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SEVERE MIGRAINE AND ITS CONTROL: A PROPOSAL FOR DEFINITIONS AND CONSEQUENCES FOR CARE

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FR participated in the Novartis Scientific Committee, and received honoraria from Lilly France.

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Authors' contributions

All authors participated in the development of the proposals and in the preparation of this manuscript.

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Abstract

Currently many patients with severe migraine do not receive appropriate treatment and are never referred to specialist headache centres. On the other hand, specialist headache centres are frequently attended by patients whose migraines could be managed adequately in the community. One reason for this may be the absence of standardised definitions of migraine severity and control and of a treatment algorithm for orientating difficult-to-treat patients to specialist headache centres. Based on a review of the relevant literature and consensus meetings, proposals have been made for these items. We propose that migraine should be considered severe if headache frequency is at least eight migraine days per month or, if headaches are less frequent, the HIT-6 score is ≥ 60 or $\geq 50\%$ of headaches require complete interruption of activity. The proposed definition of migraine control is defined on the basis of appropriate response to acute headache therapy and to preventative therapy. A treatment algorithm is proposed to assess migraine control regularly and to adapt therapy accordingly. These proposals may contribute to developing and testing strategies for management of severe disease with appropriate and effective preventive treatment strategies. With the anticipated introduction of new possibilities for migraine prevention in the near future, the time is ripe for a holistic approach to migraine management.

Keywords: Severe migraine, difficult-to-treat patients, prevention.

1. Introduction

Migraine is a common chronic neurological disease affecting around 14% of adults in Europe, most frequently women and the 18 – 50 year-old age group (1). According to the Global Burden of Disease project of the World Health Organization (WHO), migraine was the second most frequent cause, out of a total of 328 diseases evaluated, of years lived with disability worldwide in 2016 (2).

Its clinical presentation can be very variable, in terms of symptoms, frequency and intensity of headaches, and in terms of impact. In some cases, patients may experience infrequent (less than one a month) headaches which are not particularly disabling and which can be effectively treated with over-the-counter drugs bought in the pharmacy without the need to consult a physician (3). At the other end of the spectrum, in other patients, migraine headaches may be frequent (episodic migraine with high frequency and chronic migraine), with a major impact on their family, professional and social lives, and which are difficult to treat (3).

Over a decade ago, the American Migraine Prevalence and Prevention study (4), a general population survey of over 150,000 people with migraine, reported that around half the sample reported severe impairment or the need for bed rest when they experienced headaches. In addition, a similar proportion were potentially candidates for migraine prevention therapy, based on headache frequency and severity, although only thirteen percent were actually receiving such therapy. This treatment gap does not seem to have narrowed over the intervening period. In a recent (2016) study in the United States, less than five percent of individuals with chronic migraine consulted a healthcare professional for migraine, received an accurate diagnosis, and were prescribed minimal acute and preventive

pharmacological treatments (5). Similarly, people with migraine recruited from the general population in the European Eurolight study (6), only 3.4%–22.4%, according to the country, were using triptans and 1.6%–13.7% were taking preventive treatments.

One of the many possible reasons for this treatment gap is that, at the moment, there is no consensus on how patients with severe migraine should be identified nor on what should be the appropriate paradigm of care. It is clear that there exists a segment of the migraine population with severe disease, and that these patients need to be identified, in order to direct them to specialist medical care. However, current treatment guidelines do not stratify recommendations for care according to migraine severity or migraine frequency, with the exception of general criteria for prescribing preventive treatments, and segregation of episodic and chronic migraine. In addition, identifying migraineurs who require specialist care and ensuring that they receive it has unfortunately not been perceived as a major priority by public health authorities in many countries (7).

Nonetheless, with an optimal standard of care, it should be possible most of the time to minimise the risk of headaches occurring and thus attenuate the consequences of migraine on patient's lives. Appropriate migraine preventive treatment can provide a reduction in migraine severity, and indeed many clinical studies have described decreased headache frequency, decreased headache impact and improved quality of life in response to, *inter alia*, certain β -blockers (8), topiramate (9), onabotulinum toxin A (10), and monoclonal antibodies directed against CGRP or its receptor (11).

Although many people with migraine never consult a healthcare professional, for those who do consult, headache severity and frequency are the two principal reasons motivating seeking medical help (12). The first point of contact for people who wish to

consult about their headaches would usually be the general practitioner. However, migraine headaches are also a major reason for consulting neurologists, accounting for around one-third of all neurology visits according to a recent WHO report (13). Headache specialists (who, in France, are neurologists working in neurology departments or in chronic pain centres) represent the third level of healthcare provision in migraine and, in principal, are dedicated to the managed of difficult to treat migraine or migraine with complications (14). According to recommendations for headache service organisation and delivery developed by the EHF, only around 1% of patients with migraine should need to be managed in specialist headache centres, with 90% of patients being manageable in primary care (14). However, a recent (2017) survey of access to care in specialist headache centres in six countries (15) reported that access was generally saturated, generating long waiting lists to consult a headache specialist. Although part of the problem was due to inadequate supply, the principal issue was inappropriate demand, notably a lack of patient selection upstream such that patients who should be managed in primary care, such as those with infrequent uncomplicated headaches or those who had never attempted prophylaxis with preventive treatments, were being referred to specialist headache centres (15). Complementary to this finding, the My Migraine Voice study evaluated healthcare resource consumption in over 10,000 patients with frequent migraine, of whom around three-quarters had failed at least one preventive treatment (16). This study reported that only 15% had consulted a specialist headache centre, which would be the appropriate setting for management of these difficult-to-treat headaches. In addition, around one-third of the participants in My Migraine Voice had gone to an emergency department for their migraine headaches at least one in the previous year and around one quarter had been hospitalised overnight, suggesting that they are not receiving appropriate treatment (16). Studies such as these illustrate the need for

more explicit guidelines on which patients should be referred from primary care (or from general neurologists) up to a tertiary headache specialist.

Establishing operational criteria for migraine severity and control is clearly needed to improve the management and burden of severe migraine (17). In order to address the issue of identifying patients with severe migraine who may require being directed to specialist care early, we have attempted to develop definitions of severe migraine severity and its control that could be used in treatment algorithms. The proposed definitions may be of interest for stratifying patient care and also for research purposes.

2. Migraine severity

Several instruments have been developed to measure symptom severity, including the Migraine Symptom Severity Score (18) and the MIGSEV (19) (Table 1). These instruments aim to measure the intensity of symptoms during individual migraine headaches and the repercussions that they have on functioning. Within individual patients, the severity of individual headaches appears to be relatively stable over time (20). In contrast, the Migraine Disability Assessment (MIDAS) (21) and the six-item Headache Impact Test (HIT-6) (22) have been developed to assess the severity of migraine as a disease rather than the severity of individual headaches. Finally, the Global Assessment of Migraine Severity (GAMS) (23) is a patient-reported outcome measure to document the patient's perception of migraine severity.

Table 1. Instruments for assessing migraine severity

	Scope	No of items	Rater
Migraine Symptom Severity Score (18)	Severity of most severe headache	4	Patient
MIGSEV (19)	Severity of most recent headache	7	Patient
MIDAS (21)	Impaired productivity due to migraine	7	Patient
HIT-6 (22)	Impact of migraine on functioning	6	Patient
GAMS (23)	Overall disease severity	1 (Likert scale)	Patient

MIGSEV: migraine severity score; MIDAS: Migraine Disability Assessment; HIT-6: six-item headache impact test; GAMS: Global Assessment of Migraine Severity.

However, it is important to distinguish between the severity of migraine as a disease and the severity of the individual migraine attacks that occur during the course of the disease. It was pointed out over twenty years ago that the two concepts are not the same

(24). Currently, there is still no consensus on how to define or measure the severity of the migraine disease as a whole, perhaps due to the lack of progress in developing new preventive treatments until very recently. The severity of the migraine disease as a whole is a wider concept, including elements which relate to the disease, the patient, migraine management and to the social context. Disease aspects which may contribute to severity include headache intensity, headache duration and frequency, and the semiological presentation. Patient-related variables include comorbidities, psychological vulnerability, coping strategies and stress (25-30). Migraine management issues include the response to migraine prevention therapy (31) and headache medication overuse (32). Social aspects include professional and family status and social precarity (33-35). Although there is evidence for some genetic predisposition to severe migraine (36-38), several studies have indicated that the severity of migraine in the same individual may fluctuate over time (39-41).

In addition, the burden of migraine is not restricted to the acute headache attack, but is also significant during the interictal period between headaches, as demonstrated in an early Swedish case-control study that reported that, during the periods between their attacks, migraine cases perceived more symptoms and greater emotional distress as well as disturbed contentment, vitality and sleep compared to control subjects (42). More recently, in the Eurolight study (43), between 10% and 30% of participants (according to the variable) reported anxiety about their headaches, avoidance of activities, residual symptoms, stigma, social isolation, and impact on professional or social life during the period between their headaches. The proportion of participants reporting interictal anxiety or avoidance increased with the intensity and frequency of their headaches, and with the feeling of not being in

control of their migraine disease (43). This interictal burden needs to be taken into account in the definition of severe migraine.

Two widely-used patient-reported outcome measures, the Migraine Disability Assessment (MIDAS) and the six-item Headache Impact Test (HIT-6), have been developed to capture the aggregate impact of migraine on functioning over a fixed period of time. Although the two tests both measure the impact of migraine and provide a measure of severity, scores on the two tests are only moderately correlated (44, 45). The MIDAS (21) is a measure of the impact of migraine in terms of lost productivity over the previous three months. The MIDAS captures information on disability in terms of the number of days on which activities were missed or reduced due to headaches. The MIDAS also contains a question on headache frequency and another on pain intensity for the average headache. The distribution of MIDAS disability categories was assessed in the MAZE study (46), which evaluated a sample of people with migraine drawn from the general population in five countries (UK, France, Germany, Italy, and USA). In this sample, 28% of participants fell into the category of severe disability (MIDAS IV).

The HIT-6 (22) measures functional and psychological impairment over the previous month, as well as the impact of migraine headaches in general. It was developed without any *a priori* hypotheses using item response theory from a large pool of potential items related to headache severity and validated psychometrically in an Internet-based survey of headache sufferers. The test includes three questions addressing the impact of individual headaches specifically and three questions which address the impact of the migraine disease globally on different aspects of functioning. In the validation study of the HIT-6 in people with migraine drawn from the general population, 60% of participants with episodic

migraine and 70% of those with chronic migraine were categorised as having migraine headaches with severe impact (47).

Another patient-reported outcome measure, the Global Assessment of Migraine Severity (GAMS), has been developed recently to assess the perceived overall severity of the migraine disease (23). This was adapted from a similar one validated and widely used in epilepsy, the Global Assessment of Severity in Epilepsy (GASE). These scales are also very similar to the aspecific Patient's Global Impressions of Severity scale (48), which has been widely used in many areas of medicine including migraine (49, 50). In a Canadian cohort of patients with migraine, around one in ten patients with episodic migraine and one in three with chronic migraine rated their disease as 'very severe' or 'extremely severe' using the GAMS (23).

3. Migraine control

Instruments for assessing migraine control essentially correspond either to instruments for determining response to acute migraine treatment or to criteria for identifying refractory migraine (Table 2). With respect to response to acute headache treatments, a checklist was originally developed by a working group commissioned by the French health authorities (ANAES) in 2002 (51) for the purposes of ensuring that patients who would benefit from prescription of triptans were indeed prescribed them. Use of the checklist was subsequently revised in 2014 and incorporated into practice guidelines for the treatment of migraine developed by the French Headache and Migraine Research Society (*Société française d'études des migraines et des céphalées; SFEMC*) (52), as a tool to monitor treatment response. The ANAES checklist was also used in the subsequent development of the Migraine-Treatment Optimization Questionnaire (MTOQ) in North America (53). The current ANAES/SFEMC checklist consists of four closed questions on response to acute headache medication. It is recommended that, if the reply to at least one of the questions is 'No', then treatment should be changed and that the checklist be completed three months after any change in treatment. The MTOQ included criteria similar to the four original ANAES criteria, with slightly different wording, notably to specify the length of time for which a single medication intake should be effective, and added a fifth global criterion (*Are you comfortable enough with your migraine medication to be able to plan your daily activities?*) derived from the Migraine-ACT questionnaire (see below) (53). For each 'No' response, different options for treatment optimisation are proposed. The MTOQ also exists in a fifteen-item version for research purposes.

Table 2. Instruments for assessing migraine control

	Scope	No of items	Rater
ANAES/SFEMC criteria	Response to acute headache medication	4	Patient
MTOQ	Response to acute headache medication	5	Patient
Migraine-ACT	Symptom control, consistency of response	4	Patient
MTAQ	Symptom control; medication use, impact	9	Patient
HURT	Symptom control; medication use, impact	7	Patient

ANAES: Agence nationale d'accréditation et d'évaluation en santé; SFEMC: Société française d'études des migraines et des céphalées; MTOQ: Migraine-Treatment Optimization Questionnaire, MTAQ: Migraine Therapy Assessment Questionnaire; Migraine-ACT: Migraine Assessment of Current Therapy; HURT: Headache Under-Response to Treatment.

The Migraine Assessment of Current Therapy (Migraine-ACT) has much in common with the ANAES/SFEMC and MTOQ. This short four-item questionnaire was developed from a longer, 27-item questionnaire by an international team of headache specialists (54, 55). One or more 'no' answers may indicate the need to change treatment. An increasing number of 'no' answers indicates increasing treatment needs. Reductions in Migraine-ACT following a change in treatment were reported to be well correlated with improvements in MIDAS disability and quality of life scores (54).

The Migraine Therapy Assessment Questionnaire (MTAQ) (56) was developed by the US Headache Consortium in the early 2000s as a disease management tool to identify individuals whose migraine management may be suboptimal. The MTAQ contains seven questions to be answered with a Yes or a No. However, the MTAQ is not simply a treatment response questionnaire, but also addresses aspects of disease impact and medication use. Most recently, the Headache Under-Response to Treatment (HURT) questionnaire has been

developed under the aegis of the WHO's Global Campaign against Headache (57). This is a patient-reported outcome measure consisting of seven items scored on five-point Likert scales and an eighth question on diagnosis. Again, this questionnaire contains items relating to different aspects of disease, including severity, which do not all directly address control of migraine. Based on the profile of response to these questions, recommendations for the physician are made with respect to adjusting treatment if necessary.

None of the above questionnaires or checklists have yet been widely used for research purposes, in particular for identifying optimal treatment strategies for acute headache relief. However, they may be used more widely in certain countries for determining treatment response in everyday clinical practice.

The other class of instruments in this field are instruments to identify refractory migraine. This is a somewhat different notion to that of migraine control, in that implies that migraine cannot be controlled whatever the treatment, whereas uncontrolled migraine can potentially be controlled by a change in treatment.

The notion of refractory migraine is most useful with respect to response to preventive medication. In this respect, consensus statements on refractory migraine have been published by working groups from the American Headache Society (AHS) in 2008 (58) and from the European Headache Federation (EHF), most recently in 2020 (59). The AHS criteria for defining pharmacologically intractable headache are common to episodic and chronic migraine. The definition requires failure of at least two classes of preventive treatment and failure of at least three classes of acute headache medication, together with a severity criterion requiring 'significant interference with function or quality of life', defined as a MIDAS score >11. Using this definition, patients with refractory migraine accounted for

around 5% of patients attending a Spanish headache clinic although, of the patients with chronic migraine, 75% were treatment refractory (60). This definition of refractory migraine was not retained in the subsequent ICHD-3 headache classification system (61), although it has been used as an eligibility criterion to identify patients with refractory migraine for clinical trials (62). Various subsequent proposals have been made to define more precisely the type or number of preventive treatments that should have failed before the migraine can be considered refractory (17, 63, 64).

The 2020 EHF classification (59) identifies two types of uncontrolled migraine, namely resistant and refractory migraine. Resistant migraine was defined by having failed at least three classes of preventive medication, given at an adequate dose, and suffer from at least eight debilitating headache days per month for at least three consecutive months without improvement. Refractory migraine is defined by having failed all available preventive treatments and suffer from at least eight debilitating headache days per month for at least six consecutive months.

A different approach has been taken by Silberstein et al. (65) who, in 2010, proposed a system for classifying migraine control based on treatment response. Patients are classed into one of three (acute treatments) or four classes (preventive treatments) based on the number of acute and preventive medication types to which the patient is unresponsive. The classification system is then used to guide the decision as to whether the patients should be sent to a specialist headache centre, or even hospitalised. Patients who qualify for Class II or higher for both acute medication (failure to respond to ≥ 2 non-specific medication classes and ≥ 1 specific medication class) and preventive medication (failure to respond to ≥ 2 medication classes including ≥ 1 well-validated treatment, taken from a prespecified list) are

considered to warrant referral to a specialist headache centre. However, a limitation of this system is that no criteria are proposed to identify what constitutes a “response to treatment”.

4. Proposals

4.1. Scope

As mentioned previously, the motivation for these proposals stems from the need for standard definitions of migraine severity and of control that can be used to identify patients with highly disabling disease who need to be oriented to specialist migraine centres where they can be evaluated, treated and monitored. For this reason, the proposed criteria are designed to be used by a health care professional, typically a general neurologist or a primary care physician. The definition is based on criteria that can be evaluated from the patient's history. The proposed approach in no way precludes self-evaluation by the patient, and the GAMS questionnaire has been developed for this purpose (23) (see above). As discussed above, this definition is restricted to patients fulfilling the ICHD-3 diagnostic criteria for migraine with aura (ICHD-3 code 1.1), migraine without aura (1.2) and chronic migraine (1.3) (61). Medication-overuse headache is excluded since it is not a primary headache (ICHD-3 code 8.2) and the care protocol is quite different.

4.2. Proposed definition of migraine severity

The proposed definition for severe migraine combines a criterion of headache frequency and one of headache impact. We have set the minimum duration for which the criteria have to be fulfilled at three months since, in our opinion, this is the minimum period necessary to estimate reliably the stability of migraine severity over time.

The threshold for frequent headaches has been set at ≥ 8 migraine days a month in order to capture patients who are at risk for developing medication overuse headache (ICHD-3 code 8.2), which is defined as triptan use on ≥ 10 days per month (or NSAID use for ≥ 15 days per month) for a period of over three months (61). In addition, recent studies have

shown that headache impact is similar in patients with high frequency episodic migraine (≥ 8 or ≥ 10 migraine days a month) and in those with chronic migraine (66, 67). These at-risk patients are in need of more intense management, including prescription of a preventive treatment, to ensure adequate migraine control and thus prevent progression to medication-overuse headache (68). However, the choice of threshold at ≥ 8 migraine days a month is an arbitrary one, and further studies would be required to determine whether or not this is the optimal one.

While frequent migraine headaches are generally associated with a high level of disability in episodic migraine (69), we recognise that a minority of patients with infrequent headaches may report substantial impact, for example in the case of severe catamenial migraine. For this reason, we propose to include in the severe migraine definition a disability criterion for patients who do not fulfil the headache frequency criterion. For this disability criterion, the HIT-6) is the instrument recommended in French practice guidelines for evaluating headache impact (52). For the present purpose, the HIT-6 appears superior to the MIDAS, as the latter measures disability in terms of number of days of lost productivity and so is to some extent commensurate with the frequency criterion. The HIT-6 in contrast measures impact independently of headache frequency. The threshold of ≥ 60 corresponds to the definition of severe impact proposed by the developers of this measure (22). The need for complete cessation of activities during a migraine headache was also considered as an alternative criterion for severe impact. The proposed criteria for defining severe migraine are listed in Box 1.

BOX 1. Proposed criteria for defining severe migraine

Headaches fulfilling either criterion A or criterion B for at least three months

- A.** Headache frequency of at least eight migraine days per month¹
- 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 $\geq 50\%$ of headaches

¹These patients are identified as severe since they are at risk for developing medication overuse headache.

4.3. Proposed definition of migraine control

Regarding the criteria for headache control when using treatment, both acute treatment failure and preventive treatment failure are considered. For acute headache treatments, control is defined using the checklist recommended in the SFECM/ANAES practice guidelines for the treatment of migraine (52), since these are the recommendations currently in place in France. However, we recognise that the medication intake criterion may be interpreted broadly, taking into account the experience of the patient. If the headache duration is long, a second medication intake may be required and may be well accepted by the patient, and this may be considered to provide acceptable control. This follows the revision of this criterion proposed in the MTOQ (53).

For migraine prevention, the criteria are inspired by the definition of treatment-resistant migraine proposed in the 2020 EHF classification (59) with two important qualifiers. Firstly, in the EHF classification, resistant migraine is defined by having failed at least three classes of preventative treatments. A list of eleven medication classes are proposed.

However, the strength of the evidence base for efficacy of these treatments varies widely and, in addition, certain are not marketed in France or approved for migraine prevention. In our proposal, we suggest that, in order for migraine to be definitively considered uncontrolled, beta blockers and topiramate should have been offered and shown to have failed, these being the only approved treatments with a robust demonstration of efficacy for migraine prevention in France. However, we recognise that the list could be adapted for other countries where other effective preventive medications are available, such as antidepressants.

The second qualifier related to the definition of treatment response. The EHF classification considers migraine resistance to be the persistence of at least eight debilitating headache days per month for at least three consecutive months without improvement (59). However, the magnitude of the response considered as 'improvement' is not defined. We propose a definition of response to a preventive treatment as a reduction in headache frequency of <50% in episodic migraine or 30% in chronic migraine. These are the definitions of treatment response that were used in the Phase III clinical trials of topiramate (70-72) and in the principal migraine prevention trials performed since then with, for example, anti-CGRP therapies (11), and are recognised as a clinically-relevant threshold by health authorities. Finally, all medications should be given in accordance with the optimal treatment regimen, be well-tolerated, meaning that any side-effects of medication are acceptable for the patient, and none of the treatments should be contra-indicated. The proposed criteria for defining migraine control are listed in Box 2.

BOX 2. Proposed criteria for defining migraine control

Headache treatment fulfils criterion A, as well as criterion B if patient is taking medication for migraine prevention, and criterion C for both acute and preventive treatment.

- A.** Acute headache relief treatment¹ taken within one hour provides effective response, as defined by all of the following:
1. Do you obtain significant headache relief 2 hours after taking medication?
 2. Do you require only a single intake of medication for headache relief?²
 3. Is this treatment effective over at least two attacks out of three?
- B.** Migraine prevention therapy³ provides effective response, as defined by one of the following:
1. Reduction in headache frequency of at least 50% in episodic migraine
 2. Reduction in headache frequency of at least 30% in chronic migraine
- C.** All headache treatment used fulfils all of the following:
1. No contra-indication to the medication
 2. Medication given as an optimal treatment regimen (dose,³ timing, route of administration) for at least three months
 3. Medication well tolerated by the patient⁵

¹A triptan should have been tested before the headache is definitively considered uncontrolled.

²More than one intake may be considered acceptable if the inter-dose interval is large and if this is considered acceptable by the patient.

³Topiramate and a β -blocker should have been tested before the headache is definitively considered uncontrolled.

⁴A list of recommended doses is provided in the Supplementary Material online.

⁵Well-tolerated is defined as the absence of adverse events or the presence of adverse events which are considered acceptable by the patient.

4.4. Place in the management of migraine

When a person with migraine first consults, it will not generally be possible for the general practitioner to assess the severity of the migraine and an acute headache relief treatment will be prescribed. Current French management guidelines (52) recommend that patients consulting for migraine complete a headache diary and this should enable the frequency and impact of headaches to be established after a few months. On this basis, it should be possible to determine whether the migraine headaches are severe or not, either on the basis of the frequency criterion or the impact criterion. If the impact criterion is fulfilled, then we would propose as a first step to optimise the acute headache medication regimen. Optimisation should include testing a triptan, if this has not been tried previously, and whether this is the case or not, it should be ensured that the dose is appropriate and that the patient is taking the medication as soon as possible after headache onset. If this is the case, then the patient can be switched to another triptan, or a non-steroidal inflammatory drug added. If, after two or three months, this succeeds in controlling the headaches then the patient can continue with this regimen. If optimisation of acute headache treatment fails to provide adequate migraine control, then a preventive treatment should be provided.

If the frequency criterion is fulfilled, regardless of whether acute treatment is effective or not, it is proposed to initiate preventive treatment immediately in order to limit the risk of developing medication overuse headache. In addition, it is not expected that optimising the acute treatment regimen would have an impact on headache frequency, and the disease can already be considered to be severe and to require preventive treatment. However, it is important in parallel to ensure that the acute headache medication regimen is optimised, if this is not the case, in order to attenuate symptoms and to reduce the functional impact of the headaches.

First-line migraine prevention treatment can generally be managed in primary care, although in some cases the general practitioner may prefer to refer the patient to a general neurologist. In all cases, if the migraine fulfils the severity criteria, comorbidities and environmental and psychological risk factors should be evaluated and remedial action taken wherever necessary. In particular, diet, alcohol, sleep hygiene and stress should be evaluated since these are modifiable risk factors for migraine (73). Comorbidities frequently observed in patients with migraine include psychiatric disorders (notably anxiety and depression), sleep disorders, cardiovascular disorders and respiratory disorders (74). These should be carefully investigated, firstly since they may be aggravating factors for migraine severity itself, and secondly since they are deleterious to general health.

After three months of preventive treatment, the patient can be reassessed and if migraine is still uncontrolled, the preventive treatment should be changed. Topiramate or a β -blocker should be considered if they have not already been tried. If at the end of the second treatment the patient is still uncontrolled, then, and only then, should the patient be referred to a specialist headache centre. This is consistent with the recent EHF practice

guidelines (59) which recommend that patients with resistant migraine be referred to a migraine specialist. Since there is no recommended care management pathway for migraine in many countries, including France, the delay to referral is expected to be variable, depending on the individual patient's treatment history and on the healthcare resources available locally. However, we believe that failure of two adapted preventive treatments should be a trigger for referral of the patient to a specialist headache centre. Application of the proposed care algorithm is anticipated to shorten overall referral times for these patients who are difficult to treat and to reduce the time required to achieve satisfactory migraine control.

In the specialist headache centre, it will be important to verify that the patient had received optimised acute headache medication and preventive treatment in accordance with guidelines (52), to evaluate the possibility of the patient presenting medication-overuse headache (75, 76) and to adjust medication if necessary. Non-pharmacological treatment should be proposed, for example relaxation techniques, sophrology, biofeedback or cognitive behavioural therapy. Patient education and patient support at home and in the workplace should also be taken into account.

Once treatment has been optimised, the control criteria can be used on a regular basis (for example every three to six months) to assess whether migraine is controlled satisfactorily or not. If control is acceptable, preventive treatment should be continued for at least six months while lifestyle factors that influence the occurrence of migraine are addressed. If control remains acceptable, withdrawal of preventive treatment may be considered. In case of inadequate control, a full social, familial, cognitive, environmental and

psychological assessment should also be performed with the goal of identifying predisposing factors that could be addressed in order to improve migraine control (Figure 1).

5. Perspectives

The definitions of severe migraine and migraine control proposed above is based on the opinion of migraine specialists rather than evidence (which is not yet available). For this reason, they will need to be validated in clinical practice. To this end, several suggestions can be made. In particular, the internal validity of the severity definition could be tested by comparing the performance of the migraine severity definition with self-assessment using a patient-reported outcome measure such as the GAMS (23). The GAMS could also be used to test how well different thresholds of headache frequency (for example, ≥ 8 or ≥ 10 migraine days a week (66, 67) discriminate patient perceptions of migraine severity. It should also be borne in mind that the current proposal was developed by a small group of migraine specialists and that others may have another vision of how this issue should be addressed. For this reason, it would be useful to explore how this proposal could be improved through a consensus method such as the Delphi process (77). In principle, it may be possible to test the utility of the algorithm in a clinical study evaluating outcomes, such as proportion of patients controlled, time to migraine control, or time to referral to a specialist headache centre, by comparing a group of physicians strictly applying the algorithm and another following their routine practice. However, conducting such a study may be challenging.

Another important research question to address is to what extent the definitions of migraine severity or migraine control is stable over time. Such a definition will also help quantify the associations between social precarity or impact on family life on the one hand and migraine severity on the other, associations which have been suggested previously from qualitative research (78-80). A similar approach could be applied to quantifying associations between severe migraine and certain comorbidities.

Apart from its use in optimising care of patients with severe migraine, we believe that establishing a standardised definition of migraine severity, such as that proposed above, will be of use in a number of other contexts. Firstly, in epidemiological studies it can be used to determine the number of patients with migraine with severe disease. This information is important for health authorities in allocating resources for management of these patients in specialist pain centres. In addition, the information will be useful to determine the target population for the several new medications that will become available for migraine prevention in the near future. The availability of such a definition could also be useful from a health insurance perspective for identifying patients eligible for long-term disability or professional handicap status.

The most important application of a standardised definition of migraine control, the current proposal or any other validated one, would be to identify optimal treatment algorithms for migraine prevention. French practice guidelines (52) recommend starting preventive treatments taking into account headache frequency and intensity and of the resulting professional, family and social handicap, although no thresholds are provided, and when acute headache medication is being used on more than two days a week. However, currently available information, for example from the SMILE study (81), a large survey of general practitioners and neurologists in France, suggests that preventive treatment is not prescribed in a standardised way. To improve this situation, we propose that fulfilling the migraine severity criteria could be used as a yardstick for starting migraine prevention and failure to fulfil the migraine control criteria as a yardstick for changing preventive medication.

Currently, there is little information available regarding which preventive treatments, and in which sequences, provide optimal migraine control, and this situation will become more complex with the imminent introduction of several new medications. This situation emphasises the need for tools and for evidence-based guidance to inform treatment decisions for patients with severe migraine. In the long run, it should be possible to develop a stratified approach in which the therapeutic pressure can be increased in steps (switching or combining medications) so that disease control can be achieved whatever the severity, such as has been used to great success over the last decade in the field of asthma. The development of standard definitions of migraine severity and control is a prerequisite for moving forward in this direction.

It should be noted that we have performed this evaluation of defining migraine severity and control in the context of the French health system. It is possible that treatment pathways, treatment guidelines and treatment options may differ in other countries and it will be important to receive feedback on whether the proposed definition of migraine severity is universally applicable, or whether it needs to be adapted to take into account current practice in other healthcare systems.

6. Conclusions

Migraine lags a long way behind other debilitating chronic episodic diseases such as epilepsy and asthma in terms of developing a holistic approach to disease management, notably with respect to developing and testing strategies for management of severe disease with appropriate and effective preventive treatment strategies. A prerequisite for moving forward is to establish a definition and criteria for migraine severity and migraine control. We believe that the above proposals may contribute to this debate. With the anticipated introduction of new possibilities for migraine prevention in the near future, the time is ripe for a holistic approach to migraine management.

Figure Legend

Figure 1. Proposed management strategy based on severity and control assessment.

See text for further details.

HIT: Headache impact test; CM: chronic migraine; EM: episodic migraine; NSAID: non-steroidal anti-inflammatory drug.

NOTE: The involvement of different health care professionals indicated on the right is for illustration only. The relative roles of these in the management of migraine varies considerably.

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Frequency criterion

- Headache frequency ≥ 8 migraine days/month

Impact criterion

- HIT-6 score ≥ 60
- OR Complete interruption of activity for $\geq 50\%$ of headaches

Acute treatment optimisation

- Check that dose is appropriate
- Check that treatment is taken early
- IF NOT Switch triptan
- OR Add NSAID

Control (acute treatment): efficacy criteria

- Significant headache relief after 2h
- Single intake of treatment needed
- Effective in at least 2 of 3 attacks

Control (prophylaxis): efficacy criteria

- Headache frequency reduced by $\geq 50\%$ in EM
- Headache frequency reduced by $\geq 30\%$ in CM

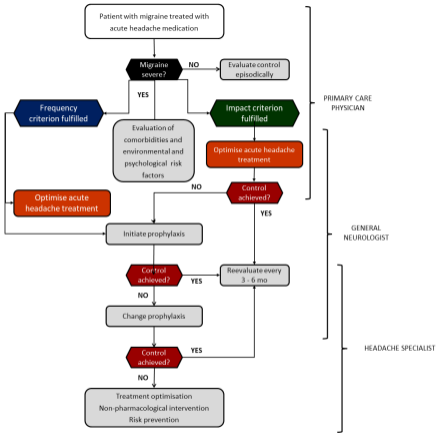


Figure 1