

Refractory Migraine: Definition, Diagnosis, Management

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Refractory Migraine: Definition, Diagnosis, Management

Outline

- *Introduction and historical perspective*
- *Defining Refractory Migraine*
- *Epidemiology*
- *Pathophysiology*
- *Pseudorefractory Migraine*
- *Treatment strategies*
- *Classification of Refractory Migraine*
- *Conclusions*

RM – Intro and History

- **Schulman and Traumuta proposed a definition for RH: 1) headaches occurring on at least 15 days per month; 2) lack of response to multiple preventive medications, given at appropriate doses over a sufficiently reasonable time; and 3) no analgesic rebound.**
- **Goadsby and others suggested definitions for intractable migraine for use in clinical drug trials generally requiring failure of several proph meds**
- Schulman EA, Traumuta G. Refractory headache. *Headache*. 1993;33:273-286
- Goadsby PJ, Schoenen J, Ferrari MD, Silberstein SD, Dodick D. Towards a definition of intractable headache for use in clinical practice and trials. *Cephalalgia*. 2006;26:1168-1170.

RM – Intro and History

- **Schulman and the AHS Refractory Headaches Special Interest Section (RHSIS, formed in 2000) have sent two surveys to the AHS 's membership in an attempt to create a consensus on the need for defining RM and how it should be done.**
- **The surveys revealed significant agreement among responders that RH should occur ≥ 15 days per month and be associated with disability. Most respondents believed the definition of RH should include an inadequate response to multiple abortive and preventative medications.**

Schulman EA, Peterlin B Lee, Siegel Sheryl E, Lake Alvin E., Markley Herbert , Lipton Richard B., Refractory Headache Perceptions: Results of an Internet Survey of AHS Members, American Headache Society, Chicago Ill 2007

Schulman et al – second survey results – Headache, 2009 in print

Why identify Refractory Migraine?

- *To better characterize the disorder and its natural history*
- *To allow further studies of mechanism*
- *To identify risk factors for progression*
- *To design consistent treatment trials*
- *To identify “best practices”*
- *To promote triage of patients to appropriate centers for care*

Nomenclature

“Intractable” - ICD-9 diagnostic coding system does include a modifier “with intractable headache” - so this could be adopted to match coding system language.

“Treatment-resistant” might lead to the need to specify which treatment(s), and then numerous subtypes based on the specific therapeutic agent.

“Severe” – but which means of grading severity? The term

“Disabling” might lead to controversy about disability grading, with a large body of legal precedent to contend with.

Problems in Refractory Headache

Definition and Classification

No lab markers – Descriptive

Consensus about what constitutes intractability is difficult – freq, disabil, response to tx...

Rather than a unique disease or group of disorders, refractoriness may just represent less treatable version(s) of many different headache disorders

A patient's "refractoriness" may change

Definition of Refractory Migraine

RHSIS met and evolved a definition for RM using the results of the surveys and a consensus iterative process which included: persistent and disabling migraines despite several adequate management trials

Schulman EA, et al: Defining Refractory Migraine (RM) and Refractory Chronic Migraine (RCM) Headache 2008;48:778-782

Levin DHMC

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 <ol style="list-style-type: none">1. Failed adequate trials of preventive medicines, alone or in combination, from at least 2 of 4 drug classes:<ol style="list-style-type: none">a. Beta-blockersb. Anticonvulsantsc. Tricyclicsd. Calcium channel blockers2. Failed adequate trials of abortive medicines from the following classes, unless contraindicated:<ol style="list-style-type: none">a. <i>Both</i> a triptan <i>and</i> DHE intranasal or injectable formulationb. <i>Either</i> nonsteroidal anti-inflammatory drugs <i>or</i> 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

Definition of Refractory Migraine

Practical “screening” version

- *Diagnosis of migraine*
- *Significant impact on quality of life, despite lifestyle changes and modification of triggers*
- *Failure of adequate trials of 3 out of 4 recommended classes of preventive medication*
- *Failure of all appropriate acute medications.*

Definition of Refractory Chronic Migraine *Practical “screening” version*

- *Diagnosis of chronic migraine (ICHD II appendix)*
- *Significant impact on quality of life, despite lifestyle changes and modification of triggers*
- *Failure of adequate trials of 3 out of 4 recommended classes of preventive medication*
- *Failure of all appropriate acute medications.*

A 1.5.1 Chronic migraine

New entrant to classification

- Headaches on ≥ 15 d/mo
- 8 or more fulfill migraine criteria or respond to migraine med
- Not due to another illness, like MOH

HA Classification Committee. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 2006; 26:742-6

RM Definition –

Impact on QOL; Lifestyle modification

- QOL as judged by patient and physician (?)
- The RHSIS debated whether an adequate trial of behavioral treatment should be included in the definition.
- But - less accessible than pharmacological treatment and more variable in their application. Thus, this requirement was not included.
- There is no threshold for headache frequency, as some individuals with relatively infrequent migraines may be refractory to treatment.
- Lifestyle and trigger modification – Some? All?

RM Definition –

Failure with prophylactic agents

1. Trials of preventive medications alone or in combination from ~~2~~ 3 out of 4 classes
 - Beta-blockers
 - Anticonvulsants
 - Tricyclics
 - Calcium channel blockers
2. Adequate 2 months at optimal or maximum tolerated dosage unless terminated early by adverse events

RM Definition –

Failure with acute treatment

- (1) both a triptan and dihydroergotamine (DHE) in either the intranasal or injectable formulation
- (2) either NSAIDs or combination analgesics.

Problems

- Not many patients seen in consultation in HA centers have gotten DHE
- Some patients may respond somewhat to acute meds but the frequency they need to use them is too high for safety

RM Definition –

RM and RDM definitions - modifiers

Modifier 1, “With or without medication overuse (MOH

- Allows for patients to carry the diagnosis of RM as well as MOH.
- Ideally, for migraine to be truly refractory, attempts to withdraw overused medication should be made.
- There are, of course, some patients who assert that their headaches do respond to acute interventions which they have to take frequently, presumably leading to MOH.
- some patients with MOH will not improve following the removal of acute medications. The use of “Probable” and multiple diagnoses might be the best approach with many of these patients.

RM Definition –

RM and RDM definitions - modifiers

Modifier 2, “With significant disability, as defined by Migraine Disability Assessment Score (MIDAS) of 11 or higher”

- designed to further characterize the population of RM based on this measure of life impact.
- 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

Other refractory headaches

Primary headache types

- *Migraine*
- *Chronic Tension-type HA*
- *Chronic Migraine*
- *Cluster Headache*
- *Paroxysmal Hemicrania*
- *SUNCT*
- *Hemicrania continua*
- *New Daily Persistent Headache*
- *Exertional Headaches*

Other refractory headaches

Secondary headache types

- *Post-traumatic*
- *Medication Overuse HA*
- *Intracranial hypertension*
- *Intracranial hypotension*
- *Neuralgias*

Medication overuse headache

- Frequent use of abortive/analgesic agents can “transform” intermittent migraine to a chronic daily headache pattern
- Mathew et al showed that frequent use of analgesics made migraines resistant to prophylactic medications
- Differentiating MOH from chronic migraine *not* related to MOH can be challenging, particularly since headache morphology is not particularly helpful (Silberstein)

Mathew NT, Kkurman R,- Perez F. Drug induced refractory headache-clinical features and management. *Headache* 1990; 30: 634-638.

Silberstein, SD, Olesen, J, Bousser, M-G, et al. The International Classification of Headache Disorders, 2nd Edition (ICHD-II) – revision of criteria for 8.2 Medication-overuse headache. *Cephalalgia*, 2005, 25:460-465.

Medication overuse headache

- Refractory migraine could be further subdivided into Refractory migraine with MOH, and Refractory migraine without aura, without MOH.
- To maintain the format and spirit of the ICHD II's current handling of MOH, it might actually be best to consider MOH to be a secondary cause of refractory headache, with the existence of subtypes: 1) Refractory MOH and 2) Non-refractory MOH (if there are any cases).
- However, there will always be patients with apparently refractory migraine in whom the role of medication overuse may be difficult or impossible to assess.

RM - Epidemiology

- Migraine 10-15% of population
- Chronic daily headache 4% of general pop
- Chronic migraine (S-L criteria) 2%
- 22% of migraine sufferers and 40 of CM have MIDAS score >22 (significant disability)
- 80% of CDH patients overuse acute meds (use on more days than not)
- So – not a stretch of the imagination to induce .5-1% of the population with RM or CRM

Pathophysiology

Why are these patients refractory to treatment?

- **Burned out pain modulating system**
- **Congenital or acquired pain modulation system dysfunction**
- **Central sensitization, cutaneous allodynia**
- **Upregulation of other pro-nociceptive systems (obesity and TNF- α , CGRP; hypothalamic mediation of pain, glial activation, etc)**
- **Migraine associated gastroparesis**
- **Hormonally related factors - menstrual**

The Definition of RM assumes there is not avoidable treatment failure – i.e.

Pseudorefractory Migraine

- 1. Wrong Diagnosis (or incomplete diagnosis)**
- 2. Wrong Treatment (for the patient)**
- 3. Wrong combination of Patient and Physician**

Lipton, RB. Silberstein, SD, Saper, JR, Bigal, ME, Goadsby, JP.
Why headache treatment fails. *Neurology* 2003;60:1064-1070

The Definition of RM also assumes no causative psychiatric or medical problems

But *contributing* medical or psychiatric issues can also lead to treatment failure:

Pseudorefractory Migraine:

Depression, Bipolar disorder, Anxiety

Insomnia, other sleep problems

Hormonal imbalances

Allergy

Other pain conditions

Treatment of RM

Although RM and RCM patients have tried and failed with typical preventive and acute therapy, more intensive or novel options can be explored:

- *Biobehavioral and other non-pharmacological treatment (not included in RM def)*
- *Creative acute treatment*
- *IV courses of Medication to “reset” system*
- *Combinations of preventive medications*
- *Psychiatric treatment*
- *Anesthetic procedures*
- *Daily opioid maintenance*

Non-pharmacological treatment

- Biofeedback
- Relaxation response (meditation)
- Physical therapy
- Massage
- Vitamin/supplement tx – Mg, petasites, B2, coenzyme Q10

Creative acute treatment

- **Triptans + NSAIDS**
- **Short acting triptan + frovatriptan**
- **Prokinetic antiemetics – to enhance gastric motility**
 - like metoclopramide (not promethazine, which may reduce gastric motility)
- **Nasal route triptan**
- **IM or SC route meds – sumatriptan SC, DHE IM, ketorolac IM 60 mg , droperidol IM 2.5 mg**

IV Medication – DHE

Why does DHE work when triptan fails?

- DHE speed of onset: IV 2–11 min, IM 30 min, SC 60 min, Nasal 60–90 min
- DHE works even when cutaneous allodynia has occurred
- Binds to brain stem serotonergic centers like dorsal raphe nuc
- Prolonged effect of active metabolite 8–hydroxy-dihydroergotamine

IV Medication – DHE

How can it work even with past failure?

- Dose must be 1 mg tid
- Course should be at least 3 days
- Nausea AE which may have prevented effectiveness can be easily prevented

IV Chlorpromazine

- 12.5 mg IV q20 min until sedated
- Use that dose q6 hours to maintain at least light sedation
- Combine with diphenhydramine
- Watch for hypotension
- Keep pt in bed during course of tx
- Monitor ECG for QT interval

IV Corticosteroids

- Dexamethasone - 2 mg Q8H for 2-3 days
- Can combine with DHE
- Followed by tapering doses orally
- Other options -
 methylprednisolone, hydrocortisone

IV Valproate

DOSE - 500 mg diluted in 20 ml normal saline I.V.

Push in 3 – 4 minutes, Q8H for 3 days

Possible AE's: dizziness (5.2%), headache (4.3%),
injection-site reactions (2.4%), injection-site pain
(2.6%), taste perversion (1.9%), and somnolence
(1.7%)

Mathew et al 2000, Horton 2000, Schwartz et
al 2002, Stillman et al 2004

IV Propofol

- Intravenous sedative-hypnotic
- Rapid induction of hypnosis
- Use subanesthetic doses – 20-30 mg I.V. push, repeat q 5 mg
- Average dose used 100-400 mg
- Close monitoring of respirations is essential

Krusz and Belanger (1999)

Mendes et al 2002

Trying new preventive medication and combinations

- Estrogen therapy (watch comb with AEDs)
- ARBs, memantine, tizanidine, SNRIs
- Beta blocker + AED (Pascual 2003, 2004)
- Beta blocker + antidepressant
 - *(watch interaction with propranolol and duloxetine – hepatic enzymatic issues leading to elevated Beta blockade.)*
- Ca Channel blockers + antidepressants
- Ca Channel blockers + Mg
- AED + antidepressants

Psychiatric treatment

- Treat Axis I disorders – depression, bipolar disorder, anxiety with pharmacotherapy + psychotherapy
- Recognize Axis II disorders (especially borderline and narcissistic PD) and alter approach accordingly
- Treat insomnia
- Family counseling, individual counseling

Anesthetic procedures

- Greater occipital nerve blocks
- Supraorbital, auriculotemporal n blocks
- Trigger point injections
- Root, facet, medial branch blocks
- Epidural anesthesia
- Occipital nerve stimulation

Daily opioid treatment

- Patient selection is crucial
- Contracts and drug screening are essential
- Choice of meds – methadone, long acting Morphine
- Tolerance is likely, AEs are frequent; success rate is low, although controversial*

*Saper, JR et al. Neurology 200462:1687-1694 -25% success

*Rothrock, J. Headache 200545:830. – 80% success (methadone)

Treatment – Retrial of old acute and preventive therapy

- Improve compliance via education about use of medications
- Improve education about AEs
- Rethink possible secondary causes or contributing medical and psychiatric problems that can be addressed
- Rethink lifestyle issues that may have been overlooked – caffeine, sleep, alcohol, drugs, exercise, nutrition, stress

Classification of RM

Options include:

- A separate ICHD chapter for Refractory headaches
- Separate sections in each chapter for refractory versions of those headaches
- A modifier (“R”) that could be attached to certain headache types

Classification of RM

- Chapter 1 - Migraine
 - 1.1 Migraine without aura
 - 1.2 Migraine with aura
 - 1.3 Childhood periodic syndromes that are commonly precursors of migraine
 - 1.4 Retinal migraine
 - 1.5 Complications of migraine
 - 1.6 Probable migraine
 - 1.7 Refractory Migraine

RM – Next steps

- Validation of the definition
- Refinement of classification
- Redefining RM and RCM based on clinical studies
- Trials of treatment in RM and RCM

Conclusions - Refractory Headache

- Refractory headaches are a poorly characterized group of disorders common in headache specialty practices which includes
 - Refractory Migraine and Refractory CM
 - Refractory cluster headache
 - New Daily Persistent headache
 - Medication overuse headache
- These patients are Refractory to multiple treatment efforts despite control of behavioral, lifestyle, and triggers

Conclusions - Refractory Migraine

- Brief definition:
 - *Diagnosis of migraine*
 - *Significant impact on quality of life, despite lifestyle changes and modification of triggers*
 - *Failure of adequate trials of 3 out of 4 recommended classes of preventive medication*
 - *Failure of all appropriate acute medications.*
- Probably represents the bulk of refractory headache patients, along with MOH (large overlap)