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Refractory Migraine

Defining Refractory Migraine and Refractory Chronic Migraine: Proposed Criteria From the Refractory Headache Special Interest Section of the American Headache Society

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Certain migraines are labeled as refractory, but the entity lacks a well-accepted operational definition. This article summarizes the results of a survey sent to American Headache Society members to evaluate interest in a definition for RM and what were considered necessary criteria. Review of the literature, collaborative discussions and results of the survey contributed to the proposed definition for RM. We also comment on our considerations in formulating the criteria and any issues in making the criteria operational. For the proposed definition for RM and refractory chronic migraine, patients must meet the International Classification of Headache Disorders, Second Edition criteria for migraine or chronic migraine, respectively. Headaches need to cause significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive medicines with established efficacy. The definition requires that patients fail adequate trials of preventive medicines, alone or in combination, from at least 2 of 4 drug classes including: beta-blockers, anticonvulsants, tricyclics, and calcium channel blockers. Patients must also fail adequate trials of abortive medicines, including *both* a triptan *and* dihydroergotamine (DHE) intranasal or injectable formulation and *either* nonsteroidal anti-inflammatory drugs (NSAIDs) *or* combination analgesic, unless contraindicated. An adequate trial is defined as a period of time during which an appropriate dose of medication is administered, typically at least 2 months at optimal or maximum-tolerated dose, unless terminated early due to adverse effects. The definition also employs modifiers for the presence or absence of medication overuse, and with or without significant disability.

Key words: migraine, chronic migraine, refractory, intractable, definition, classification

Abbreviations: AHS American Headache Society, ICHD International Classification of Headache Disorders, MOH medication overuse headache, MIDAS Migraine Disability Assessment Score, R-CM refractory chronic migraine, RH refractory headache, RHSIS Refractory Headache Special Interest Section, RM refractory migraine

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INTRODUCTION

Despite advances in headache therapies, there remains a group of sufferers with refractory (intractable, treatment-resistant) headache who fail to respond to or cannot tolerate current evidence-based treatments. Although the concept of refractory headache (RH) has a long history, there have been few attempts to formalize an operational definition. The International Classification of Headache Disorders, Second Edition (ICHD-2)[1] does not include a definition for RH. Goadsby et al[2] was first to propose specific criteria for intractable migraine and cluster

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headache. The International Classification of Diseases, Ninth Revision, Clinical Modification[3] includes "intractable" as a modifier for both migraine (including migraine variant, atypical migraine, migraine variant posttraumatic) and cluster headache, but does not include criteria for use of the modifier. A well-accepted definition would be useful in epidemiological research and in the identification of patients requiring an enhanced level of medical care.

The Refractory Headache Special Interest Section (RHSIS) of the American Headache Society (AHS) has endeavored to develop criteria for both refractory migraine (RM) and refractory chronic migraine (R-CM). The process has included an Internet survey of AHS members, the appointment of a Ad Hoc Definition Committee, and the production of this Special section of *Headache*. In this article, we review the results of the survey and present our current working operational definitions for RM and R-CM.

Internet Survey of AHS Members on RH.—In March 2006, the members of RHSIS sent a 16-question, self-administered Internet questionnaire to 1261 AHS members. The survey was designed to gauge the interest of AHS members in RH, to assess the perceived need for a formal RH designation, and to gather ideas for formulating a definition. Respondents were asked for their opinion regarding appropriate criteria for RH, including headache frequency, degree of disability, response to medications, and the medical settings for diagnosis. Also queried were beliefs about pathophysiology, whether RH should be added to the ICHD-2 classification, and interest in attending a course on the subject. Finally, practitioners were also asked how they currently treat this subset of headache patients and which treatments they believed to be most effective.

The RHSIS survey generated the highest response rate to any AHS Internet survey, with 220 members (17%) returning responses. Of the respondents, 78.9% believed the definition should include an inadequate response to multiple abortive and preventive medications. Almost two-thirds of the respondents (63.6%) believed that an RH definition should be limited to headache occurring 15 days or more per month, and 55.3% believed it should be associated with disability. When asked if RH should be added to the ICHD-2 classification system, 57.5% believed it should be added, while 8.5% determined it should not, and 34% were unsure. More than 4 out of 5 respondents (83.6%) expressed interest in further education on RH, such as a focused RH course at the AHS Annual Meeting.

Development of Proposed Criteria for RM and R-CM.—The RHSIS charged a subcommittee (the authors of this manuscript) with formulating a definition for RH, beginning with what is believed to be the most prevalent forms: RM and R-CM. We agreed that the definition should be operational in nature, attempt to have worldwide applicability, and also address disability. Most importantly, we hoped it would expedite appropriate care in RM patients. There was consensus that the definition should address both the use and effectiveness of acute and preventives medications with modifiers for disability and medication overuse.

The proposed criteria were formulated by consensus of the subcommittee. Tools in crafting the criteria included the results of the Internet survey, a review of the literature and collaborative discussions (Table).[4] Although not included in the proposed criteria, it is implicit that the headache diagnosis is accurate and the patient has been compliant with the failed treatments. The following text provides commentary on each element of the proposed definition.

Primary Diagnosis.—ICHD-2 migraine or chronic migraine. The group agreed that limiting our definition to RM was an appropriate starting point and that incorporating additional primary headache disorders into the definition would add complexity. In addition, modifiers such as medication overuse headache (MOH) already exist. There are formal guidelines in place for the treatment of migraine, although they will almost certainly require some modification in the RM patient.

Refractory.—Headaches must cause significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive medicines with established efficacy. We agreed that to be refractory, a headache must impair quality of life. We did not set a threshold for headache frequency, as some individuals with relatively infrequent migraines may

Table.—Proposed Criteria for Definition of Refractory Migraine and Refractory Chronic Migraine

Criteria	Definition
Primary diagnosis	A. ICHD-II migraine or chronic migraine
Refractory	B. Headaches cause significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive medicines with established efficacy 1. Failed adequate trials of preventive medicines, alone or in combination, from at least 2 of 4 drug classes: a Beta-blockers b. Anticonvulsants c. Tricyclics d. Calcium channel blockers 2. Failed adequate trials of abortive medicines from the following classes, unless contraindicated: a. *Both* a triptan *and* DHE intranasal or injectable formulation b. *Either* nonsteroidal anti-inflammatory drugs *or* combination analgesics
Adequate trial	Period of time during which an appropriate dose of medicine is administered, typically at least 2 months at optimal or maximum-tolerated dose, unless terminated early due to adverse effects
Modifiers	With or without medication overuse, as defined by ICHD-2 With significant disability, as defined by MIDAS ≥11

DHE = dihydroergotamine; ICHD = International Classification of Headache Disorders; MIDAS = Migraine Disability Assessment.

be refractory to treatment. Although all possible triggers may not be eliminated (eg, weather change), those that are modifiable should be addressed and avoided. Certain lifestyle factors such as stress and mood disorders should be optimized.

The committee debated whether an adequate trial of behavioral treatment should be included in the definition. Although a number of meta-analytic studies have shown that biofeedback, relaxation, and cognitive–behavior therapy are efficacious for migraine,[5] behavioral treatments are less accessible than pharmacological treatment and more variable in their application. We therefore elected to define "refractory" as failure of the most commonly available pharmacological treatments with recognized efficacy.

We decided to include both acute and preventive agents, as one alone would not constitute optimal treatment. Adequate trials of prophylactic agents were defined (see below). Acute agents should be tried in adequate doses, as early as possible, and in sufficient trials to establish efficacy.

1. Failed adequate trials of preventive medicines, alone or in combination, from at least 2 of 4 drug classes: (1) beta-blockers; (2) anticonvulsants; (3) tricyclic antidepressants; (4) calcium channel blockers. The specific classes were picked because they have shown clinical efficacy in evidence-based guidelines for migraine prevention.[6] The group struggled with determining the number of preventive medicine classes necessary before meeting the criteria for RM. For example, some argued that a patient should have failed a drug from each of the 3 best evidence-based classes (beta-blockers, anticonvulsants, and tricyclics), noting weaker evidence for calcium channel blockers. While a trial in each class is preferable, the optimal definition may depend upon the consequences of receiving the label "refractory." For example, if this designation leads referral to a higher level of care (ie, referral to headache center), then time needed to evaluate the effectiveness of each agent separately may inappropriately delay referral. Polypharmacy may be a more effective treatment option, including a simultaneous trial of medications from more than one category.
2. Failed adequate trials of abortive medicines from the following categories, unless contraindicated: (1) *both* a triptan *and* dihydroergotamine (DHE) intranasal or injectable formulation; (2) *either* nonsteroidal anti-inflammatory drugs (NSAIDs) *or* combination analgesics. A patient may not respond to a triptan and yet may respond to DHE, regardless of formulation. Trials on both a triptan and

DHE, regardless of formulation, are a reasonable threshold. We agreed that NSAIDs or combination analgesics were effective agents in individuals. They are also more accessible in third world countries where triptans are limited in choice or unavailable. Finally, some patients have a medical contraindication to triptans and DHE. This led to the caveat of including the qualifier "unless contraindicated," effectively lowering the threshold for meeting the criteria.

Adequate Trial.—An adequate trial is defined as a period of time during which an appropriate dose of medicine is administered, typically at least 2 months at optimal or maximum-tolerated dose, unless terminated early due to adverse effects. Trials of a preventive 2 months in length were considered the shortest time before labeling a drug ineffective, especially with gradual upward titration. Although longer trials would be preferable, it was agreed this time frame would prolong the time necessary to meet refractory criteria, and could prevent patients receiving the appropriate level of care.

Modifiers.—Modifiers include the following:

1. With or without medication overuse (MOH), as defined by ICHD-2 (new appendix criteria open for a broader concept of chronic migraine).[7] Ideally, for migraine to be identified as refractory, patients should be withdrawn from medications with the potential for causing MOH. The group debated this point but elected in this preliminary proposal to leave MOH as a modifier. This modifier exists in the ICHD-2. In addition, the new criteria for chronic migraine no longer require that the headaches revert to a more episodic form after drug withdrawal in order to meet criteria for MOH.[7] Patients with chronic migraine and MOH now have 2 diagnoses. Some patients do undergo drug withdrawal, may remain abstinent from the offending medication for several months, remain refractory, and return to overuse of analgesics or abortives. This group would be classified as R-CM with MOH, and we believe it should be distinguished from R-CM without MOH. Also, because this definition was to have worldwide application, it may not be practical to avoid medication overuse in a less developed country. Using it as a modifier is a reasonable compromise.

2. With significant disability, as defined by Migraine Disability Assessment Score (MIDAS) of 11 or higher. There was a general agreement that disability must be addressed in the definition. The MIDAS was selected because it is widely used, well accepted as a valid and reliable measure of disability, and was highly correlated with physicians' perceptions of the need for medical care.[8] The extent of disability may be a factor in deciding the appropriate level of care.

DISCUSSION

The Committee recognizes that the optimal definition of RH is determined by the context of diagnosis and the consequences of assigning this label in that context. If the consequence of labeling is referral to a specialist, the diagnostic threshold should be lower than if the consequence is use of a high-risk invasive treatment.

There are several shortcomings of this definition. Some of the aspects remain conceptual, despite the goal for the criteria to be operational. For example, "impairment in quality of life" is admittedly defined in broad terms. A more formal definition might involve specific cut-scores on a specific health-related quality of life (HRQoL) measure. We suspect that the choice of measure and cut-score might be controversial. The disability modifier could be qualitative, evidence that the headaches significantly interfere with a patient's ability to work, attend school, or participate in family or social activities. There may be contention about what MIDAS score would equate to the level of significant disability to meet the modifier criteria. In spite of this limitation, one advantage of a standardized measure for the disability modifier is the potential to measure a significant improvement in functional performance, despite continued intractability of the pain. In fact, this has long been an important goal in some forms of behavioral treatment.

What constitutes sufficient "improvement" from a preventive? A possible operational definition might be a sufficient improvement after preventive treatment so that adding a different or additional preventive would not be necessary. However, even the

accepted criteria for a prophylactic agent are vague and need to be individualized. "Lack of response" to acute medicine is more descriptive than a definitive parameter. Is achieving a sustained pain-free state a reasonable endpoint? Although this is a high threshold, shouldn't we expect this for our patients?

These criteria are meant as a starting point. We expect this to be a work in progress. The operational criteria will depend upon where the physician and patient live and what will be done with individuals whose headaches are labeled refractory. We acknowledge that there will undoubtedly be criticisms, which may lead to further modification and improvement of the proposed definition. Adequate field-testing will bring some of the deficiencies to light. It is our hope that these proposed criteria will stimulate further clinical and scientific attention to the nature of RM, its prevalence, and how best to treat those who suffer with it.

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