pins and needles) symptoms that start in the hand and gradually involve the arm and face. Uncommon auras include brainstem symptoms (dysarthria, vertigo, tinnitus), motor weakness (hemiplegic migraine), and strictly monocular visual symptoms (retinal migraine) [2]. In most cases, migraine aura is followed or accompanied by a headache that can have migraine features or not. In a minority of cases, aura occurs without any headache, thus it is possible to receive a diagnosis of migraine without having any headache.

3.1.3. *Distinguish migraine from other headaches and facial pain*

A careful history permits to distinguish migraine from other primary headaches, notably tension headache or cluster headache and from trigeminal neuralgia that is much less prevalent (Table 1). Key clinical features for a proper diagnosis

Table 1 – Discriminating features of the main primary headaches and trigeminal neuralgia.

	Migraine	Tension-type headache	Cluster headache	Trigeminal neuralgia
Attack duration	4–72 h	Hours to days, or unremitting	15–180 min	Seconds to two minutes
Unilaterality	Usually unilateral	Usually bilateral	Strictly unilateral	Strictly unilateral
Pain location	Usually frontotemporal, sometimes occipital or diffuse	Circumferential or bitemporal or occipital	Orbital and/or temporal	V2/V3 >> V1
Type of pain	Usually pulsating	Usually pressing, tightening	Overwhelming	Electric shock, shooting, stabbing or sharp
Pain during routine physical activities (walking, climbing stairs)	Often aggravated by routine activities, Seeks calm	Not aggravated by routine physical activity	Not aggravated by routine activity Restlessness or agitation	Not aggravated by routine activity Aggravated by speaking, drinking, chewing
Pain Intensity	Moderate to severe	Mild to moderate	Severe to very severe	Severe to very severe
Digestive symptoms	Usually nausea and/or vomiting	Usually none	Rare nausea and/or vomiting	None
Sensorial symptoms	Usually phonophobia and photophobia Frequent osmophobia	Often none; sometimes photophobia OR phonophobia (not both) No osmophobia	Possible phonophobia and photophobia	None
Dysautonomic features*	Possible	None	Prominent*	Rare
Other possible features	Cranial and cervical tenderness, cutaneous allodynia	Cranial and cervical tenderness	Cranial and cervical tenderness Circadian periodicity of attacks	Precipitated by innocuous stimuli within trigger zones that are predominantly reported in the perioral and nasal region. Contraction of facial muscles on affected side

* Lacrimation, conjunctival injection, eyelid oedema, forehead and facial sweating, nasal fullness, rhinorrhea, ptosis, miosis.

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Box 4. ICHD-3 diagnostic criteria for chronic migraine [2].

A. Headache (migraine or tension-type-like) on ≥ 15 days/month for > 3 months, and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for *1.1 Migraine without aura* and/or criteria B and C for *1.2 Migraine with aura*
C. On ≥ 8 days/month for > 3 months, fulfilling any of the following:
1. criteria C and D for 1.1 Migraine without aura
2. criteria B and C for 1.2 Migraine with aura
3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.

are the duration of attacks without any treatment, the associated symptoms and the behavior during attacks.

3.2. *Distinguish episodic and chronic migraine*

Patients with < 15 headache days per month have episodic migraine. Chronic migraine is defined by 15 or more headache days per month, for more than three months, which, on at least eight days per month, meet ICHD-3 criteria for migraine with or without aura (Box 4). About 3% of persons with episodic migraine develop chronic migraine in a year [24], through a process called ''transformation'', ''chronification'' or ''progression'' [5]. Chronic migraine has a major impact on physical, mental, and socioeconomic functioning, and is associated with a worse quality of live than episodic migraine [6].

3.3. *Check for risk factors for chronic migraine and comorbidities*

Comorbidities of migraine (i.e., disorders that are more prevalent in migraineurs than in controls) include anxiety, depression, sleep disorders, asthma and other respiratory conditions, chronic non-headache pain, cardiovascular disorders, and other less common disorders (Table 2). Any of these comorbidities is associated with an increased risk of progression from episodic to chronic migraine, and the risk is further increased when multiple comorbidities are present [25] (Supplementary material - Appendix 1).

The improvement of comorbidities may possibly improve the treatment outcomes for migraine and vice versa. Among the modifiable risk factors for migraine progression, the highest strength of evidence is demonstrated for headache frequency at baseline, depression, and medication overuse [5,25,26].

In order to improve the management of migraine, the frequency of headaches and use of acute medications must be monitored by a headache calendar, and the psychiatric comorbidities must be systematically evaluated by the Hospital Anxiety and Depression (HAD) scale. An increased score on the HAD scale may reveal the emotional burden of debilitating migraine attacks, or a definite psychiatric disorder, or a combination of both.

Table 2 – Risk factors for chronic migraine [5,25].

Risk factors for transformation		Levels of evidence [5]	Potential preventive or curative intervention
Sociodemographics	Female gender	Fair	Non modifiable
Lifestyle factors	Low socioeconomic status of family	Fair	
Habits	Caffeine intake	Fair	Education, withdrawal/reduction of use
Major live events	Obesity	Medium	Education, healthy diet and physical exercise
	Major life events including history of abuse	Fair	Prevention of physical, emotional and sexual abuse Stress regulation techniques
Headache features	Frequency of headache days	High	Prophylactic treatment of migraine
	Persistent/frequent nausea with migraine	Medium	Prophylactic treatment of migraine
	Cutaneous allodynia	Medium	Prophylactic treatment of migraine
Comorbidities	Depression	High	Systematic HAD scale, treatment and/or referral
	Asthma and other respiratory conditions	Medium	Treatment or referral for treatment
	Non-cephalic pain (low back/neck pain, arthritis)	Medium	Physical activity, physical therapy, education about risks of medication overuse, avoidance of opiates
	Head and neck injury	Fair	Education, helmet when appropriate
	Snoring	Medium	Sleep management techniques, avoidance of
	Insomnia	Fair	benzodiazepines and hypnotics, specific treatments
	Hypertension, cardiovascular diseases	Unknown	Systematic screen for high blood-pressure, treatment or referral for treatment
Acute treatment	Acute medication overuse	High	Education, avoidance of opiates
	Inadequate acute treatment	Medium	Optimization of acute treatment

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3.4. Screen for medication overuse and medication overuse headache

Medication overuse headache (MOH) is a headache occurring at least 15 days/month and developing as a consequence of regular overuse of acute headache medication for more than 3 months (Box 5). An overuse is defined as a regular use of simple analgesics (paracetamol, acetylsalicylic acid, NSAIDs) for at least 15 days a month, or a regular use of triptans, combination-analgesics, ergotamines, opioids, or any combination of the mentioned drug-classes for at least 10 days a month. Opiates and combined analgesics induce the highest risks for MOH (level of evidence high) [27]. Medication overuse often parallels high frequency of headache, and might be either a consequence, or a promotor of migraine chronification, or both [28]. Accordingly, chronic migraine can now be diagnosed whether or not medication overuse is present [2].

The role of medication overuse in patients with chronic migraine should not be overemphasized because it may lead to suffering, stigmatization of patients as responsible for their own disorder, and diversion from other efficient therapeutic interventions [29].

3.5. Assess headache-related disability

The disability relies on the frequency and intensity of headache and coping strategies of the patient and should be formally evaluated at each visit by the use of the headache impact test (HIT-6). Evidence showed that patients with 8 or more monthly headache days have a similar reduction of their quality of life as patients with chronic migraine [30]. Therefore, severe migraine should be diagnosed according to the recently proposed French criteria in any patient having 8 or more monthly migraine days and in any patient having a HIT-6 score of 60 or above and/or having markedly debilitating attacks [31] (Box 6) (Supplementary material - Appendix 2).

Box 5. ICHD-3 diagnostic criteria for medication overuse headache [2].

A. Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder
B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
C. Not better accounted for by another ICHD-3 diagnosis.

Box 6. Diagnostic criteria for severe migraine [31].

A. Headache frequency of at least 8 migraine days per month
B. Headache frequency < 8 migraine days per month, but associated with at least one of the following criteria:

1. HIT-6 score ≥ 60
2. Necessitating complete interruption of activity for ≥ 50% of headaches

3.6. Discuss trigger factors and their avoidance

Migraine triggers are factors that alone or in combination provoke attacks in people prone to migraine [32]. The role of triggers is often overestimated, and even sometimes misunderstood as causal for the disorder itself. Indeed, stimuli like bright lights, noises, smells or chocolate are commonly incriminated, but photophobia, phonophobia, osmophobia and craving for foods are characteristic symptoms of the prodromal phase of migraine. True migraine triggers do exist and are often self-evident, like menstruations and alcohol. Although lifestyle changes may be encouraged in patients with insufficient sleep, poor physical fitness or unhealthy diet, it should be made clear that lifestyle improvements will not cure migraine. Moreover, unnecessary avoidance behaviors of true and supposed triggers can negatively affect quality of life, and may even contribute to increased headache trigger sensitivity and subsequent migraine activity [33].

3.7. Check for resistant or refractory migraine

To further characterize patients with severe migraine, the European Headache Federation (EHF) recently proposed criteria for resistant and refractory migraine [34]. A debilitating headache causes serious impairment to conduct activities of daily living despite the use of pain-relief drugs with established efficacy at the recommended dose and taken early during the attack. Failure of at least two different triptans is required to qualify the nonresponse to acute treatment [34]. Resistant migraine is diagnosed after the failure of at least 3 classes of prophylactic migraine medications and refractory migraine, after the failure all of available preventatives (Box 7, Box 8). Drug

Box 7. European Headache Federation diagnostic criteria for resistant migraine [34].

A. Established diagnosis of migraine without aura and/or migraine with aura or chronic migraine according to ICHD3 criteria
B. Debilitating headache for at least 8 days per month for at least 3 months
C. Failure and/or contraindication to 3 drug classes with established evidence for migraine prevention, given at an appropriate dose for an appropriate duration

Box 8. European Headache Federation diagnostic criteria for refractory migraine [34].

A. Established diagnosis of migraine without aura and/or migraine with aura or chronic migraine according to ICHD3 criteria
B. Debilitating headache for at least 8 days per month for at least 6 months
C. Failure and/or contraindication to all drug classes with established evidence for migraine prevention, given at an appropriate dose for an appropriate duration

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Box 9. Acute migraine treatment optimization questionnaire M-TOQ [37].

- Are you able to return quickly to your normal activities (i.e. work, family, leisure, social activities) after taking your migraine medication?
- Can you count on your migraine medication to relieve your pain within 2 h for most attacks?
- Does one dose of your migraine medication usually relieve your headache and keep it away for at least 24 h?
- Are you comfortable enough with your migraine medication to be able to plan your daily activities?
- Is your migraine medication well tolerated?

failure includes lack of efficacy or lack of tolerability. Prophylactic medications are divided by pharmacological classes.

3.8. *Perform a physical examination*

A physical exam should include a systematic assessment of blood pressure. The examination is typically normal in migraine patients in between attacks. During attacks, examination may show pallor, hypo or hypertension, neck stiffness or tenderness, cutaneous allodynia, and sometimes, cranial dysautonomic symptoms. Cutaneous allodynia and neck pain may persist between attacks [35].

3.9. *Discuss complementary examinations*

In case of red flags in the familial or individual medical history, or in the physical examination, perform neuroimaging and other tests to confirm or exclude a cause of secondary headache and/or aura [36]. Neuroimaging plays no role in the positive diagnosis of migraine and in the distinction between migraine and other primary headache disorders.

3.10. *Assess efficacy and tolerability of the current acute migraine treatment*

At each visit, review the current acute treatment, namely the type of migraine medication, number of days of intake (headache calendar), tolerance, dose, timing and route of administration, and the respect of contraindications. Efficacy and tolerability can be systematically assessed with the self-administered Migraine Treatment Optimization Questionnaire (M-TOQ) (Box 9) [37].

Table 3 – Recommendations about the diagnosis and assessment of migraine.

	Concerning the diagnosis and assessment of migraine, we recommend to	Strength of the recommendation
Rd1	Use ICHD-3 criteria to diagnose migraine and distinguish migraine from tension-type headache, cluster headache and trigeminal neuralgia	Strong
Rd2	Consider cerebral MRI and other appropriate tests only when there is a suspicion of another disorder causing secondary headache and/or aura-like symptoms, notably in case of: Migraine attacks appearing after the age of 50 years; Atypical aura because of acute onset, duration > 60 min, side-locked symptoms, or absence of visual symptoms; Chronic migraine since less than one year; Abnormal physical examination	Strong
Rd3	Perform or refer for emergent neuroimaging and/or other appropriate tests any patient presenting headache with: Sudden-onset (thunderclap); Recent-onset or recently worsening (< 7 days); Associated fever (without other obvious general cause); Associated neurological signs; Associated features suggestive of intoxication (particularly CO); A context of immune deficiency	Strong
Rd4	Encourage the use of a headache calendar in any patient with migraine	Strong
Rd5	Assess comorbidities, and emotional burden with the HAD scale	Strong
Rd6	Assess headache-related disability with the HIT-6 sale	Strong
Rd7	Assess blood pressure at each visit	Strong
Rd8	Assess efficacy and tolerability of acute migraine medications at each visit with the Migraine Treatment Optimization Questionnaire (M-TOQ)	Strong
Rd9	Provide appropriate reassurance, agree on realistic objectives and propose an individualized therapeutic strategy combining: An optimized acute treatment; Lifestyle improvements (regular hydration, sleep, meals and exercise); Management of modifiable risk factors for migraine chronification notably depression and medication overuse; A prophylaxis for eligible patients	Strong
Rd10	Refer patients: With brainstem, hemiplegic or retinal aura to a neurologist; With severe migraine (French criteria) to a neurologist or a physician certified by the national ''*Diplôme Inter-Universitaire Migraine et Céphalées*''; With resistant or refractory migraine (EHF) to a neurologist certified by the ''*Diplôme Inter-Universitaire Migraine et Céphalées*'' or a tertiary headache center	Strong

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3.11. *Recommendations about the diagnosis and assessment of migraine*

The recommendations are summarized in the Table 3.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurol.2021.07.001.

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Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment

suppl. Informations

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ABSTRACT

The French Headache Society proposes updated French guidelines for the management of migraine. This article presents the second part of the guidelines, which is focused on the pharmacological treatment of migraine, including both the acute treatment of attacks and the prophylaxis of episodic migraine as well as chronic migraine with and without medication overuse. The specific situations that can be encountered in women with migraine are also discussed, including pregnancy, menstrual migraine, contraception and hormonal replacement therapy.

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1. Introduction

Migraine is the second most common neurological disease after tension-type headache but, many affected patients remain undiagnosed and undertreated. Despite the existence of highly efficient treatments to alleviate headache (acute treatments) and decrease the frequency of attacks (preventative treatments), most patients with migraine in France remain undertreated. The French Headache Society has prepared revised guidelines to provide healthcare professionals with practical and up-to-date recommendations to optimize diagnosis and treatment of migraine, with the aim of improving the quality of life of affected patients and their relatives.

The guidelines have been divided into three parts. The first part presents guidelines for the diagnosis and assessment of migraine [1]. The second part, presented herein, is focused on the pharmacological treatment of migraine, including both the acute treatment of attacks and the prophylactic treatment of episodic migraine as well as chronic migraine with and without medication overuse. The specific situations that can be encountered in women with migraine are also discussed, including pregnancy, menstrual migraine, contraception and hormonal replacement therapy. The third part presents guidelines for the non-pharmacological treatments of migraine [2].

2. Methods

Methods are described in the first part of the updated guidelines [1] (Appendix 1).

3. Acute migraine treatment

3.1. *What are the goals of acute migraine treatment?*

The goals of acute migraine treatment are to obtain freedom of pain two hours after medication intake (significant pain relief is also acceptable) with 24 hours sustained response and without (or with minimal) adverse events. The relief of associated symptoms (photophobia, phonophobia, nausea and vomiting) and the ability to resume activities must also be evaluated.

In attacks of migraine with aura, the goals of acute treatment are the same as in attacks of migraine without aura for patients with headache. In addition, the acute treatment should ideally involve reduction of aura duration, but there is currently no such effective pharmacological treatment (Box 1).

Box 1. Management of migraine with aura.

1. Treatment of migraine attack
Instruct the patient to take a nonsteroidal anti-inflammatory drug (NSAID) at the beginning of the aura and a triptan at the onset of headache, even though the aura symptoms are still present. Triptans are probably not effective when given during the aura and before the onset of headache. No pharmacological treatment has proved efficacy to stop aura.
2. Prophylactic treatment
Regarding the initiation of a prophylactic treatment, follow the general recommendations for migraine (Rt15 and Rt16), considering that auras may be debilitating even in the absence of bothersome headache. Prescribe prophylactic treatments recommended for migraine in general. In some patients with troublesome auras, lamotrigine can be used and can be prescribed by a neurologist (Table 2a).
3. Prevention of stroke
Migraine with aura is associated with an increased risk of ischemic stroke. Educate the patients to prevent cardiovascular outcomes by encouraging smoking cessation, prescribing progestin-only contraceptive or non-hormonal contraception (see chapter V), regularly assessing blood pressure, and promoting regular exercise.

3.2. *What are the acute migraine treatments with demonstrated efficacy?*

3.2.1. *Analgesics (Table 1)*

Evidence shows that paracetamol (acetaminophen) is effective in reducing migraine pain, but only in attacks of mild-to-moderate intensity with few bothersome symptoms [3,4]. Evidence shows that the combination of paracetamol and caffeine with or without aspirin [5,6], and the combination of paracetamol and metoclopramide [7] are as effective as sumatriptan 50 mg at relieving acute migraine headache (level of evidence high). Evidence shows that acetylsalicylic acid (ASA; aspirin) with or without metoclopramide, and most nonsteroidal anti-inflammatory drugs (NSAIDs) are effective acute migraine treatments [8–13]. Because of the potential risk of medication overuse headache, the use of paracetamol, aspirin and NSAIDs should not regularly exceed 14 days per month [14,15].

Combination medications including caffeine increase the risk of migraine chronicization and their use must not exceed eight days per month [16]. Opioids are not recommended to treat migraine attacks as they exacerbate nausea, increase the risk of medication overuse headache, and carry the risk of misuse and abuse (level of evidence high) [14,15].

3.2.2. *Triptans*

Triptans are agonists of 5-HT_{1B}/5-HT_{1D} receptors. Triptans inhibit the release of vasoactive and pro-inflammatory neuropeptides [including calcitonin-gene-related peptide (CGRP)] and are vasoconstrictors. Seven triptans are available in France with different formulations (Table 2). Evidence shows that triptans are highly effective at relieving acute migraine pain (level of evidence high), and are superior to ergots, and superior or equal to NSAIDs and paracetamol (level of evidence medium) [17–20]. There is little difference in efficacy between different types of oral triptans, but a study in 2013 found that eletriptan was the most effective triptan at relieving pain at two and 24 hours, rizatriptan was the second most effective triptan at two hours but did not have the same

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Table 1 – Non-specific acute migraine treatments (MA: specific French Market Approval for the acute treatment of migraine headache).

Analgesics	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Dose, route	Main side effects	Main contraindications[a]
Acetylsalicylate acid, aspirin	High	Strong	1000 mg (tablet, powder, disintegrating tablet) Maximum 3000 mg/day	Acetylsalicylate: digestive disorder hemorrhage, allergy, Reye syndrome	Acetylsalicylate: active gastroduodenal ulcer, hemorrhagic risk, pregnancy, asthma, severe hepatic, cardiac or renal insufficiency, hypersensitivity, pregnancy
Acetylsalicylate + metoclopramide (MA)	High	Strong	900 mg + 10 mg (powder) Maximum 3/day	Metoclopramide: dyskinetic syndrome, restlessness psychiatric disorder, endocrine disorder	Metoclopramide: gastrointestinal hemorrhage, digestive perforation, history of dyskinesia, extrapyramidal syndrome, children
Paracetamol	High (in mild-to-moderate attacks)	High in mild attacks, moderate in moderate attacks, not recommended in severe attacks	500, 1000 mg (tablet) Maximum 4 g/day	Paracetamol: hepatic and hematologic toxicity	Severe hepatic insufficiency
Paracetamol + caffeine	High	Low	500 mg + 50 mg (tablet) Maximum 6 tablets/day	Caffeine: palpitation insomnia	

NSAIDs	Level of evidence	Strength of recommendation	Dose, route	Main side effects	Main contraindications[a]
Diclofenac	High	Strong	25, 50, 100 mg (tablet) Maximum 150 mg/day	Hemorrhagic syndrome	Active gastroduodenal ulcer Hypersensitivity to NSAIDs Hemorrhagic risk (cerebral, digestive other), severe hepatic or renal insufficiency, pregnancy (after the 5th month)
Flurbiprofen	High	Strong	8.75 mg (tablet) Maximum 5 tablets/day	Digestive disorder, dyspepsia, nausea, diarrhea, constipation	
Ibuprofen (MA)	High	Strong	200, 400 mg (tablet) Maximum 1200 mg/day		
Indomethacin	Medium	Moderate	25, 75 mg (tablet) 100 mg (suppository) Maximum 300 mg/day	Dizziness, asthenia	
Ketoprofen (MA)	High	Strong	100, 150 mg (tablet) 100 mg (suppository) Maximum 200 mg/day		
Naproxen	High	Strong	550, 1000 mg (tablet) Maximum 1100 mg/day		

NSAIDs: nonsteroidal anti-inflammatory drugs.
[a] Contraindications and side effects are not exhaustive, but listed according to frequency occurrence. Interactions are not given. Refer to Vidal.

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Table 2 – Specific acute migraine treatments (MA: specific French Market Approval for the acute treatment of migraine headache).

Triptans	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Dose (route)	Main side effects	Main contraindications[a]
Almotriptan (MA)	High	Strong	12.5 mg (tablet) Maximum 25 mg/day	Paresthesia of extremities, nausea, feeling of cold, dizziness, asthenia, ''chest syndrome'' (feeling of constriction in the chest and neck), flushing, somnolence Rare cases of coronary spasms, severe hypertension, serotonin syndrome	Coronary heart disease Wolff Parkinson White syndrome Myocardial infarction Peripheral arterial disease Raynaud TIA and stroke Uncontrolled hypertension Serious hepatic or renal insufficiency Concurrent treatment with a MAO inhibitor Cross allergy with sulfonamides (except for rizatriptan and zolmitriptan)
Eletriptan (MA)	High	Strong	20 or 40 mg (tablet) Maximum 80 mg/day		
Frovatriptan (MA)	High	Strong	2.5 mg (tablet) Maximum 5 mg/day		
Naratriptan (MA)	High	Strong	2.5 mg (tablet) Maximum 5 mg/day		
Rizatriptan (MA)	High	Strong	5, 10 mg (tablets), 10 mg (disintegrating tablet) Maximum 20 mg/day		
Sumatriptan (MA)	High	Strong	50 mg (tablets) Maximum 300 mg/day 10/20 mg (nasal spray) Maximum 40 mg/day 6 mg (subcutaneous injection) Maximum 12 mg/day		
Zolmitriptan (MA)	High	Strong	2.5 mg (tablet/disintegrating tablet) Maximum 10 mg/day Nasal spray 5 mg (not available in France)		

Gepants	Level of evidence	Strength of recommendation	Dose, route	Main side effects	Main contraindications[a]
Rimegepant (not available in France in 2021)	High	Strong	75 mg (tablet) Maximum 75 mg/day	Nausea Rare severe allergic reaction	History of hypersensitivity reaction to rimegepant
Ubrogepant (not available in France in 2021)	High	Strong	50 mg, 100 mg (tablets) Maximum 200 mg/day	Nausea, drowsiness Rare severe allergic reaction	History of hypersensitivity reaction to ubrogepant
Ditans	**Level of evidence**	**Strength of recommendation**	**Dose, route**	**Main side effects**	**Main contraindications[a]**
Lasmiditan (not available in France in 2021)	High	Moderate	50 mg, 100 mg (tablets) Maximum 200 mg/day No more than one dose should be taken in 24 hours (FDA)	Common (> 2%): dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, muscle weakness Significant driving impairment Central nervous system depression (dizziness, sedation) Rare (1%): hallucinations, euphoria Risk of misuse or abuse Rare cases of serotonin syndrome	Should be used with caution if used in combination with alcohol, cannabis or other CNS depressants No driving within the first 8 hours after intake (FDA)

NSAIDs: nonsteroidal anti-inflammatory drugs; FDA: Food and Drug Administration.

[a] Contraindications and side effects are not exhaustive, but listed according to frequency occurrence. Interactions are not given. Refer to Vidal.

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efficacy at 24 hours, and oral sumatriptan 100 mg was the third most effective treatment at two hours and maintained efficacy at 24 hours [18]. A systematic review of the effectiveness of the various routes and doses of sumatriptan concluded that subcutaneous sumatriptan 6 mg shows the greatest efficacy in terms of complete pain relief at two hours, provides more rapid pain relief than the other routes but has higher levels of adverse events (level of evidence high) [21]. Because of pharmacokinetic and genetic factors, a patient unresponsive to one triptan may respond to others, and a patient not tolerating one triptan may tolerate others [22].

Triptans are contraindicated in patients with increased cardiovascular risk. Evidence from post-marketing studies and real-life practice shows that triptans are safe and do not induce cardiovascular adverse events when contraindications are respected.

In patients with long migraine attacks, headache and other symptoms may return within 48 hours after initial successful treatment with a triptan. These relapses may be treated by repeating the triptan, but there is a risk of further relapses with this solution. In patients with troublesome relapses, simultaneous treatment at the beginning of the attacks with a combination of a triptan and an NSAID has proven efficacy [23]. Because of the potential risk of medication overuse headache, the use of triptan should not regularly exceed eight days per month [14,15].

Approximately 30–40% of persons with migraine experience insufficient efficacy and/or tolerability to triptans for acute treatment [24–26]. A recent systematic review suggested that a proportion of patients with insufficient efficacy and/or tolerability to one triptan may benefit from switching to a higher dose of the same triptan (sumatriptan 50 mg to 100 mg, eletriptan 40 mg to 80 mg), switching to a different formulation (nasal spray, subcutaneous, oral disintegrating tablet), switching to a different triptan, taking the triptan earlier in the attack, and/or combining a triptan with an NSAID (level of evidence fair) [22]. There are currently no available data about the proportion of patients who may benefit from a third triptan after failure to respond to an initial two triptans [22]. Women treated with triptans have a higher risk for headache recurrence and adverse events than men, despite similar rates of efficacy [27]. Other factors increasing risk of insufficient efficacy and/or tolerability to triptans include attacks with aura [28], severe baseline headache severity, photophobia, phonophobia, nausea, and comorbid depression [22].

3.2.3. *Ergots*

Ergotamine (combined with caffeine) is an older acute migraine treatment that is still occasionally used. Ergots are associated with an increased risk of serious adverse effects (level of evidence high) [29] and are contraindicated in patients with increased cardiovascular risk. Dihydroergotamine (DHE) is the best tolerated of this class, but still has more adverse effects than NSAIDs and triptans.

3.2.4. *Anti-emetics*

Evidence shows that oral and intravenous metoclopramide, and oral domperidone are effective in the treatment of nausea associated with migraine attacks, and may improve the absorption of other oral acute migraine treatments (level of evidence high) [7,13,30,31].

3.2.5. *Gepants*

Gepants are small antagonists of the calcitonin gene-related peptide (CGRP) receptor. Evidence shows that oral ubrogepant and rimegepant are effective at relieving pain associated with acute migraine [32–34]. There is a lack of evidence regarding the efficacy of gepants relative to other antimigraine treatments and in patients having insufficient efficacy and/or tolerability to triptans [35]. Gepants seem to cause less side effects than triptans, but could potentially carry a cardiovascular risk, although evidence to support or refute this concern is not available at the moment [36]. Since some oral gepants are currently investigated in the prophylactic treatment of migraine, gepants could potentially be associated with a reduced risk of medication overuse headache as compared to the other acute migraine drugs, although currently available evidence is insufficient to support or refute this hypothesis. By June 2021, gepants have no market approval in France.

3.2.6. *Ditans*

Lasmiditan is a highly selective 5-HT1_F receptor agonist without vasoconstrictive properties. Evidence shows that lasmiditan is effective at relieving migraine pain [37–39]. There is a lack of evidence regarding the efficacy of lasmiditan relative to other antimigraine treatments and in patients having insufficient efficacy and/or tolerability to triptans. Lasmiditan does not constrict the coronary arteries either in vitro or in vivo, and does not appear to carry the same cardiovascular risk as triptans [36]. Adverse effects of lasmiditan include central nervous system depression and marked sleepiness. Therefore, the United States Food and Drug Administration (FDA) issued a warning that driving should be proscribed during eight hours after lasmiditan intake. Therapeutic doses of lasmiditan were associated with a significant increased risk of drug-liking effects as compared to placebo, suggesting there is a potential risk of lasmiditan misuse or abuse (level of evidence medium) [40]. Effects of lasmiditan in relation to medication overuse headache are unknown. As of June 2021, lasmiditan has no market approval in France.

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3.3. *Recommendations on acute migraine treatment*

The recommendations are summarized in the Table 3.

Table 3 – Recommendations on acute migraine treatment.

Concerning education and initial strategy of acute treatment, we recommend to		Strength of the recommendation
Rt1	Explain the goals of acute treatment, namely complete relief of headache two hours after medication intake with 24 hours sustained response and without adverse events	Strong
Rt2	Explain to patients with migraine with aura that there is currently no pharmacological treatment proved effective in stopping aura	Strong
Rt3	Explain that acute treatments must be taken early (within one hour of headache onset), with an adequate dosage and a route adapted to the severity of digestive symptoms	Strong
Rt4	Explain that the use of acute treatments should be limited to a maximum of eight days per month, because overusing medication carries the risk of medication overuse headache	Strong
Rt5	Encourage patients to use a headache calendar (headache frequency, intensity and acute medication), which will be reviewed at each visit	Strong
Rt6	Prescribe an acute treatment with an NSAID and a triptan, both chosen according to previous treatments and patient's preference	Strong
Rt7	Provide an education about the strategy for acute migraine treatment: a. When headache is mild, the patient should take an NSAID, and add a triptan in case of insufficient response after one hour b. When headache is moderate or severe, the patient should take a triptan, and add an NSAID in case of insufficient response after one hour c. In migraine with aura, the patient should take an NSAID at the beginning of the aura and a triptan at the onset of headache	Strong
Rt8	Avoid prescribing opiates to treat migraine due to the risks of misuse, abuse, and of medication overuse headache	Strong
Rt9	Prescribe a combination of paracetamol and metoclopramide in patients with contraindications or intolerance to NSAIDs, aspirin and triptans	Moderate
Rt10	Prescribe oral or parenteral metoclopramide (suppository or intravenous) to treat attacks with severe nausea or vomiting	Strong
Rt11	Explain that the efficacy and tolerability of the acute treatment is evaluated after three attacks, and plan a follow-up visit	Strong
Concerning the evaluation and optimization of acute treatment, we recommend to		Strength of the recommendation
Rt12	Use the Migraine Treatment Optimization Questionnaire (M-TOQ) at each visit and optimize the acute treatment in any patient responding "No" to one or more items	Strong
Rt13	Choose one or several strategies to optimize efficacy and/or tolerability of acute treatment and educate the patient a. To treat as early as possible into the headache phase b. To increase the dose of NSAID and/or triptan when applicable c. To combine a triptan and an NSAID simultaneously when attacks are resistant to a triptan alone and/or when relapses are troublesome d. To switch to a non-oral formulation (NSAID suppository; sumatriptan nasal spray or subcutaneous) and/or add metoclopramide in case of bothersome digestive symptoms e. To switch the NSAID to another NSAID f. To combine a triptan	Strong
Rt14	Diagnose resistance to a. NSAIDs only after complete inefficacy of at least two NSAIDs, used with adequate dose and route, each tested on at least three distinct attacks b. Triptans only after complete inefficacy of at least two triptans, used with adequate dose and route, each tested on at least three distinct attacks	Strong

NSAIDs: nonsteroidal anti-inflammatory drugs.

4. Prophylactic treatment

4.1. *What are the goals of prophylactic treatment of migraine?*

The preventative treatment aims at reducing monthly migraine days by at least 50% in episodic migraine and by at least 30% in chronic migraine. Prophylaxis also aims at reducing consumption of acute treatments, intensity and duration of attacks, and improving quality of life. Most patients under prophylaxis will still have attacks, and must be instructed how to treat them (see above).

In migraine with aura, the aims are also to reduce the frequency, duration and severity of auras, but there is a lack of high-quality studies investigating the effectiveness of drugs

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Table 4 – Oral prophylactic treatments: dosage, side effects and contraindications.

Treatment (French Market Approval, yes or no)	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Daily dosage Minimum–Maximum (mean daily dosage)	Main side effects	Main contraindications
Amitriptyline (yes)	High in EM Fair in CM	Strong in EM Moderate in CM	10–100 mg (25 mg) Once at dinner time	Dry mouth, somnolence, weight gain	Absolute: glaucoma, prostatic adenoma Relative: obesity
Beta-blocker					
Propranolol (yes)	High in EM Fair in CM	Strong in EM Weak in CM	20–240 mg (80 mg) BID or once in the morning (extended release)	Common: asthenia, poor tolerance to effort Rare: depression	Absolute: asthma, heart failure, atrio-ventricular block, bradycardia Relative: depression
Metoprolol (yes)	High in EM Unknown in CM	Strong in EM Not recommended in CM	50–200 mg (100 mg) Once in the morning (extended release)		
Nebivolol (no)	Medium in EM Unknown in CM	Moderate in EM Not recommended in CM	5–10 mg (10 mg) Once in the morning		
Atenolol (no)	High in EM Fair in CM	Moderate in EM Weak in CM	50–200 mg (100 mg) Once in the morning		
Timolol (no)	High in EM Unknown in CM	Moderate in EM Not recommended in CM	10–60 mg (20 mg) BID		
Candesartan (no)	Medium in EM Fair in CM	Strong in EM Weak in CM	8–32 mg (16 mg) BID or once a day	Hypotension	Absolute: heart failure, renal artery stenosis, renal impairment, pregnancy Relative: hypotension
Flunarizine (yes)	High in EM Fair in CM	Moderate in EM Weak in CM	5–10 mg (5 mg) Once in the evening Stop after 6 months	Common: somnolence, weight gain, depression Rare: parkinsonism	Depression, obesity, Parkinson disease, parkinsonism, pregnancy
Lisinopril (no)	Fair in EM Unknown in CM	Moderate in EM Not recommended in CM	5–40 mg (20 mg) Once a day	Hypotension, dry cough, exanthema, impaired renal function	Angio-edema, renal artery stenosis, renal impairment, hyperkaliemia, pregnancy
Lamotrigine (no)	Fair in migraine with aura	Weak in migraine with aura Not recommended in migraine without aura	25–300 mg (100 mg) Once or twice a day	Common: dizziness, insomnia Rare: serious hypersensitivity reactions, depression, suicidal ideation	Absolute: hypersensitivity to lamotrigine, breastfeeding Relative: previous allergy to another antiepileptic
Levetiracetam (no)	Medium in EM Fair in CM	Weak in EM Weak in CM	500–3000 mg Twice a day	Irritability, depression	Relative: renal impairment
Oxetorone (yes)	Fair in EM Unknown in CM	Moderate in EM Not recommended in CM	60–180 mg (120 mg) Once in the evening	Common: somnolence Rare: diarrhea, parkinsonism	Parkinson disease, parkinsonism, pregnancy
Pizotifene (yes)	Medium in EM Unknown in CM	Moderate in EM Not recommended in CM	50–300 mg (150 mg) BID	Common: sedation, weight gain	Obesity, glaucoma, prostatic adenoma, pregnancy
Topiramate (yes)	High in EM High in CM	Strong in EM Strong in CM	50–200 mg (100 mg) Once or twice a day	Common: paresthesia, weight loss, cognitive effects (word-finding difficulties), depression Rare: renal calculi, acute myopia with secondary angle closure glaucoma	Absolute: hypersensitivity to topiramate, pregnancy, glaucoma, severe pulmonary disease, metformin use, hepatic disease, nephrolithiasis, renal failure Relative: depression, suicidal ideation
Valproate (no)	High in EM Medium in CM	Strong in EM Moderate in CM Do never use in women of childbearing potential	250–2000 mg (750 mg) Once in the evening or twice a day	Common: nausea, weight gain, somnolence, tremor, alopecia, ASAT, ALAT increase, hepatitis	Absolute: liver disease, pregnancy, mitochondrial disease Relative: obesity Do never use in women of childbearing potential
Venlafaxine (no)	Fair in EM Unknown in CM	Weak in EM Not recommended in CM	37.5–300 mg (75–150 mg) Once a day	Common: nausea, dry mouth, hyperhydrosis	Hypersensitivity to venlafaxine

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specifically for such purposes. Since prophylactic drugs have been investigated in populations mixing migraine patients with and without aura, migraine with aura is mostly treated with the same preventatives as migraine without aura (Box 1).

4.2. *What treatments are effective for migraine prophylaxis?*

Oral medications with a demonstrated efficacy in the prophylaxis of migraine are listed in Table 4. A large meta-analysis showed efficacy in the prevention of episodic migraine in at least three randomized controlled trials (RCTs) against placebo for amitriptyline, flunarizine, metoprolol, pizotifen, propranolol, topiramate and valproate [41]. Effective drugs in episodic migraine with less than three RCTs against placebo showing efficacy, and available in France, include several beta-blockers (atenolol, bisoprolol, timolol) and two other antihypertensives (lisinopril, candesartan), one anti-epileptic (levetiracetam), one antidepressant (venlafaxine) and one antihistaminic (oxetorone). In addition, fair-quality evidence supports the use of lamotrigine in the prophylaxis of migraine with aura. A once-daily dosage might improve adherence to the oral migraine prophylactic drugs [29].

Evidence shows efficacy of anti-CGRP and anti-CGRP-receptor monoclonal antibodies (CGRP-MABs) in both episodic and chronic migraine. Evidence shows that onabotulinum toxin A is an effective prophylactic treatment of chronic migraine but not episodic migraine.

4.2.1. *Antihypertensives*

High-quality evidence shows that propranolol, the most well studied beta-blocker, is effective in episodic migraine [42]. A recent meta-analysis of four non-placebo-controlled studies suggests that propranolol may also have a benefit in chronic migraine, with an efficacy comparable to that of valproic acid and flunarizine [42]. Evidence shows that metoprolol reduces headache frequency in episodic migraine, while atenolol, bisoprolol and timolol have lower efficacy and have been less studied [42].

Two placebo-controlled trials showed that candesartan 16 mg is superior to placebo and non-inferior to propranolol in episodic migraine [43,44]. Candesartan was shown to be effective in chronic migraine in a single RCT [43]. Evidence from a single trial for each drug shows that telmisartan [45] and lisinopril [46] are effective in episodic migraine.

4.2.2. *Flunarizine*

Evidence from two meta-analyses shows that flunarizine, a calcium-channel blocker without blood pressure influence, is effective in the prophylaxis of episodic migraine [41,47]. Flunarizine also showed efficacy in chronic migraine in a single non-placebo-controlled randomized trial [48]. Flunarizine can induce parkinsonism, the risk of which increases with older age, presence of comorbidities, exposure to high doses and longer duration of exposure [49]. In France, prescription of flunarizine is limited to six months.

4.2.3. *Antiepileptics*

Topiramate and valproic acid are the most commonly studied antiepileptics used in migraine prophylaxis and evidence shows they are both effective in episodic migraine [41]. Topiramate 100 mg/day has clearly demonstrated efficacy in the prevention of chronic migraine, both with and without medication overuse [50,51]. Sodium valproate may have some efficacy in chronic migraine [52,53].

Two meta-analyses showed that levetiracetam was effective in episodic migraine [41,54]. Levetiracetam also showed efficacy in chronic migraine in one study, but was inferior to valproic acid [53]. Currently, levetiracetam is not widely used in migraine prophylaxis in France.

Evidence from small-sized trials and a meta-analysis suggest that lamotrigine is effective in the prevention of migraine with aura, achieving a reduction in the frequency of attacks and the duration of aura (Box 1) [41,55]. There is not any proof of efficacy of lamotrigine in migraine without aura. Lamotrigine must not be used in the prophylaxis of migraine without aura.

4.2.4. *Antidepressants*

Evidence from old studies [56–58] and two metanalyses shows that amitriptyline is superior to placebo to reduce headache by 50% in episodic migraine [41,59]. Data show that amitriptyline has an efficacy in episodic migraine comparable to that of propranolol [60] and topiramate [61]. Amitriptyline may have some efficacy in chronic migraine [62]. Some older studies have suggested that fluoxetine [63–66] and venlafaxine at a dosage of 150 mg [67,68] might reduce the frequency of migraine attacks. A 2015 Cochrane review concluded that the use of selective serotonin reuptake inhibitors (SSRIs) for migraine prophylaxis was not supported by evidence [69]. A 2020 systematic review and metanalysis concluded that serotonin-norepinephrine reuptake inhibitors (SNRIs) were superior to placebo in the prophylaxis of migraine, and most of the analyzed trials included venlafaxine [70].

4.2.5. *Pizotifen*

Pizotifen was shown to be more effective than placebo in nine RCTs [41].

4.2.6. *Oxetorone*

There is very limited evidence that oxetorone is superior to placebo in the prophylaxis of episodic migraine [20]. Oxetorone has market approval in France and is widely used in primary and secondary care for migraine prophylaxis [71].

4.2.7. *OnabotulinumtoxinA*

OnabotulinumtoxinA has established efficacy in the prevention of chronic migraine with or without medication overuse, but is not superior to placebo for the treatment of episodic migraine (level of evidence high) [72]. OnabotulinumtoxinA proved superiority to placebo when administered according to the PREMPT RCT protocol with 155–195 units injected at 31–39 sites in seven muscles all over the face, skull and neck, repeated every three months [73,74]. At least six months of treatment (two cycles of injections) seem necessary to observe maximal efficacy [73,74]. Since the pivotal trials published in 2010, evidence showing efficacy, tolerance and safety of onabotulinumtoxinA in chronic migraine at long-term (108 weeks) have been published [75,76]. Side effects are minimal. OnabotulinumtoxinA should be administered

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according to the PREEMPT injection protocol, i.e. injecting 155 U-195 U to 31–39 sites every 12-weeks.

4.2.8. *Monoclonal anti-CGRP and anti-CGRP-receptor antibodies*

Calcitonin-gene related peptide (CGRP) is the main neuropeptide released by the trigeminal nerve and responsible for migraine headache. Monoclonal antibodies targeting the CGRP pathway (CGRP-MABs) belong to a new specific therapeutic class, including erenumab, eptinezumab, fremanezumab and galcanezumab, the first blocking the CGRP-receptor and the other three blocking CGRP itself (Table 5). CGRP-MABs have demonstrated efficacy in the prevention of both episodic migraine and chronic migraine without and with medication overuse, including in patients refractory to two to four previous oral preventive treatments (level of evidence high) [77,78]. RCTs have demonstrated excellent safety and tolerability of the four CGRP-MABs in the short-term (at 3 months). During RCTs, the rate of discontinuation for adverse events was remarkably low. The overall incidence of adverse events was similar in active and placebo treatment groups, except for injection-site reactions (pain, erythema), which were more common with CGRP-MABs but were transient and mostly mild-to-moderate (level of evidence high). Post-hoc analyzes have shown the superiority of CGRP-MABs over placebo in the speed of onset of efficacy, the achievement of a super-response with 75% or even 100% reduction in the monthly number of migraine days, the rate of efficacy in the most severely affected patients (previous failure of prophylaxis and/or medication overuse), the reduction of migraine-related functional impact and the improvement of productivity and quality of life (level of evidence medium) [79].

No direct comparison has been made between the CGRP-MABs, but a recent meta-analysis showed no difference between them in terms of efficacy and safety (level of evidence high) [80]. There is currently no available data about the proportion of patients who may respond to a second CGRP-MAB after failure to respond to an initial one, and about the proportion of patients who may respond to the MAB targeting the CGRP-receptor after failure to respond to one of the MABs targeting CGRP and vice-versa. A recent RCT compared erenumab to topiramate, but the results are not available [81]. The LIBERTY [82], FOCUS [83] and CONQUER [84] RCTs showed superiority of erenumab, fremanezumab and galcanezumab respectively over placebo in patients with a documented history of failure of two to four classical oral migraine preventative medications, because of inefficacy or intolerance (level of evidence high). The trial with eptinezumab is still ongoing. Based on these studies, the French Transparency Commission decided that erenumab, fremanezumab and galcanezumab was indicated in patients having at least eight monthly migraine days and a history of failure to at least two oral prophylactic medications. Only neurologists can prescribe CGRP-MABs in France.

There is currently no evidence about the long-term safety of CGRP-MABs. Given the vasodilation role of CGRP, a prolonged blockade of CGRP pathways might increase the consequences of a potential cardiac or cerebral ischemic event. There are currently not any warning signs from RCTs [77–84] and from extension phases of RCTs, including for erenumab with a follow-up of five years [85,86], but patients with a history of cardiovascular disorder were not included in the RCTs. There is a need for long-term pharmacovigilance surveys [87]. There are currently very limited data about CGRP-MABS and pregnancy. In a recent survey of the safety profile of erenumab, galcanezumab and fremanezumab in pregnancy, no specific maternal toxicities, patterns of major birth defects, or increased reporting of spontaneous abortion were found [88]. Finally, there are currently no data on the incidence and consequences of neutralizing antibodies during long-term treatment with CGRP-MABs. Given the cost of CGRP-MABs, there is an important need for large cost-efficacy studies [79].

4.3. *What is the evidence for prophylactic treatment of medication overuse headache?*

There has been a long debate about the practical strategy in patients with chronic migraine with medication overuse

Table 5 – Injectable prophylactic treatments: dosage, side effects and contraindications.

Active component (French Market Approval, yes or no)	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Daily dosage Minimum–Maximum (mean daily dosage)	Side effects	Contraindications
OnabotulinumtoxinA (yes)	High in CM Not efficient in EM	Strong in CM Not recommended in EM	31–39 injections of 155–195 UI (195 UI) in 7 muscular groups, quarterly	Injection site pain	Absolute: myasthenia gravis, amyotrophic lateral sclerosis
Anti-CGRP or CGRP-receptor antibodies					
Erenumab (yes)	High in EM High in CM	Strong in EM Strong in CM	70–140 mg SC monthly	Injection site pain or redness, constipation, allergy	Myocardial infarction, stroke, TIA, uncontrolled vascular risk factor Pregnancy
Eptinezumab (no)	High in EM High in CM	Strong in EM Strong in CM	100–300 mg IV quarterly		
Fremanezumab (yes)	High in EM High in CM	Strong in EM Strong in CM	225 mg SC monthly 675 mg SC quarterly		
Galcanezumab (yes)	High in EM High in CM	Strong in EM Strong in CM	240 mg SC the first month, then 120 mg SC monthly		

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headache (MOH). Some authors recommended a two months abrupt and complete withdrawal before considering the introduction of prophylaxis [89]. Nevertheless, when patients with MOH are treated solely by withdrawal without any other preventive treatment, about one-third cannot tolerate or will not complete the process, one-third withdraws and improves, and one-third withdraws but does not improve [89,90]. Furthermore, evidence shows that the frequency of headache is significantly reduced in patients with chronic migraine receiving prophylaxis with topiramate, onabotulinumtoxinA or CGRP-MABs, whether or not they overuse acute medication at inclusion (level of evidence high) [91]. Of note, patients overusing opioids were not included in GCRP-MABs trials. In MOH, recent evidence suggests that the best therapeutic strategy is withdrawal combined with preventive treatment from the start (level of evidence medium) [92]. Evidence also suggests that educating patients about the risks of migraine chronicization induced by medication overuse can improve global outcomes (level of evidence fair) [93].

4.4. *Recommendations for pharmacological prophylaxis of migraine*

The recommendations are summarized in the Table 6. These recommendations will be updated after marketing approval of eptinezumab and oral gepants.

Table 6 – Recommendations for pharmacological prophylaxis of migraine.

Regarding the initiation of prophylactic treatment, we recommend to		Strength of the recommendation
Rt15	Determine individual patient's eligibility to prophylaxis based on the patient's preference, headache diary or calendar, criteria for severe migraine and chronic migraine, HIT-6 and HAD scales	Strong
Rt16	Initiate a prophylactic treatment in any patient a. Using acute medications eight days or more per month since at least three months b. With severe migraine according to French criteria c. With chronic migraine according to ICHD-3 criteria d. With a HIT-6 scale of 60 or more e. With debilitating migraine attacks despite optimization of acute treatment	Strong
Regarding patient education and optimal follow-up plan, we recommend to		
Rt17	Explain the goals of prophylactic migraine treatment a. The objective is to reduce monthly migraine days by 50% in episodic migraine and by 30% in chronic migraine b. Efficacy will be judged during the third month of treatment (weeks 8–12) c. Prophylaxis also aims at reducing consumption of acute treatments, intensity and duration of attacks, and improving quality of life d. Failure can be due to insufficient efficacy and/or tolerability	Strong
Rt18	Start an oral prophylaxis as monotherapy and at a low-dose, and increase progressively to achieve optimal daily dose, taking into account possible side effects	Strong
Rt19	Explain that adherence to the prophylaxis is mandatory. When appropriate, prescribe once-daily dosage to improve compliance	Strong
As first-line prophylaxis for episodic migraine, our recommendations are		Strength of the recommendation
Rt20	Prescribe propranolol or metoprolol as first-line medication in any suitable patient with episodic migraine, because of the high level of evidence of efficacy	Strong
Rt21	Prescribe amitriptyline, candesartan or topiramate as first-line medication in patients with episodic migraine not suitable to beta-blockers, depending on the patient's preferences and comorbidities	Strong
As first-line prophylaxis for chronic migraine, our recommendations are		Strength of the recommendation
Rt22	Prescribe topiramate as first-line medication in any suitable patient with chronic migraine, because of the high level of evidence of efficacy	Strong
Rt23	Prescribe another recommended prophylaxis in patients with chronic migraine not suitable to topiramate, depending on the patient's preferences and comorbidities	Strong
Rt24	In patients with chronic migraine and medication overuse headache, prescribe a first-line prophylactic medication and advise an ambulatory withdrawal of the overused acute medication	Strong
To evaluate and adapt the prophylactic treatment, our recommendations are		Strength of the recommendation
Rt25	Assess efficacy, tolerability, compliance, and burden of migraine by interview, review of the calendar, and systematic use of HIT-6 and HAD scales at each visit. The efficacy of the prophylaxis should be evaluated after the third month of treatment except for onabotulinumtoxinA whose efficacy should be evaluated after six months	Strong
Rt26	In case of efficacy and good tolerability, continue the prophylaxis for 6–12 months, then decrease slowly before considering cessation. Restart the same treatment if the frequency of attacks increases again during decrease or after cessation	Strong

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Table 6 (*Continued*)

To evaluate and adapt the prophylactic treatment, our recommendations are		Strength of the recommendation
Rt27	In case of insufficient efficacy and/or tolerability, choose one or several strategies to optimize the prophylaxis, and educate the patient a. Check for compliance b. Check for medication overuse, including analgesics for non-headache pain c. In case of insufficient efficacy and good tolerability, increase daily doses to the maximal recommended dose with an acceptable tolerance d. Switch to another prophylaxis	Strong
Regarding switching prophylaxis in episodic migraine, our recommendations are		Strength of the recommendation
Rt28	After failure of the first prophylaxis in episodic migraine, select a second recommended medication, depending on the patient's preferences and comorbidities	Strong
Rt29	After failure of two prophylactic medications in patients with less than eight migraine days per month, select another recommended medication depending on the patient's preferences and comorbidities	Strong
Rt30	After failure of at least two prophylactic treatments in patients with at least eight monthly migraine days, prescribe a CGRP-MAB selected among erenumab, fremanezumab and galcanezumab, based on the patient's preferences	Strong
Regarding switching prophylaxis in chronic migraine, our recommendations are		Strength of the recommendation
Rt31	After failure of the first oral prophylaxis in chronic migraine, select a second recommended oral medication, based on the patient profile, comorbidities, and the patient's preferences	Strong
Rt32	After failure of at least two oral treatments including topiramate in chronic migraine, prescribe a treatment with onabotulinimtoxin A or a CGRP-MAB selected among erenumab, fremanezumab and galcanezumab, based on the patient's preferences	Strong
For prophylaxis of resistant or refractory migraine, our recommendations are		Strength of the recommendation
Rt33	After failure of a CGRP-MAB in a patient with refractory episodic migraine, consider switching to another CGRP-MAB, with or without combination with an oral prophylactic medication	Moderate
Rt34	After failure of a CGRP-MAB in a patient with refractory chronic migraine, consider switching to another CGRP-MAB, or to treatment with onabotulinimtoxin A, both with or without combination with an oral treatment	Moderate

CGRP-MABs: calcitonin-gene-related peptide-receptor monoclonal antibodies.

5. Specific situations in women with migraine

5.1. *Migraine and pregnancy*

5.1.1. *What is the impact of pregnancy on migraine?*

Migraine without aura usually improves or even ceases during pregnancy, especially after the first trimester (level of evidence high) [94,95]. However, 20% of women with migraine will have at least one migraine attack during pregnancy [96]. Unlike migraine without aura, migraine with aura can persist, worsen or even start during pregnancy [94,95].

5.1.2. *Which medications can be used for acute migraine treatment during pregnancy?*

Evidence shows that paracetamol (acetaminophen) [97,98] and triptans have a good safety profile (level of evidence high) [99–104]. The French reference center for teratogenic agents (CRAT) recommends to favor sumatriptan after failure of paracetamol, and zolmitriptan or rizatriptan after failure of sumatriptan [105]. NSAIDs are contraindicated after 24 weeks of pregnancy due to the risk of premature closure of the ductus arteriosus [97]. NSAIDs exposure close to the conception may increase the risk of miscarriage (level of evidence fair) [106]. Some studies suggested to avoid NSAIDs during the first trimester [97], but a recent large database study found that the risks of spontaneous abortion and major birth defects did not differ between women exposed and non-exposed to ibuprofen (level of evidence medium) [107].

5.1.3. *Which medications can be used for migraine prophylaxis during pregnancy?*

Beta-blockers are not associated with an increased risk of malformations (level of evidence high) [108–110]. Amitriptyline may be used [97,98,105] and studies [85,104] suggesting an increased risk of fetal/child adverse events are scarce (level of evidence fair). The French CRAT states that published data about the use of amitriptyline during pregnancy are numerous and reassuring [105]. Neonatal symptoms may rarely appear in the first days of life of newborns when the mother took high doses of amitriptyline until delivery. Symptoms are usually transient and mild (respiratory distress, hyperexcitability, tone disturbances, slowed transit, sedation). A neonatal withdrawal syndrome may also occur and seems to be favored by an abrupt cessation of amitriptyline before childbirth [105].

According to the French CRAT, venlafaxine may be used during pregnancy in women with depression requiring a pharmacological treatment, and may thus be used in women with depression and associated migraine during pregnancy.

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5.1.4. *Which migraine medications are contraindicated during pregnancy?*

Valproic acid is contraindicated because of a significant increased risk of severe fetal malformations as well as of cognitive deficits, mental retardation and autism in children exposed in utero. Topiramate is contraindicated in pregnant women and in those who wish to become pregnant because of an increased risk of severe malformations in fetuses exposed in utero. Candesartan and lisinopril are contraindicated because of fetal renal toxicity [97,105]. All the ergots are contraindicated [105]. Because of the absence of data, CGRP-MABs should not be used during pregnancy.

5.1.5. *Impact of migraine on pregnancy*

A recent meta-analysis showed that migraine is associated with an increased risk of preeclampsia and low birth weight (level of evidence high) [86].

5.1.6. *Recommendations for management of migraine before and during pregnancy*

The recommendations are summarized in the Table 7.

5.2. *Menstrual migraine*

5.2.1. *How to diagnose menstrual migraine?*

ICHD-3 recognizes two types of attacks in relation with menstruation, which is defined as the endometrial bleeding resulting either from the normal menstrual cycle or from the withdrawal of exogenous estrogens [111]. *Pure menstrual migraine* is diagnosed when attacks are occurring exclusively on day 1 ± 2 (i.e., days -2 to +3, there is no day 0) of menstruation in at least two out of three menstrual cycles, and at no other times of the cycle. *Menstrually-related migraine* is diagnosed when attacks are occurring on day 1 ± 2 of menstruation in at least two out of three cycles, and additionally at other times of the cycle.

Many women over-report an exclusive association between migraine attacks and menstruation, and only 8% have pure menstrual migraine [112]. Compared to other migraine attacks, menstrual attacks are mostly without aura (level of evidence medium) [113,114], and are longer, more disabling, more often associated with nausea and less responsive to acute treatment (level of evidence fair) [112].

Table 7 – Recommendations for management of migraine in women desiring pregnancy and during pregnancy.

Recommendations for management of migraine in women desiring pregnancy		Strength of recommendation
Rw1	Explain that migraine can be treated during pregnancy and in case of breastfeeding but self-medication should be formally avoided	Strong
Rw2	Explain that migraine usually improves during pregnancy, notably after the first trimester and in migraine without aura	Strong
Rw3	Explain that migraine does not modify the overall outcome of pregnancy, but is associated with an increased risk of gravid hypertension and preeclampsia	Strong
Rw4	For acute migraine treatment in women desiring pregnancy a. Prescribe paracetamol for mild attacks b. Prescribe triptans for moderate or severe attacks c. Avoid NSAIDs and aspirin (> 500 mg/day) because of the potential risk of early miscarriage	Strong
Rw5	For the prophylaxis of migraine in women desiring a pregnancy a. Stop current prophylactic medication whenever possible b. Contraindicate sodium valproate, topiramate, candesartan, lisinopril, and CGRP-MABs c. When prophylaxis is necessary, propose a non-pharmacological approach (lifestyle changes, exercise, neuromodulation, acupuncture) and/or prescribe amitriptyline, propranolol or metoprolol	Strong
Recommendations for management of migraine during pregnancy		**Strength of recommendation**
Rw6	Plan regular follow-up visits during pregnancy when remission of bothersome attacks was not achieved during the first trimester	Strong
Rw7	For acute treatment of migraine during pregnancy a. Prescribe paracetamol for mild attacks b. Prescribe a triptan for moderate or severe attacks, and after failure of paracetamol. Favor sumatriptan and use rizatriptan or zolmitriptan after failure of sumatriptan c. Contraindicate NSAIDs and aspirin (> 500 mg/day) after 24 weeks of pregnancy, and limit their use before 24 weeks	Strong
Rw8	Regarding migraine prophylaxis during pregnancy a. Encourage lifestyle changes and adapted exercise to each woman b. Propose neuromodulation and acupuncture to women asking for a non-pharmacological approach c. When pharmacological prophylaxis is necessary, prescribe propranolol, metoprolol or amitriptyline (propranolol and amitriptyline can be used during breastfeeding)	Strong
Rw9	In case of bothersome migraine during pregnancy, the patient should be managed both by a neurologist and a gynecologist	Strong

NSAIDs: nonsteroidal anti-inflammatory drugs; CGRP-MABs: calcitonin-gene-related peptide-receptor monoclonal antibodies.

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5.2.2. *What are the effective treatments for menstrual migraine?*

Triptans, NSAIDs, paracetamol, and the combination of aspirin with caffeine are effective acute treatments for menstrual migraine (level of evidence high) [112,114]. Women with frequent migraine including menstrual attacks are eligible for standard prophylactic medications. In women with a regular hormonal cycle, some studies have shown that menstrual attacks may be prevented by short-term perimenstrual (sequential) prophylaxis. Naproxen is effective (level of evidence fair) [115] and its use may be relevant in case of associated dysmenorrhea [116]. Three triptans were shown to be effective (frovatriptan and naratriptan 2.5 mg twice daily, zolmitriptan 2.5 mg three times daily) (level of evidence high) [117], but they were used at high daily doses and this strategy should be balanced with the limit of eight monthly days of intake in order to prevent triptan overuse. Cutaneous estradiol (1.5 mg/day for 7 days) is effective (level of evidence fair) [118], but its use may delay the attack some days later, following hormonal withdrawal (level of evidence fair) [116,118,119]. Overall, we do not recommend these short-term perimenstrual prophylactic strategies (strength of recommendation: strong against).

In eligible women, hormonal contraception can be used with the purpose of preventing menstrual migraine, either with an extended-cycle regimen and a shortened hormone-free interval, or with a continuous regimen (level of evidence fair) [118]. In patients with migraine with aura, combined hormonal contraception (CHC) is contraindicated because of the increased risk of stroke, and progesterone-only contraceptives can be used (see below).

5.2.3. *Recommendations for management of menstrual migraine*

The recommendations are summarized in the Table 8.

5.3. *Migraine, contraception and hormonal replacement therapy*

5.3.1. *Does contraception aggravate migraine?*

There is no data on the risk of migraine for non-oral contraception and for oral combined hormonal contraception (CHC) containing estradiol. No study is available about the impact of the levonorgestrel intrauterine device on migraine.

5.3.2. *Is there a vascular risk of contraception in migraine?*

The risk of ischemic stroke is significantly increased in migraine with aura. CHC significantly increases the risk of stroke in woman with migraine with aura (level of evidence high) [120,121]. In addition, arterial risk factors (age > 35, smoking, familial history of stroke or myocardial infarction, arterial hypertension, dyslipidemia, diabetes, obesity) are synergic with migraine (level of evidence high) (Box 2). Progestative contraception is not associated with an increased risk of ischemic stroke (level of evidence medium) [119]. Levonorgestrel intrauterine device is not contraindicated in migraine with aura (level of evidence high).

Box 2. Type of contraception recommended according to the arterial risk factors and type of migraine.

First step: check for arterial risk factors before prescriptions of hormonal contraception

- Age > 35
- Smoking, familial history of stroke or myocardial infarction
- Arterial hypertension
- Dyslipidemia
- Diabetes
- Obesity

Second step: choose contraception according to the arterial risk factors and type of migraine

- Migraine without aura
  - Absence of any arterial risk factor: every hormonal contraception can be used
  - ≥ 1 risk factor: oral combined contraception is contraindicated; progestin-only contraception is possible
- Migraine with aura
  - Oral combined contraception is contraindicated; progestin-only contraception is possible

5.3.3. *What is the impact of menopause and hormonal replacement therapy (HRT) on migraine?*

While menopause, especially natural menopause, is frequently associated with an improvement of migraine, perimenopause is often associated with more frequent migraine attacks [122]. The impact of hormone replacement therapy on migraine course is debated [116,119]..

Table 8 – Recommendations for diagnosis and treatment of menstrual migraine.

Recommendations for diagnosis and treatment of menstrual migraine		Strength of the recommendation
Rw10	Diagnose menstrual migraine according to ICHD-3 criteria, with the use a prospective headache diary over three months	Strong
Rw11	Treat menstrual attacks following recommendations for any acute attack, i.e. with an NSAID and/or a triptan	Strong
Rw12	In women with bothersome menstrual migraine who are already under hormonal contraception, propose a continuous intake of the contraception or a shortened hormone-free interval	Strong
Rw13	Women with bothersome menstrual migraine, the treatment and especially hormonal interventions should be decided by the primary care physician and a gynecologist	Strong

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5.3.4. *Recommendations for contraception and hormonal replacement therapy in women with migraine*

The recommendations are summarized in the Table 9.

Table 9 – Recommendations for contraception and HRT prescription in women with migraine.

Recommendations for contraception in women with migraine		Level of evidence	Strength of the recommendation
Rw14	Before prescribing any hormonal contraception, always screen for migraine, with and without aura, in addition to other arterial risk factors	High	Strong
Rw15	In women with migraine *without* aura a. CHC can be prescribed in the absence of any other arterial risk factor b. When any arterial risk factor is present, contraindicate CHC and propose progestin-only or non-hormonal contraception	High	Strong
Rw16	In women with migraine *with* aura, contraindicate CHC and propose progestin-only or non-hormonal contraception	High	Strong
Recommendations for HRT prescription in women with migraine		**Level of evidence**	**Strength of the recommendation**
Rw17	Before any HRT prescription, always screen for migraine with and without aura in addition to other arterial risk factors	High	Strong
Rw18	HRT is not contraindicated in migraine without other vascular risk factor	Medium	Strong

HRT: hormonal replacement therapy; CHC: combined hormonal contraception.

Disclosure of interest

ADU has received honoraria for consultancies or speaker panel from Abbvie, Amgen, Eli Lilly, Lundbeck, Novartis and TEVA. SdG received honoraria from Abbvie/Allergan, Boerhinger, Lilly, Novartis, Teva. CR received consultant or speaker fees from Allergan/Abbvie, Homeperf, Lilly, Lundbeck, Novartis et Teva. ADO received honoraria from Allergan, Amgen, Lilly, Lundbeck, Novartis, TEVA. PG has received honoraria for consultancies or speaker panel from Abbvie, Lilly, Lundbeck, Novartis, TEVA, Allergan, Biogen Idec, Sanofi, Merck-Serono, Roche. EGM received honoraria Allergan, Bayer, BMS, Boehringer, Lilly, Lundbeck, Medtronic, Novartis, Pfizer TEVA. MLM has received financial support to the institution (département d'évaluation et traitement de la douleur du CHU de Nice and/or le FHU InovPain) and honoraria from Allergan, Amgen, Boston Scientific, Grunenthal, Lilly, Lundbeck, Medtronic, Novartis, Pfizer, ReckittBenckiser, Saint-Jude, Sanofi-Aventis, Teva, UPSA, Zambon. CL has received honoraria from Amgen, Grunenthal, Homeperf, Lilly, Lundbeck, Novartis, SOS oxygène, TEVA. JM has received consultant or speaker fees from Lilly, Teva and Novartis and financial support for congress from Amgen, Novartis, SOS Oxygene, Homperf and Elsevier. XM has received financial support from Allergan, Biogen, Bristol Myers Squibb, Grünenthal, Lilly, Teva, Merck-Serono, Novartis, Roche, and Sanofi-Genzyme and non-financial support from SOS Oxygène, not related to the submitted work. DV declare that he has no competing interest. GD has received honoraria for consultancies or speaker panel from Abbvie/Allergan, Amgen, Eli Lilly, Lundbeck, Novartis and TEVA.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurol.2021.07.006.

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Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 3: Non-pharmacological treatment

suppl. Informations

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ABSTRACT

The French Headache Society proposes updated French guidelines for the management of migraine. This article presents the third part of the guidelines, which is focused on the non-pharmacological treatment of migraine, including physical exercise, dietary supplements and plants, diets, neuromodulation therapies, acupuncture, behavioral interventions and mindfulness therapy, patent foramen ovale closure and surgical nerve decompression.

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1. Introduction

Migraine is the second most common neurological disease after tension type headache, but many affected patients remain undiagnosed and undertreated. Besides medications, non-pharmacological approaches can be proposed both for the acute and prophylactic treatment of migraine. Non-pharmacological approaches include heterogeneous techniques with various qualities of evidence.

The French Headache Society has prepared revised guidelines to provide healthcare professionals with practical and up-to-date recommendations to optimize diagnosis and treatment of migraine, with the aim of improving the quality of life of affected patients and their relatives. The guidelines have been divided into three parts. The first part presents guidelines about the diagnosis and assessment of migraine [1]. The second part proposes guidelines for the pharmacological treatment of migraine [2]. The third part, presented herein, is focused on the non-pharmacological treatment of migraine, including physical exercise, dietary supplements and plants, diets, neuromodulation therapies, acupuncture, behavioral interventions and mindfulness therapy, patent foramen ovale closure and surgical nerve decompression.

2. Methods

Methods are described in the first part of the updated guidelines [1] (Online material).

3. Is physical exercise effective for migraine prophylaxis?

Recent systematic reviews and meta-analyses provide moderate-quality evidence that aerobic exercise therapy can decrease the number of migraine days in patients with migraine (level of evidence medium) [3–5]. Although the type of physical activities varied according to the studies, multi-weekly aerobic exercise (endurance) has a clear benefit [3,4,6]. Exercise therapy can be efficient when used as the sole preventative option and might also potentiate pharmacological prophylaxis [7,8].

The benefit of yoga for migraine prevention remains uncertain: a recent meta-analysis including six low-quality randomized-controlled trials (RCT) in migraine and tension-type headache patients revealed a global benefit but which related to tension-type headache [9]. However, a more recent, not included, large RCT showed a benefit of yoga as add-on therapy for migraine prevention, with positive outcomes on headache days, disability and quality of life [10]. Up to now, evidence remains too scarce to make any recommendation for this activity.

4. What is the evidence concerning dietary supplements and plants?

Studies show that co-enzyme Q10 supplementation (mostly 300 mg/day) (level of evidence fair) [11,12], high-dose riboflavin (vitamin B2, 400 mg/day) (level of evidence fair) [13–15], oral magnesium (600 mg/day) (level of evidence fair) [16,17], and oral melatonin (mostly immediate-release 3 mg) (level of evidence fair) [18] may be of potential benefit for migraine prophylaxis. Some data suggest that feverfew may have a small positive effect on migraine prophylaxis, but other studies are negative (level of evidence for efficacy unknown) [19]. Studies show that butterbur is effective in the prophylaxis of migraine (level of evidence moderate) [20,21] but preparations are heterogeneous with a risk of hepatotoxicity in those containing pyrrolizidine alkaloids.

5. What is the evidence concerning diets?

Specific diets (gluten-free, lactose free...) should not be recommended as data are too scarce to make any recommendation for a specific diet for migraineurs [22]. Further studies are needed to confirm the encouraging results of ketogenic diets in overweight migraine patients [22,23].

6. What neuromodulation therapies are effective in migraine?

Neuromodulation therapies were evaluated in a 2020 systematic review and meta-analysis [24] (Table 1). For the acute treatment of migraine, the number of well-conducted studies is limited. Conditioned pain modulation by non-painful remote electrical neuromodulation (REN) is effective (level of evidence medium). This neuromodulation technique relates on the principle that pain inhibits pain. Single pulse transcranial magnetic stimulation (TMS), with a portable self-administered device, is effective for migraine with aura [25] (level of evidence fair). One open-label study suggested that it might be of interest even in migraine without aura [26]. Supra-orbital transcutaneous electrical nerve stimulation (TENS) is possibly effective (level of evidence fair) [27,28]. Non-invasive vagus nerve stimulation (VNS) is ineffective [29] (level of evidence fair for inefficacy).

Concerning migraine prevention, everyday self-administered supra-orbital TENS is effective (level of evidence medium) [30–32]. Data concerning occipital TENS are inconclusive [33,34]. High frequency repetitive TMS on the primary motor cortex (M1) is effective (level of evidence fair) [35–37]. Percutaneous electrical nerve stimulation (PENS) or electroacupuncture is possibly effective [38–40] (level of evidence fair). Data concerning transcranial direct current stimulation (tDCS) are heterogeneous and inconclusive overall [24]. Self-administered non-invasive percutaneous VNS is ineffective [41–44] (medium level of evidence for inefficacy). Invasive occipital nerve stimulation is probably effective for chronic migraine prevention [45–47] (level of evidence medium), but no implantable device is currently FDA approved or CE marked in this indication.

7. What is the efficacy of acupuncture for migraine prophylaxis?

Acupuncture can be effective over sham in the short-term prophylaxis of episodic migraine (level of evidence medium),

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Table 1 – Neuromodulation devices with proven efficacy and available in France.

Stimulation method Device™ (FDA cleared, CE marked)	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Availability	Practical use
Remote electrical neuromodulation (REN) (Yes)	Medium in acute migraine treatment	Moderate in acute treatment	Available online but not yet in France, price to be determined	Self-administered by the patients on his forearm for migraine attack treatment for 30–45 min, controlled by smartphone app
Single pulse transcranial magnetic stimulation (Yes)	Fair in acute aura treatment	Moderate in acute aura treatment	Available online but not in France, no data on a French availability or price	Self-administered by the patients for migraine with aura attack treatment: single-pulse on the occiput, repeated once 30 sec later, to be performed as soon as possible after the aura starts
Supra-orbital transcutaneous electrical nerve stimulation (TENS) (Yes)	Fair in acute migraine treatment Medium in migraine prevention	Weak in acute treatment Moderate in migraine prevention	Available online, for devices with acute and prophylactic settings	Self-administered by the patients on his forehead, 20 min every day for preventive treatment, punctual use for 60 min for migraine attack treatment
High frequency repetitive TMS on the primary motor cortex (Yes)	Fair in migraine prevention	Weak in migraine prevention	Classical rTMS device in the neurologist's office	Up to 3 sessions/week performed by a neurologist on the primary motor cortex for up to 4 consecutive weeks. $\geq$ 600 pulses per session, 10 Hz, 70 to 80% of the resting motor threshold. Further studies are needed to specify conditions and settings, especially to define sessions' rate for long-term use This technique should be restricted to tertiary centers until further studies are available (expert opinion)

TMS: transcranial magnetic stimulation.

and has similar efficacy and fewer side effects than many of the standard pharmaceutical agents [48–50]. Long-term studies of acupuncture in episodic migraine, and studies in chronic migraine are lacking.

8. What is the efficacy of behavioral interventions and mindfulness therapy for migraine prophylaxis?

Studies evaluating behavioral therapies and mindfulness meditation are highly heterogeneous regarding settings (size, comparator arms, and endpoints), risk of bias and results. One major limitation relates to the endpoint used for prophylactic treatment: some studies have negative results on headache days, but the awaited effect of these techniques is more related to improvement of disability, quality of life and ability to function with migraine than on the classical headache day reduction endpoint [51].

Behavioral therapies include relaxation, biofeedback and cognitive behavioral therapy. Depending on endpoints, inclusion criteria and analyses, divergent results have been reported in meta-analyses. A meta-analysis concluded that most of the 21 studies conducted up to 2018 to assess the efficacy of behavioral or cognitive-behavioral therapies such as coping strategies, biofeedback, relaxation, and eye movement sensitization for migraine prophylaxis are of very low quality [52]. This Cochrane meta-analysis concluded that there is an absence of high-quality evidence to determine whether psychological interventions are effective for migraine prophylaxis in adults and that it remains uncertain whether there is any difference between psychological therapies and controls on the reduction of migraine days. Another meta-analysis, including all types of headache disorders, concluded that psychological treatments were promising to reduce headache frequency even though the diversity of treatment modalities and the heterogeneity of protocols limited interpretation of data [53]. A previous review focused on cognitive behavioral therapy acknowledged the methodology inadequacy but suggested a potential benefit [54]. Behavioral therapy can be used as add-on to classical pharmacological treatment [55].

Wide heterogeneity also exists regarding mindfulness-based stress reduction benefit for migraine prophylaxis. Likewise, meta-analyses showed conflicting results [56,57], but a more recent narrative review [51], and two new large randomized studies [58,59] suggest that mindfulness-based stress reduction may have beneficial effects, not always on headache days but on disability and quality of life.

Because of their safety and acceptability, behavioral therapies and mindfulness-based stress reduction should be considered in patients with episodic or chronic migraine with significant stress, anxiety or migraine induced-disability, as add-on therapy to pharmacological treatments (level of evidence fair).

The evidence regarding the efficacy of hypnosis is too scarce to make any recommendation [60–62].

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9. What is the efficacy of patent foramen ovale closure?

Patent foramen ovale (PFO) is more frequent in migraineurs than in non-migraineurs but randomized controlled trials on PFO closure in migraine failed to demonstrate a significant benefit of PFO closure on the primary endpoints [63–66]. To date, screening for a PFO and PFO closure is not recommended for migraine prophylaxis (level of evidence strong).

10. What is the efficacy of surgical nerve decompression?

Data supporting surgical nerve decompression are very scarce and mostly based on retrospective and unblinded studies [67,68]. Up to now, we do not recommend such procedures.

11. Recommendations for non-pharmacological treatment of migraine

The recommendations are summarized in the Table 2.

Amgen, Novartis, SOS Oxygene, Homperf and Elsevier. EGM received honoraria Allergan, Bayer, BMS, Boehringer, Lilly, Lundbeck, Medtronic, Novartis, Pfizer TEVA. SdG received honoraria from Abbvie/Allergan, Boerhinger, Lilly, Novartis, Teva. ADO received honoraria from Allergan, Amgen, Lilly, Lundbeck, Novartis, TEVA. PG has received honoraria for consultancies or speaker panel from Abbvie, Lilly, Lundbeck, Novartis, TEVA, Allergan, Biogen Idec, Sanofi, Merck Serono, Roche. MLM has received financial support to the institution (*Département d'évaluation et traitement de la douleur du CHU de Nice* and/or le FHU InovPain) and honoraria from Allergan, Amgen, Boston Scientific, Grunenthal, Lilly, Lundbeck, Medtronic, Novartis, Pfizer, ReckittBenckiser, Saint-Jude, Sanofi-Aventis, Teva, UPSA, Zambon. CL has received honoraria from Amgen, Grunenthal, Homeperf, Lilly, Lundbeck, Novartis, SOS oxygène, TEVA. XM has received financial support from Allergan, Biogen, Bristol Myers Squibb, Grünenthal, Lilly, Teva, Merck-Serono, Novartis, Roche, and Sanofi-Genzyme and non-financial support from SOS Oxygène, not related to the submitted work. CR received consultant or speaker fees from Allergan/Abbvie, Homeperf, Lilly, Lundbeck, Novartis et Teva. ADU has received honoraria for consultancies or speaker panel from Abbvie, Amgen, Eli Lilly, Lundbeck, Novartis and TEVA.

The author DV declares that he has no competing interest.

Table 2 – Recommendations for non-pharmacological treatment of migraine.

	For non-pharmacological treatment of migraine, our recommendations are	Strength of recommendation
Rnpt1	Encourage any patient with migraine to practice weekly aerobic exercise as an alternative or a supplement to pharmacological prophylaxis	Strong
Rnpt2	In patients with episodic migraine asking for a prophylactic treatment with limited side-effects, propose co-enzyme Q10, high-dose riboflavin or melatonin	Moderate
Rnpt3	Do not prescribe plants for the prophylaxis of migraine because feverfew has no demonstrated efficacy and butterbur has a heterogeneous composition carrying a risk of hepatotoxicity	Strong
Rnpt4	In patients with episodic migraine asking for non-pharmacological treatments or achieving insufficient efficacy with pharmacological treatments, propose neuromodulation therapies, favoring remote electrical neuromodulation for the acute migraine treatment and supra-orbital transcutaneous electrical nerve stimulation for migraine prevention	Strong
Rnpt5	In patients with episodic migraine asking for non-pharmacological treatments or achieving insufficient efficacy with pharmacological treatments, propose acupuncture as an alternative or a supplement to pharmacological prophylaxis	Strong
Rnpt6	In patients with episodic or chronic migraine with significant stress, anxiety, or migraine-induced disability, propose behavioral therapies (relaxation, biofeedback and cognitive behavioral therapies) or mindfulness-based stress reduction as add-on therapy to pharmacological treatments	Strong
Rnpt7	Do not recommend PFO closure for migraine prophylaxis	Strong

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurol.2021.07.009.

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