

## Views and Perspectives

### Defining the Pharmacologically Intractable Headache for Clinical Trials and Clinical Practice

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The terms refractory headache and intractable headache have been used interchangeably to describe persistent headache that is difficult to treat or fails to respond to standard and/or aggressive treatment modalities. A variety of definitions of intractability have been published, but as yet, an accepted/established definition is not available. To advance clinical and basic research in this population of patients, a universal and graded classification scheme of intractability is needed, and must include a definition of failure, to which and how many treatments the patient has failed, the level of headache-related disability, and finally, the intended intervention (clinical or research) and intensity of the intervention. This paper addresses each of these variables with the intent of providing a graded classification scheme that can be used in defining intractability for clinical practice interventions and clinical research initiatives.

**Key words:** intractable headache, refractory headache, migraine, clinical trial

(*Headache* 2010;50:1499-1506)

#### DEFINING INTRACTABLE HEADACHE

The terms refractory headache and intractable headache have been used interchangeably to describe a variety of clinical symptoms associated with persistent headache that is difficult to treat or fails to respond to standard headache treatments. The common definition for “intractable” is not to be guided; not manageable or docile; uncontrollable; refractory, stubborn.<sup>1</sup> In review of the headache literature, these terms have been used interchangeably as their definitions appear to overlap. Establishing a

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Accepted for publication July 15, 2010.

consistent nomenclature is important and herein, the term intractable headache is used as a single and preferred term to describe this group of patients with headache that is hard to treat, relieve, or cure.

A clear understanding of the pathophysiological mechanisms underlying intractable headache are lacking; therefore, establishing a definition or classification scheme based on mechanism(s) is not currently possible. Diagnosis of intractable headache therefore is based on the response to either acute or prophylactic therapy, or both, the level of headache-related disability. Moreover, any classification scheme of intractability must be graded according to the *type and number of treatments* to which the patient is refractory (eg, acute and/or preventive), the

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*Conflict of Interest:* Metronic, Inc. provided educational support for this project. S.D. Silberstein and D.W. Dodick serve as advisors and clinical research participants for Metronic, Inc. S.H. Pearlman received consulting honoraria for her participation in this project.

*clinical setting* (eg, primary care vs tertiary specialty care), the *intervention* for which the term intractable is being used (eg, referral to a specialist; enrollment into prophylactic drug study), and the *intensity* of the intervention (eg, hospitalization; enrollment into a device or intracranial surgery trial). This paper addresses each of these variables with the intent of providing a graded classification scheme that can be used in defining intractable headache for clinical practice interventions and clinical research initiatives.

### **DEFINING INTRACTABLE HEADACHE FOR CLINICAL RESEARCH: THE RATIONALE**

Investigators, regulatory authorities and members of the pharmaceutical industry worldwide have struggled with creating a definition of intractability that can be used to determine patient eligibility for headache clinical trials. Most clinical trials have involved subjects meeting clear diagnostic criteria for migraine, chronic tension-type headache (CTTH), chronic migraine, or even cluster headache. The frequency of these attacks, response to previous therapies, and levels of disability are all included in the previous definitions.

However, the definition of intractability used for clinical trials has differed resulting in the inclusion and exclusion of different populations of patients.<sup>2-5</sup> This precludes treatment comparisons and the ease with which study results can be generalized. When patients are recruited for a procedural study, such as patent foramen ovale (PFO) closure, peripheral or deep brain stimulation, or pharmacological investigative trials, it is important that the definition of intractability used to determine eligibility match the intensity or invasiveness of the treatment modality. It is also important that the same definitions are used across studies so that target populations of patients are easily identified in clinical practice, and the results of these trials appropriately incorporated into clinical practice. This is especially important since some regulatory agencies require replicate studies that show efficacy for approval. Furthermore, establishing an accepted classification of intractable headache is necessary for the development of treatment guidelines and evidence-based practice

parameters, which should be based on studies using homogenous patient populations with similar disease severity.

### **DEFINING INTRACTABLE HEADACHE IN CLINICAL PRACTICE: THE RATIONALE**

Intractable headache appears to be defined differently among different areas of specialty. For example, in the primary care setting, intractable headache may be defined based on failure to respond to 1 or 2 triptans, thereby providing an indication for a specialist referral. Alternatively, failure to respond to a generic triptan may be needed in order to qualify patients for insurance coverage of a branded triptan. Similarly, other patients may be classified as intractable following failure of 1 or more preventive medications, and failure to respond to 1 or more generic antidepressants (eg, tricyclic antidepressant [TCA], selective serotonin reuptake inhibitor [SSRI]) is often necessary before patients can get coverage for a newer branded serotonin-norepinephrine reuptake inhibitor (SNRI). In specialty practices, however, a different definition of intractable is often required for insurance carriers to approve hospitalization or procedural/surgical treatments (eg, occipital nerve block).

In primary, secondary, and tertiary care settings, intractability also needs to be defined according to treatment outcomes, failure to respond to treatment, disability, and the intended purpose of defining the headache as intractable (eg, hospitalization, specialist referral, etc.). While there are regional differences in health care delivery systems, reimbursement policies, and the availability of work-related disability benefits, patients in certain countries applying for disability or social security benefits may need to meet a definition of intractability, in addition to disability, to prove their condition is severe enough for temporary or permanent disability benefits.

Consequently, the variations in previous definitions of intractable headache and the lack of an appropriately graded classification scheme based on the clinical setting, the intended clinical intervention, and the intensity of the intervention, has made it difficult to determine which patients may warrant aggressive surgical or experimental protocols. Such a

classification scheme would serve as the basis for patient triage and treatment as well as determination of eligibility for clinical trials with study interventions that may vary considerably according to invasiveness, intensity, and therefore risk to the subject.

## REQUIREMENTS FOR DETERMINING INTRACTABILITY

**Headache Type.**—The specific headache type must be ascertained before assessing headache intractability. If the primary headache disorder is a primary headache, such as migraine, headaches must meet the specified diagnostic criteria such as International Classification of Headache Disorders – 2nd edition diagnostic criteria for migraine with or without aura.<sup>6</sup> Intractability can then be defined based on failure to respond to acute treatment, preventive treatment, aggressive inpatient/ambulatory infusion, or invasive therapies.

**Headache-Related Disability.**—The role of disability in defining and classifying intractable headache has not been clearly established. The term intractable headache by itself does not infer or reflect disability. If a headache is frequent and untreatable, but has no disabling impact on the patient, it may be appropriate to do nothing, but it still is considered as intractable. For example, some chronic primary headache disorders that are resistant to acute and prophylactic therapies (CTTH) may, in certain individuals, impose minimal disability, and such patients would not be considered for enrollment into a clinical trial of deep brain stimulation. However, a measure of disability using a validated instrument has been shown to correlate with the intensity of treatment required by the patient<sup>7</sup> and should be used in any classification scheme of intractable headache. Therefore, establishing a single standardized working definition that defines disability is also clearly warranted.

Common validated instruments used to identify patients with disability related to headache include the migraine disability assessment (MIDAS) tool<sup>8</sup> and the headache impact test (HIT-6) scale.<sup>9</sup> These 2 instruments identify those patients with mild, moderate, or severe headache-related disability. Establish-

ing clear criteria for levels of disability and illness severity is essential in order to identify which patients may or may not be best treated with invasive or experimental approaches.<sup>10</sup>

Herein, specific recommendations are proposed to further define when a patient with intractable headache may have or lack sufficient disability to warrant more aggressive treatment. For example, moderate or severe disability may be an indication for referral to a headache specialist. Those with severe disability may be considered for more aggressive treatment, such as hospitalization, or possibly participation in a clinical trial. Clearly additional studies are needed to further explore and define how the role of disability is assessed in patients with intractable headache, and how disability outcomes can be used as validated stratification measure in assessing illness severity and participation in clinical trials.

**Defining Treatment Failure in Intractable Headache.**—Lipton and colleagues proposed several reasons why standard headache treatments fail, and these reasons should be considered in the clinical evaluation of patients with treatment-resistant headache.<sup>11</sup>

1. Diagnosis is incomplete or incorrect.
2. Exacerbating factors are unrecognized: medication overuse; psychological conditions; hormone factors. This requires ascertainment of these factors, and in certain circumstances (eg, overuse of acute headache pain medications) stratification based on the variable.<sup>12</sup>
3. Pharmacotherapy is inadequate: too low a dose; incorrect dose escalation; inadequate duration of treatment; wrong type of medication; non-compliance. This often, but not always, requires obtaining medical records or accurate diary information.
4. Non-pharmacologic treatment is inadequate: cognitive and behavioral interventions; lifestyle modifications including sleep-wake schedule, caffeine consumption, alcohol consumption, medications that may exacerbate the disorder (eg, phosphodiesterase inhibitors, nitrates). In clinical trials these interventions need to be standardized.

5. Presence of risk factors or comorbid conditions: depression; obesity; anxiety; among others. Screening instruments are very useful for their identification.
6. Unrealistic expectations. In clinical trials outcomes are prespecified.

While trigger, behavioral and non-pharmacological management of patients is a staple of good clinical practice, incorporating all of these variables into a classification scheme, intended for clinical practice interventions or clinical trial eligibility would be complex, difficult to use, overly cumbersome, and bordering on prohibitive.

In acute headache treatment, headache intractability is defined by failure to respond to standard acute treatments, contraindications to acute treatments, or intolerance to the selected treatment. In preventive headache treatment, intractability is defined as failure to respond or contraindications/intolerance to standard preventive treatments. However, specific criteria for how many medications should be tried, the definition of failure (eg, <50% reduction in frequency or severity of headache attacks), and the duration of treatment required for determining failure is not well defined and varies throughout the literature. For example, D'Amico and colleagues do not consider it sufficient to try 1 medication of each pharmacological class (eg, 1  $\beta$ -blocker, 1 antiepileptic, etc) as suggested by Goadsby.<sup>13,14</sup> They proposed that a patient should have adequate courses of all first-line preventive drugs for episodic migraine as suggested by the International Guidelines,<sup>6</sup> and patients should be permitted to receive adequate courses of second- or third-line prophylactic treatments. Some state that different agents within a therapeutic class should be tried because they may work by different mechanisms.<sup>10</sup>

We propose a graded classification scheme of defining intractability to acute and preventive treatments based on the patient's previous response/failure to proven acute or preventive therapies (Table 1 or 2, respectively). Specifically, regarding intractability to acute medications, patients may meet 1 of 3 different groups (Table 1): Class I is defined as

**Table 1.—Defining Intractable Headache Based on Response to Acute Treatments**

Class	Previous Response to Therapy
Class I (mild)	Failure of adequate response to 2 different classes of non-specific acute treatments (eg, NSAIDs, combination analgesics)
Class II (moderate)	Above plus failure to respond to triptans or ergot derivatives.† If contraindicated, failure to respond to oral dopamine antagonists or parenteral NSAID
Class III (severe)	Above plus failure to respond to oral or parenteral opioids or corticosteroids or parenteral dopamine antagonists in adequate doses and appropriate formulation

†Ergot derivatives include dihydroergotamine (DHE).  
NSAID = non-steroidal anti-inflammatory drug.

mild and includes those who failed to achieve an adequate response to 2 different classes of non-specific acute treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) or combination analgesics. Class II is considered moderate and includes failure to respond to NSAIDs or combination analgesics along with triptans or ergot derivatives. If a patient has a contraindication for any of these types of medications, failure to respond to dopamine antagonists or antiemetics or parenteral NSAID may be substituted. Class III is considered severe and includes failure of NSAIDs or combination analgesics, oral or parenteral opioids or corticosteroids or parenteral dopamine antagonists.

Intractability to preventive medications may be stratified based on the number of medications tried. Class I is defined as failing an adequate trial of a commonly recognized and proven preventive therapy including  $\beta$ -blockers, tricyclic antidepressants, verapamil or flunarizine, sodium valproate (or divalproex sodium), topiramate, or combination therapies. Class II, or moderate, is defined as failing 2 of these agents noted above (or in Table 3). Class III is considered to be severe and includes failure of an adequate trial of 3 drugs noted above (or listed in Table 3). Class IV is considered to be very severe and includes those

**Table 2.—Defining Intractable Headache Based on Response to Preventive Treatments**

Class	Previous Response to Therapy
Class I (mild)	Failure of adequate treatment trial of any drug in Table 5 (may not be contraindication)
Class II (moderate)	Failure of adequate treatment trials of 2 drugs in Table 5 where 1 must be from a to f
Class III (severe)	Failure of adequate treatment trials of 3 drugs† in Table 5 where 2 must be from a to f
Class IV (very severe)	Above plus failed aggressive infusion or inpatient treatment and/or failure to respond to detoxification treatment in subjects with acute headache pain medication overuse

All must be of adequate dose and duration (drug contingent). †Failed medical management, defined as failure or contraindication (1 medicine only) to 3 preventive medications, where 2 must be of different types from a to f below. Failure is contingent on the headache disorder. For episodic migraine it is often defined as <50% reduction in frequency of headache days or attacks. For chronic migraine, treatment failure is defined as <30% reduction in headache days.<sup>19,20</sup> Headache day is defined as at least 4 hours of continuous pain with a peak intensity that is at least moderate severity.

patients who have failed aggressive infusion or inpatient treatment and failed to respond to detoxification treatment in those with acute headache pain medication overuse. This proposed classification allows stratification of intractability based on illness severity as reflected by the incremental failure to an increased number of therapies.

Defining a patient as intractable is not unique to those with headache. Similar issues exist in the assessment and treatment of epilepsy and in the definition of intractable epilepsy. The outcome in epilepsy is often freedom from seizures (remission). Approximately 30% of patients with epilepsy do not achieve remission with standard, effective antiepileptic medications.<sup>15,16</sup> Some patients have intractable epilepsy at outset and may need early aggressive interventions.<sup>15</sup> Similar to epilepsy, the use of consistent definitions for treatment failure, including acute and preventive treatments, will help identify the level of intractability thereby making it easier to progress patients through

defined treatment protocols and also to identify candidates for specific clinical trials.<sup>12</sup>

**Stratifying Intractable Headache Patients Based on Severity.**—Once a complete history of treatment failures (acute and preventive) is documented, a better understanding of the patient's overall disease severity can be understood. Clear definition and stratification of patients according to clinical symptomatology and history of medication failures will enhance the likelihood of identifying specific treatments and strategies for these difficult-to-treat patients. Table 4 illustrates how a clear definition of medication failure can be used to identify those patients who warrant referral to specialty care.

Stratifying the patient's illness severity will also allow clinical trials to recruit well-defined groups of subjects that have similar clinical profiles of intractable headache, thereby increasing the chances of identifying effective and ineffective treatment strategies for these challenging headache patients. Table 5 proposes a stratification method where the patient's history of acute and preventive treatment failures is used as the basis to qualify for participation in selected intractable headache trials. Clinical trial

**Table 3.—Prophylactic Therapies Used to Determine Level of Intractability**

(a) $\beta$ -blockers (shown to be effective)
(b) Tricyclic antidepressants
(c) Verapamil or flunarizine
(d) Sodium valproate (or divalproex sodium)
(e) Topiramate
(f) Combination therapy that includes at least 1 drug of type a-e; the second drug can be from any type (a-e or g-j). The drugs must be of different types (eg, a combination of 2 anticonvulsants is not acceptable)
(g) Gabapentin
(h) Other treatments with at least 1 positive placebo-controlled trial
(i) Non-steroidal anti-inflammatory drugs
(j) Metabolic enhancers (ie, Vitamin B2 or CoQ10)

Failure is defined as no therapeutic or unsatisfactory effect, or intolerable side effects. For clinical trials of invasive therapies (eg, PFO closure) US regulatory authorities require failure (defined as no therapeutic or unsatisfactory effect, or intolerable side effects) to 3 preventive medications (contraindication to 1 medicine only), where 2 must be of different types from a to f. Patients must also have at least moderate migraine disability as measured by a MIDAS score  $\geq 11$  or a HIT-6 score  $\geq 56$ .

**Table 4.—Stratifying the Intractable Headache Patient for Clinical Practice**

	Acute Treatment Severity (Table 1)	Preventive Treatment Severity (Table 2)	Consider Disability†
Referral to specialist should be considered	≥Class II	≥Class I	≥Mild
Referral to headache specialist warranted	≥Class II	≥Class II	≥Mild
Hospitalization may be warranted		≥Class III	≥Moderate

†Disability levels may be determined using validated migraine disability instruments (MIDAS, HIT-6).

recruitment can also specify the specific types of patients needed for specific studies. A clinical trial recruiting for an invasive therapy will include a different stratum of patient intractability than a clinical trial recruiting patients for a drug study.

**SUMMARY**

Establishing a context-related definition for intractable headache is clearly needed to eliminate the current chaos and confusion that is scattered throughout clinical research studies, within the published literature, and among clinical practices that care for these patients. Not only is a clear understanding of medication history and disability needed, other relevant clinical challenges remain.<sup>10,14,17</sup> For example, what is an acceptable or standard definition of an adequate trial length for preventive or acute medications? (Currently, the length of what is considered an adequate trial varies across studies.<sup>14,15</sup>) What are adequate doses and dose escalation regimens of medications? How can screening help identify confounding

factors (eg, medication overuse headache) in this high-risk population?

This paper, along with others,<sup>10,14</sup> has focused on identifying the need of establishing a classification scheme for intractable headache using specific criteria for illness severity, and defining adequate pharmacological treatment failures and severity of disability. However, there are no prospective trials validating recommendations as to how to stratify the intractable headache patient. The definitions included herein are proposed as a starting point for future clinical trials and clinical practice. Determining the utility and ease of use in practice will require further study.

Health care providers must always use clinical judgment to review the patient’s headache condition, either primary or secondary, and all possible coexisting conditions that may confound diagnosis and treatment. As clearly reviewed by Goadsby and Olesen, for some patients, exceeding the recommended treatment dose provides sufficient relief, and surgical intervention or risk of polytherapy may not be

**Table 5.—Stratifying the Intractable Headache Patient for Clinical Trials**

	Acute Treatment Severity (Table 1)	Preventive Treatment Severity (Table 2)	Consider Impact of Disability
Acute clinical trial (low risk)	≤Class II		≥Mild
Acute clinical trial (moderate risk)	Class III		≥Moderate
Preventive clinical trial (low risk)		≤Class III	≥Mild
Preventive clinical trial or surgical intervention (moderate risk)		≥Class III	≥Moderate
Intracranial surgery (high-risk experimental procedures)		Class IV	Severe

necessary.<sup>14,18</sup> Indeed, there is no replacement for expert clinical experience in identifying when alternate treatment strategies may be tried such as polytherapy, non-pharmacological treatments, and combinations thereof, and when to move to more aggressive treatment approaches that may provide the patient relief from significant disability and long-term suffering.

The authors also acknowledge that there may be regional limitations in generalizing any classification of intractable headache, especially when the criteria for intractability rely on the failure of specific medications or headache-related disability as measure by specific instruments. There may be differences in the availability of certain medications and regional differences in the approach to the management of primary headache disorders. Moreover, the disability instruments may not be translated or validated in certain populations. Nevertheless, the general criteria and principles outlined in this paper can be modified according to regional differences in the availability of certain medications and instruments used to measure the burden of illness.

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