REFRACTORY CHRONIC MIGRAINE: DEFINITION, CHALLENGES AND SELECTED OUTPATIENT TREATMENTS

Lawrence Robbins, M.D.

Refractory Chronic Migraine (RCM) results in a great deal of disability for patients and has a huge impact on their quality of life. In order to provide a framework for other physicians and health care providers, this author initiated the Refractory Headache Special Interest Section of the American Headache Society. This committee of headache specialists seeks to define a standard of diagnosis for health practitioners and raise awareness of improved treatments for headache. Since its inception, the committee has primarily focused on the critical area of RCM definition. Chronic migraine (CM) is outlined in Table 1. Chronic migraine occurs in approximately 2% of the population; we do not yet know the epidemiology or rate of occurrence of RCM.

Table 1. Appendix Criteria for A.1.5.1 Chronic Migraine (Headache Classification Committee 2006)

A. Headache (tension-type and/or migraine) on 15 days per month for at least 3 months
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria for 1.1 Migraine without aura
C. On 8 days per month for at least 3 months, headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura

1. Has at least 2 of a-d
   a) Unilateral location
   b) Pulsating quality
   c) Moderate or severe pain intensity
   d) Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

   And at least one of a or b
   a) Nausea and/or vomiting
   b) Photophobia and phonophobia

2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above

D. No medication overuse and not attributed to another causative disorder

The current proposed criteria for RCM are summarized in Table 2.[1,2]

Table 2.

Proposed Criteria for Definition of Refractory Migraine and Refractory Chronic Migraine

From the Refractory Headache Special Interest Section: Elliott A. Schulman, MD; Alvin E. Lake III, PhD; Peter J. Goadsby, MD, PhD; B. Lee Peterlin, DO; Sherry Siegel, MD; Herbert J. Markley, MD; Richard B. Lipton, MD

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 trails 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 doses, 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 $\geq$ 11

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

The definition of RCM is a work in progress; the final version may be quite different than that cited in Table 2. We may want to add modifiers as to the degree of refractoriness (mild, moderate or severe). In some patients, RCM improves or resolves over time, while others worsen. These situations need to be addressed in the definition.[3]

Challenges of Refractory Migraine [3]

There are a number of major challenges in dealing with RCM. These include: 1) What does the role of disability play, and should disability help to define RCM? 2) How resistant to the myriad of treatments does one have to be? 3) There is no accepted, identifiable biological marker for RCM; 4) The degree of refractoriness can change over time, improving or worsening. What role does this varying severity play? 5) There are various subsets of RCM – post-traumatic headache, RCM with or without MOH, with or without major psychiatric comorbidities, etc. Each category requires a different approach.

Pathophysiology.[4]

We are just beginning to look beneath the surface as to what causes RCM. Some of the issues are:

1) What is the role of genetics in drug resistance and inheritance of chronic headaches?
2) What structural changes (in white matter or iron deposition) play a role?
3) What part does central sensitization and plasticity have?
4) How much involvement is peripheral vs. brainstem vs. cortical?
5) How does MOH affect the structure and function of the nervous system?
6) What is the physiologic impact of psychiatric comorbidities? Do depression and/or anxiety fuel the headaches?

Continuing research is critical in order to answer these questions. We do know several risk factors that may drive the development of RCM. These include lifestyle issues such as medication overuse, sleep habits, caffeine overuse and obesity. [5] While pharmacotherapy may be the cornerstone of treatment, other modalities are no less important. The patient must manage his or her triggers with regards to sleep, food and caffeine. Exercise and weight reduction are encouraged. Stress, another major trigger, may be relieved by practicing biofeedback and/or yoga. Depending on the origin of the pain, physical therapy and massage may help. Problems with the teeth, jaw, eyes or neck should be addressed.

Medication Overuse Headache

Table 1, Part D, refers to the overriding condition of Medication Overuse Headache (MOH). MOH is a critical issue that must be addressed early in the treatment of any form of headache.[6] Abortive medication overuse is a major risk factor for the progression of migraine into RCM. Some patients have medication overuse without an increase in headache. In others, overuse of abortives is the principal cause for the headaches. The criteria for MOH are listed in Table 3. Note that the headache progresses instead of subsides over time, and the calls for prescription refills will become more frequent with the

progression. When treating patients with MOH, the offending drugs will need to be withdrawn or limited. While we do not know with any certainty the percentage of RCM patients where MOH is a major contributor, we do know that MOH should be one of the first considerations when a patient presents with worsening headaches.

Table 3.
Appendix Criteria for A8.2 Medication Overuse Headache
(Headache Classification Committee 2006)

A. Headache present on ≥ 15 days/month
B. Regular overuse (>10 days/month or > 15 days/ month, depending on the medication) for > 3 months of 1 or more acute/symptomatic treatment drugs as defined under sub forms of 8.2
C. Headache has developed or markedly worsened during medication overuse

Psychiatric Comorbidities

Significant abuse in childhood, whether sexual, physical or emotional, may predispose one to develop RCM, separately or in conjunction with other central sensitization syndromes such as fibromyalgia, irritable bowel syndrome, chronic pelvis pain or TMD. Important comorbidities include anxiety, depression, the bipolar spectrum, personality disorders, somatization and post-traumatic stress disorder.[7] The author has published several articles on the bipolar spectrum and personality disorders and how they relate to migraine patients; a brief synopsis will be discussed here.

Bipolar Spectrum. The bipolar spectrum is seen relatively often in headache patients and particularly among migraineurs.[8] The depression and hypomania of the bipolar spectrum complicate treatment; in RCM patients, these issues must be recognized. Bipolar disorder is not an easy condition to have, or to deal with in a patient or family member. The clinical spectrum of bipolar is an evolving concept: mania is better recognized than is hypomania with milder bipolar features. Symptoms of mania include euphoric mood, distractibility, flight of ideas, grandiosity, thoughtlessness, risk-taking, increase in general activity, excessive involvement in pleasurable activities (sex, spending ,gambling), pressured speech, excited or irritable mood, and insomnia. Hypomanias, with milder versions of these symptoms, can be missed if a doctor relies solely on the patient's own history; it is important to talk with a family member or significant other to get a complete history. In addition, brooding or irritable pessimism may be a manifestation of hypomania. During these periods, many people will lose jobs or damage relationships.

The prevalence of bipolar disorder is at least 4% in the general population, but bipolar illness is seen with increased frequency in the migraine population.[9] Studies have indicated that from 7.2% to 8.6% of migraine patients fit the bipolar spectrum. [9] [10] Conversely, in assessing patients with bipolar spectrum disorders for migraine, several studies have indicated an increased risk. One study indicated that, in bipolar patients, 14.9% of the men and 34.7% of the women had a lifetime occurrence of migraine.[11] Additional studies of the bipolar population resulted in a lifetime migraine prevalence of 39.8% (men) and 44% (women). [12] Recognizing bipolarity in headache patients has a significant impact. When not diagnosed, these patients often are given antidepressants alone, with predictably poor results. While some benefit, these medications generally are not effective for the bipolar spectrum and may trigger mania or hypomania. The presence of bipolar illness complicates treatment of RCM. Mood stabilizers that help both conditions, such as lamotrigine or sodium valproate, are important. Psychotherapy plays a vital role with these patients.

Personality Disorders and Migraine. In patients with certain personality disorders, failure on the part of the physician to recognize Axis II pathology puts both doctor and patient at risk. Patients with antisocial, borderline or paranoid personality disorders may wreak havoc on an unsuspecting medical practice.

Approximately 10-15% of people have features of a personality disorder. [13] There are a number of personality disorders, and some exhibit more dangerous and difficult behavior than others. The general characteristics of personality disorders include lack of insight, poor response to psychotherapy and other therapeutic interventions, difficulty with attachments and trust, a sense of entitlement and the creation of chaos and distress among family, friends and co-workers. Comorbid substance abuse is common. Personality disorders range from the mild to the very severe. Patients with personality disorders will take on various roles: victim, rescuer or persecutor. When they turn persecutor, they can be dangerous to the person they have their sights set on. Seeing a therapist for a long time helps to some degree. However, goals and expectations must be limited. The plasticity of the brain is important, as some people improve naturally over time. The following are disorders that may be seen in RCM patients:

Antisocial Personality Disorder. These people have no regard for the rights of others. They tend to be irritable and impulsive in demeanor. They are exploitative, often see themselves as superior, and can be very opportunistic in getting what they want. Antisocials are deceitful, may steal from those around them, and often have trouble with the law. They rarely show remorse.[13]

Borderline Personality Disorder. This type of personality shows instability of mood, poor self-image and pervasive abandonment fears. There is an identity disturbance and major boundary issues. Borderlines usually demonstrate impulsiveness, and quick shifts of

depression to anxiety to irritability. There are chronic feelings of emptiness or severe loneliness, plus anger and even suicidal behavior. Under stress, they can become paranoid. Problems with drug abuse or other addictive behaviors may coexist, as well as sleep disturbances with insomnia. Severe borderlines will react with high drama and create chaos for everyone around them. They tend to have a split view, seeing people as wonderful or terrible, with nothing in between. Suicide becomes more likely as patients age in to their upper twenties and thirties. Suicide is also more common within a week of discharge from a psychiatric unit.[14]

There are other personality disorders which are not as dangerous for the people around them. Although PD characteristics seem extreme, they are often overlooked, and health care providers may react by treating these patients in a dysfunctional manner. The problem begins with not recognizing the personality disorder.

One previous study on borderline personality (BPD) concluded that BPD comorbidity with migraine is associated with increased disability from the headaches.[15] In addition, among those with BPD, there was an increase in medication overuse headache, and headaches were more severe. There was a higher degree of depression among those with BPD, more unscheduled visits for acute headache treatment, and a lesser chance of adequate response of headache medications. Those with BPD were more severely affected by headaches, and more inclined to be refractory to treatment.[15]

Another study indicated that the incidence of BPD was increased in migraineurs.[15] The author's recent study of 1000 migraineurs indicated that 5.5% of patients had a moderate or severe personality disorder.[16] There is ample evidence that transformed migraine is associated with more prevalent psychopathology, including PD, than is episodic migraine. BPD itself is the mental health equivalent of chronic pain. These patients do suffer constantly with feelings of depression, anxiety and loneliness.

In my experience, the two most important prognostic indicators for those with PD are impulsivity and substance abuse. Treatment for those with PD necessitates a caring, but stern, approach. Limits must be set on physician contact, including telephone calls, and no abuse of staff should be tolerated. Referral to mental health professionals should be emphasized. Psychotherapists and psychiatrists who are experienced with this population are vital to the adequate management of the patient. Many PD patients do not do well with traditional, insight-oriented therapy treatment, but are better managed long-term with a dialectical behavioral approach. For a therapy to be beneficial, it must be consistent and long-term. A psychoeducational approach may also help. Unfortunately, many PD patients will not continue in therapy, even with encouragement and support. Our therapeutic goals for the PD patient are relatively modest.

Medications, though limited, may be beneficial for the impulsivity, aggression, self-mutilation, anxiety and depression components of PD.[17] While there are no specific medications indicated for those with PD, the Axis I symptoms are more amenable to pharmacotherapy. Antidepressants, mood stabilizers, and antipsychotics may ameliorate symptoms. Some of these medications may lessen headache pain as well. PD patients with severe, chronic pain present additional challenges for treatment. It is important to limit and closely monitor addicting medications: opioids and benzodiazepines are best avoided, particularly with BPD. The diagnosis of a moderate or severe personality disorder alters both our goal and approach, and greatly complicates the treatment for chronic migraine.

Outpatient Treatments for RCM

New Technologies and Pharmacotherapies

There are a number of therapeutic options for RCM, including inpatient treatment. New approaches, such as transcranial brain stimulation (TMS), are in various stages of development and will come along. TMS has the potential to alleviate RCM without side effects. There is currently one newer type of TMS machine in use in the US, the Neurostar machine. It is FDA- indicated for the treatment of depression. There is another type of TMS unit in development by the company Neuralieve, which will be primarily used as a migraine abortive. It has the advantage of being readily available in a patient's home.

Occipital nerve stimulation has been beneficial for a small number of RCM patients. Techniques of implantation have improved but the technical challenges need to be overcome; the leads tend to migrate away from the occipital nerve, for example. Other implantable stimulators are being studied, such as the Bion microstimulator and the Precision Implantable Stimulator for Migraine. It is too early to know what, if any, role these will play.

In pharmacotherapy, there are a number of emerging compounds that may eventually come to market. These include newer abortives, such as 5-HT_{IF} drugs. These work on the 5-HT F receptor, while the current triptans target B and D. CGRP antagonists, such as olcagepant and telcagepant, may be very useful. Gap junction blockers at the neural-glial level are being assessed. Finally, glutamate receptor antagonists are currently in Phase III trials.

Five Approaches to RCM

For the remainder of this article, the author has highlighted five possible approaches, some of which may be combined. For a RCM patient, the choice of therapy depends on a number of variables. These include age, psychiatric comorbidities, tendency towards

addiction, sleep, medical conditions, etc. Comorbidities often steer where we go with medications: conditions such as IBS, fatigue or psychiatric conditions have to be considered. Of course, the familiarity and confidence with a particular therapy on the part of the treating physician plays a major role in selection. There is no algorithm for migraine treatment. The choices of medication will vary for each patient depending on headache severity and comorbidities.

Long-acting Opioids

In my practice, long-acting opioids are the most commonly utilized approach for RCM. The best candidate for LAO's is the person who has done well on short-acting opioids (SAO) and who does not have characteristics of a personality disorder. The following summarizes certain LAO studies and describes guidelines for using LAO's in chronic migraineurs.

In a recent study, we assessed 115 patients with refractory chronic migraine who were treated with long-acting opioids during a 6 year period. This was a select group of patients who had all done well previously with short-acting opioids. Avoidance of opioid-induced hyperalgesia is important in chronic patients; however, all of the patients in this study had already been on short-acting opioids for at least a year.[18]

Sixty-five percent of the patients did well for at least 9 months on the opioid; the average duration of use of the opioid was 4.5 years. Forty-four percent of the patients reported adverse events. Patients with an increased chance of success included younger patients, high copers, and those without previous opioid abuse. Predicators of failure were those with personality disorders, older patients, and, in particular, those with previous abuse of the short-acting opioids. In this study, anxiety, depression, bipolar depression, ADD, exercise, working, disability, fatigue or cigarette smoking did not significantly change the long-term outcome. In one of our previous studies (1999)[19], a significantly lower rate of success (13%) was obtained compared to the more recent study (65%). This was, in part, due to an altered standard of success utilized in the recent study.

In 1997, Saper and associates assessed refractory chronic daily headache with scheduled long-acting opioids, particularly methadone.[20] There was a small subset of patients who did well. Similar results were obtained from Rothrock[21] and from Robbins.[18] Subsequently, Saper and his associates soured on the use of the opioids. An unpublished study from Rothrock indicated that in the chronic migraine patients who were responsive at two months to the methadone treatment, over 70% continued to maintain a response at one year.[22] Rothrock found that patients tend to either respond to relatively low doses, or not respond at all. His studies also indicated that virtually all of the positive responders, when tapered off of the methadone, did relapse into their frequent headache patterns.[22]

Short-acting (SAO) versus Long-acting (LAO) Opioids. Short-acting generally refers not only to how long a drug carries the desired effect, but the speed of the onset of the drug, and how fast it drops off toward the end of the dose. Quick onsets and fast dropoffs are major determinants for abuse.[23] SAO's are not necessarily quick-onset medications. Most oral SAO tablets are slow to take effect. A short duration of action then leads to frequent administration by the patient, and overuse may occur. However, it has not been proven conclusively that SAO's lead to more abuse than LAO's. Although certain drugs are easily abused, such as oxycodone CR, it is the person, not the drug, who governs abuse. While some abusers have only one drug of choice, many will tend to abuse a succession of drugs.

Several previous studies have evaluated daily opioids for severe chronic daily headache.[20 21 24] While success rates have been relatively low, they represent patients who have failed the usual ministrations, and who have few options available. The advantages of long-acting opioids include:

1. avoidance of the "end-of-the-dose" phenomenon, with mini-withdrawals throughout the day
2. consistent dosing one or two times daily, which decreases the obsession with the next dose
3. maintenance of stable blood levels
4. avoidance of the acetaminophen, aspirin and NSAIDs that are included in many short-acting preparations
5. probable diminished risk of significant abuse
6. better compliance, with less psychological dependency on the drug

Disadvantages of the long-acting opioids include:

1. social stigma
2. fatigue and constipation
3. difficulty in obtaining scripts, with no refills available
4. need for frequent office visits and monitoring
5. risk of opioid-induced hyperalgesia
6. risk of abuse, although probably less than the SAO's
7. interactions with other sedating drugs and alcohol
8. risk of overdose

Opioid Abuse. Opioid abuse is much more common than true addiction. In general, using opioids for therapeutic reasons other than pain constitutes abuse. In a headache practice, the most common reasons for abuse are using the opioids to alleviate moods, anxiety or depression.

Patients in our previous study were assessed for behaviors typical of opioid abuse or overuse. The criteria that we used included: early refill requests, dose escalations, insistence on increasing doses, abusive treatment of the staff regarding refills, false reports of stolen or lost medications, utilizing the opioid for depression or anxiety, using the opioid for other pains not discussed with the physician, receiving similar medication from other physicians, unexpected or abnormal urine screening test results, using illicit drugs or alcohol, missing, canceling, or refusing appointments, selling the drugs, obtaining opioids from non-medical arenas, frequent ER visits for opioids, hoarding, forging or altering scripts, borrowing or stealing similar medications from family and friends, physical signs of overuse or addiction, and calls to the physician from family members with concerns about patient overuse.[25] [26]

There is a range of abuse, from the person who samples his spouse's codeine prescription once in a while to the addict who obtains hundreds of opioid tabs from the internet. We cannot paint all abusers with one broad brush. Some situations need watching, such as the patient who took her mom's pills because she had excess pain; this behavior is a red flag and the patient may be an abuser. For a different patient, one who has already been prescribed low dose, long-acting morphine, the discovery of undisclosed opioid prescriptions from other sources must be regarded as severe abuse; in this situation, discontinuation of the opioids is necessary.

It is not always clear how serious the abuse is. Minor aberrant behaviors are often overlooked. It is not as if any one aberrant behavior warrants immediate discontinuation of an opioid, but most of the serious overuse situations have previously had a number of minor abuse occurrences. Physicians must pay attention to red flags, particularly those that arise early in the relationship with the patient. In my experience, pain patients who raise objections to urine tests usually have a drug problem. Specimen collections should be random and not scheduled. Urine testing serves two purposes : one is to identify other substances that are present, though they should not be. Another is to measure the levels of the prescribed substance for compliance. When there is no opioid present, there is sometimes a lab error or test insensitivity, but it may be that the patient has been binging early on, and has run out of drugs before the visit.[27] Another possibility is that the patient is selling the drugs.

In those who self-medicate, a drug is used for a purpose other than the intended one, such as using an opioid as a mood stabilizer or enhancer. Opioids can be both calming and stimulating, often giving a brief burst of energy, and then a tranquil period.

Chemical coping is all too common, but is poorly understood and under-researched.[28] All addicts are chemical copers to some degree, but not all people who cope chemically are addicts. The person who utilizes one or two pills of hydrocodone a day for stress and anxiety is not an addict by definition, but is certainly using chemicals to cope. The severe patients basically live for the drug; their lives are controlled by procurement of the drug, and they have few coping skills outside of using the drug.[29] They will self-escalate their drug use, particularly during periods of high stress.

As much as 35% of patients with chronic pain may fall under the definition of chemical copers.[30] There are gender differences, with women using the substances primarily for anxiety, stress and depression. Women are at somewhat of an increased risk for chemically coping than are men.[29] Men may utilize the drugs for anxiety and depression, but also use them out of boredom, particularly when they are disabled by their pain. For some men, there is a strong relationship between substance abuse and sensation seeking.[29]

While physical dependence and tolerance are to be expected with long-term opioid use, addiction is not. Addiction constitutes a biologic and behavioral disease. Most abusers can stop using the drug when harm occurs, but an addict cannot. Whether a patient with previous addictions should be treated with long-acting opioids is a complicated issue. It should be approached on a case-by-case basis and is dependent on a number of factors. Among the considerations:

1. What substances were abused
2. How many years the patient has been clean
3. Whether the patient successfully completed treatment
4. The quality of the support system
5. Any comorbid psychiatric conditions[31]
6. Assessment of risk factors

Previous studies have indicated that risk factors for opioid abuse include cigarette smoking, previous drug abuse, a strong family history of drug abuse, stress, young age, early sexual abuse, poor support, low level of functioning due to headache or other pain, pain embellishment, and certain psychiatric conditions.[32] [33] [34]

An NIMH analysis identified certain problems that carried an increased risk for substance abuse. Of those with anxiety, 25% had a substance use problem, as did 33% of those with OCD and 61% in the Bipolar I category. Unipolar depression also carried a higher risk, but not as much as bipolar. Among PD patients, 84% of those with antisocial personality disorders were substance abusers.[35] Also, patients with somatization are probably at a higher risk. Untreated ADHD in older adolescent boys carried a 75% risk of substance abuse, while treated ADHD in this category falls to a 25% risk. The boys without ADHD had

an 18% overall abuse rate.[36] Our study indicated that those with personality disorders were at increased risk for abuse, but that other psychiatric conditions did not lead to more abuse.

Successful Management of Long-Acting Opioids. The physician must have knowledge and experience in the use of these drugs. The patient has to be reliable, and well known to the practitioner. Many of the problems occur with new patients; it is prudent to wait several visits before prescribing the long-acting opioids, after the physician can establish that there has been little or no previous abuse.

Patients must have demonstrated an adequate response to short-acting opioids. To avoid opioid-induced hyperalgesia, we restrict use to patients who have received SAO's for one year or more. The patient must truly be refractory to the typical ministrations, with multiple adequate trials of the usual preventive medications. Previous abuse of opioids should exclude patients; in this author's view, previous abuse of SAO's almost always leads to abuse of the LAO's. Pseudoaddiction is certainly encountered, but seems to be rare in headache patients. Be wary of the patient who claims he or she can tolerate almost no medications except for the opioids.

The use of opioids in patients under thirty should be restricted. Younger patients are more likely to develop tolerance; in older patients, particularly after age 65-70, the brain has lost the ability to do the "neuronal gymnastics" necessary in the development of tolerance. Therefore, older patients may remain on the same low dose for a number of years. If a younger patient fulfills all the requirements, such as truly being refractory, is normal psychologically and at low risk for addiction, he or she may be the exception to the age rule. Management of those with chronic migraine involves a biopsychosocial approach. Patients must not rely simply on the drug in order to function. While medications may be a mainstay of therapy, other interventions must be employed. Active coping should be strongly encouraged with each visit, and may involve a variety of approaches. These may include seeing a psychotherapist, physical therapist or other practitioner, or using self-help approaches such as exercise or biofeedback. Passive coping is a major predictor of disability in chronic pain patients. Those patients who rely only on opioids have less chance of sustaining long-term relief. Even though pharmacotherapy is the cornerstone of treatment, it is only part of a more comprehensive plan.

There are three distinct phases in the use of opioids. The first phase is the initiation of treatment. This includes the initial screening and risk assessment, the doctor's decision as to which opioid to utilize, and the doctor-patient discussion and signing of an opioid agreement. Prior to initiation of LAO's, an assessment of the following should be done: pain level, moods, social and family functioning, work status, physical functioning, and activities of daily living.[37]

The intermediate phase is comprised of the diligent monitoring of the patient while on the opioid. This must include ongoing assessment of the patient's pain level and overall functioning, with a watchful eye for signs of abuse. The physical exam on a return visit needs to assess for slurring of words, abnormal gait, and pupillary abnormalities. Do not assume that low risk patients will never abuse the opioids. During the maintenance phase of opioid prescribing, it is remarkable how many seemingly low-risk patients do misuse the drugs.

Patients usually respond fairly quickly to an opioid; if they have not responded by two to four weeks of a low dose, there usually will not be an adequate response.[22] If patients do not report an improvement in functioning, or if functioning declines, consideration should be given for withdrawal from the opioid. Some patients have an improvement in pain but a decline in activity, possibly due to sedation or other opioid-related side effects.

The third phase is switching or withdrawing the opioids when abuse has occurred, or there is lack of efficacy. Withdrawing or switching an opioid may be exceedingly difficult in some patients. Each of these phases involves a learning curve on the part of the practitioner, and proper documentation by staff members.

In my experience, using higher doses of the opioid rarely works out in the long term. They place the patient at increased risk of addiction and abuse, and complications from withdrawal. It may be thought that, given the great variation in individual responses, the opioid should be increased or "pushed" to whatever level is beneficial. However, medical and regulatory considerations should be limiting factors in keeping the opioid dose at a low level. The choice of opioid may be key; some have been shown to have less abuse potential. The long-acting fentanyl patch is subject to less abuse than oxycodone CR. The once or twice daily, long-acting morphine preparations have not been subjected to widespread abuse.

Methadone may be more effective than some of the other medications, but has a litany of problems associated with it. Besides the social stigma, high protein binding is a risk, which may lead to irregular drug levels, difficulty with withdrawal, and an increased risk for sudden death.[38] If methadone is used, it should be started at a very low dose of no more than 5-10 mg. a day, and titrated slowly. Patients placed on methadone require close monitoring, and other sedatives must be reduced or discontinued. The usual dosing range in my practice is:

methadone, 5 to 40 mg. per day
morphine, 20 to 90 mg. per day
oxycodone, 20 to 60 mg. per day
Fentanyl patch, 12.5 to 50 mcg. per day

Some type of written opioid agreement should be part of the doctor-patient alliance, although there is a lack of evidence that these agreements do much good for the majority of the patients. There is no standard opioid contract; practices should adapt one for their own purposes. There are several resources on opioid agreements, such as the AAPM website, *www.painmed.org*, the American Pain Society website, *www.ampainsoc.org*, the Federation of State Medical Boards, Inc., *www.fsmb.org*, and the US DEA, *www.usdoj.gov/dea*. In addition there is an excellent article on agreement contracts by Fishman, 1999.[39]

The treatment of breakthrough pain is controversial. Most of the breakthrough studies have been concerned with cancer pain, where the average number of breakthroughs is 4 per 24 hours.[40] For patients with non-cancer breakthrough pain, such as chronic daily headache, I tend to minimize the total opioid and avoid layering pain medicines on top of each other. Prescribing short-acting medications, such as hydrocodone, for chronic headaches greatly increases the abuse rate. The occasional patient can remain on a low dose of the long-acting opioid, with one or two SAO's such as hydrocodone per day, but, in general, try to avoid these SAO's.

Minor aberrant behaviors are often overlooked. It is not as if any one aberrant behavior warrants immediate discontinuation of an opioid, but most of the serious overuse situations have previously had a number of minor abuse occurrences. Physicians must pay attention to red flags, particularly those that arise early in the relationship with the patient.

Botulinum Toxin Injections (BoNT-A)

Botulinum toxin type A (US trade names: Botox and Dysport) has been utilized as a migraine and chronic daily headache preventive since the 1990's.[41] The results of studies have varied widely. Two Phase III studies (PREEMPT 1 and 2) with 1,384 CM patients, found Botox useful for improving functioning and reducing disablility. One of the studies was very positive in reducing headache days.[42] The preponderance of evidence points to BoNT-A as being safe and efficacious, in this author's opinion.

There are a number of possible explanations as to why BoNT-A may alleviate pain. One of BoNT-A actions is as an anti-inflammatory at the neuronal level. BoNT-A may block the release of substance P. More importantly, it may also inhibit the level of secretion of calcitonin gene-related peptide (CGRP).[41] CGRP has now been recognized as a key inflammatory mediator, a vital cog in the cascade leading to headache. Efforts are underway to develop drugs that are CGRP antagonists, which is one of the actions of

BoNT-A. BoNT-A may also block the release of certain other neuropeptides that contribute to the "inflammatory soup." This neuropeptide blockage, along with BoNT-A inhibitory effects on the excitatory neurotransmitter glutamate, results in a lessening of peripheral sensitization. With the use of BoNT-A, there is also a decrease in central sensitization.[43] Relatively few other compounds have an effect on central sensitization, which is so vital to the pathophysiology of chronic migraine.

As with a number of migraine treatments, the results of BoNT-A studies do vary. A number of variables may explain some of the differences, including: [41]

1) headache severity, chronicity and degree of refractoriness
2) medication overuse
3) patients with differing types of pain ("imploding" vs. "exploding")
4) different methods of assessing outcomes and
5) differences in the number of units of BoNT-A used , and the location of injections.

In a number of BoNT-A studies, the high placebo response rate has been difficult to overcome in proving efficacy. The optimal mechanics of BoNT-A administration are still a work in progress.[44] I usually average 50 units per treatment, but 100 or 200 may be more effective. The injections are most often administered frontally and temporally, with 9 to 12 total injections. There are some patients who do well with as little as 25 units[45], while, at the other end of the range, some outliers respond only to 250 (or more) units.

For some patients, we "chase the pain" and administer additional injections around the area of pain. For those with occipital pain, posterior injections may be very helpful. If patients do not respond to the first treatment, it is worthwhile to repeat BoNT-A at least once more. BoNT-A is expensive, but relatively safe. Of course, BoNT-A may be combined with various medication approaches.

Side effects to BoNT-A tend to be minimal; occasionally patients experience a mild droop of one eye. Some have reported numbness or other sensations around the areas of injection. Generalized weakness should not occur with the low doses that are used. On occasion, patients experience an increase in headaches for one to two weeks.

Daily or Frequent Triptans

Some patients respond only to triptan medications (sumatriptan, naratriptan, rizatriptan, almotriptan, zolmitriptan, frovatriptan, eletriptan). Several studies have described the use of daily triptans for the preventive treatment of CDH.[46] [47]

Short-lasting adverse events are often encountered with triptan use. These include paresthesias, fatigue, chest heaviness, jaw or neck discomfort, etc.[48] Chest symptoms are, with rare exceptions, not of cardiovascular origin. Cardiac ischemia due to triptan use is

rare.[48] Triptans do constrict coronary vessels, but this is a mild and short-lived effect. Despite widespread triptan use, the number of adverse cardiac events has been limited. Echocardiography and electrocardiography generally have been normal after triptan uses, even in the presence of chest symptoms.

The primary issue with frequent triptan use, assuming rebound headache is not present, is long-term adverse events. The cardiovascular system would be the most likely for possible long-term sequelae. Chronic ischemic changes, valvular abnormalities, or fibrosis are theoretical considerations. To date, there is no evidence of long-term triptan use producing any of these adverse events. This has not been systematically studied, however. The number of patients throughout the world who have utilized triptans on a near-daily basis is unknown. Until these patients have been studied, it is reasonable and prudent to do cardiac monitoring, as well as hematologic tests.

The following describes a study that we did on frequent triptan use.[46] The patients in this study were never instructed to use triptans on a daily basis. They self-discovered that a dose of triptans would alleviate headache for most or all of the day. Most patients in this study had a long history of headache refractory to usual medications. They finally had found a medication (a triptan) that would alleviate the headache for some time. Most of the patients had been using frequent triptans through their primary care physician. A minority of our patients had increased the amount of triptans prescribed. Patients were withdrawn from triptans in order to determine if rebound headache was present. The only patients who continued on triptans were those who: 1) had been determined to truly be refractory to other approaches 2) experienced no or minimal side effects 3)had rebound headaches excluded and 4) signed a "Frequent Triptan Informed Consent" form. Many patients did not meet these criteria and the triptans were discontinued.

One goal of this retrospective study of a large group of patients was to evaluate the cardiac safety of triptans. A secondary objective was to assess the hematologic tests that were performed in these patients.

For most of the treatment course, most patients (97 of 118) averaged 1 tablet daily (50 mg. sumatriptan, 2.5 mg. naratriptan, 10 mg. rizatriptan, 5 mg. zolmitriptan). Eight patients used only ½ tablet daily, while 8 others used 1.5 tablets on a daily basis. Five patients consumed 2 tablets daily. Ninety patients used the triptan every day, while 28 patients averaged 4 to 5 days a week. All of the patients would occasionally go for several days without a triptan, or occasionally take a drug holiday for a week or more.

Forty patients had taken a triptan for 6 months to a year, 37 for 2 to 4 years. Forty-one patients had taken daily triptans for 4 or more years: 29 for 4 to 6 years, and 12 for more than 6 years.

The patients were monitored for several years. Routine laboratory (hematologic) tests were done, including complete blood counts and chemistries. No abnormality was felt to

be due to the triptans. Electrocardiograms were performed on all of the 118 patients, and no abnormality was determined to be from the triptan. Eight patients did have abnormal electrocardiograms. Echocardiograms (with Doppler) were done on 57/118 patients, and 10 were abnormal. The attending cardiologist did not feel that any of these abnormalities were due to triptan use. Twenty patients underwent stress tests, and all were normal.

Nine patients felt that the triptans contributed to fatigue. Five patients had mild chest tightness, at times, possibly due to the triptans; cardiac disease was ruled out. Three patients felt that the triptans contributed to nausea.

Because these patients decided on their own to use triptans on a daily basis, adverse events would be expected to be low. If patients were not tolerating the medication well or were having significant adverse effects, they would not choose to continue the triptan on a frequent basis. There were no adverse consequences from frequent triptan use over a prolonged period.

Stimulants

When prescribed for headache patients, stimulants may be beneficial for various comorbidities, such as attention deficit hyperactivity disorder (ADHD), depression, and fatigue. In addition, stimulants do not cause the weight gain that is seen with a number of other current headache preventives. Amphetamines have been shown to possess intrinsic analgesic properties, primarily through brain catecholamine activity. They also intensify the analgesic effects of certain opioids.[49] Stimulants have been utilized to counteract the sedation encountered by opioids. An excellent review article on stimulants as adjuncts for opioids concluded that, "The evidence suggests that amphetamine drugs may enhance the effect of opioids and, at the same time, decrease somnolence and increase cognitive performance." [50]

As a group, central nervous system (CNS) stimulants cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity.[51] Caffeine, the most widely consumed stimulant in the world, is believed to act by several mechanisms of action in the pre-frontal cortex and other areas of the brain. These include translocation of extracellular calcium, inhibition of phosphodiesterase, and adenosine receptor antagonism, resulting in decreased fatigue and increased mental alertness. [51]

Nicotine, the active ingredient in tobacco, specifically stimulates nicotinic receptors in the autonomic ganglia, resulting in euphoria, arousal, relaxation, and improved attention, learning, problem solving, and reaction time.[51] However, in very high doses, nicotine causes blockade of autonomic ganglia, resulting in respiratory depression and severe hypotension.

Amphetamine and its derivatives, such as methylphenidate, demonstrate indirect CNS and PNS effects similar to cocaine. Like cocaine, they initially increase levels of catecholamines. However, amphetamines do this by a different mechanism of action. They accomplish this effect by causing the release of intracellular stores of catecholamines and inhibiting monamine oxidase (MAO).[51] The major cause of the behavioral effects of amphetamines is thought to be due more to release of dopamine rather than norepinephrine.[51] This ultimately results in increased alertness, decreased fatigue, decreased appetite, and insomnia as well as the usual "fight or flight" response characteristic of adrenergic stimulation in the PNS.

Amphetamines have been known to possess independent analgesic activity, possibly due to release of norepinephrine. The effect was felt to be about the same as that of ibuprofen. Also, stimulants may potentiate the analgesic actions of opioids.[50] The most commonly studied combination has been dextroamphetamine and morphine. Methylphenidate has also been studied as an opioid adjunctive medication. In one small study, the use of dextroamphetamine for patients with tension and migraine headache was assessed. It concluded that dextroamphetamine was viable as a preventive medication for chronic tension and migraine headaches in some subjects.[52] In another case report, a man was successfully treated with methylphenidate for his refractory episodic cluster headaches.[53]

One of our previous studies assessed 73 chronic migraineurs who had been prescribed stimulants in addition to their other medications. While the stimulants were primarily prescribed for certain comorbidities, their effect on headaches was also assessed. Seventy-five percent of the patients who were placed on the stimulants remained on them for at least 9 months. Thirty-four percent of the 73 patients both remained on the stimulants and reported positive efficacy with regard to headache. Forty-one percent of the patients suffered at least one adverse event, while only 2 patients abused the stimulant.[54]

Stimulants have proven utility for certain conditions, such as ADHD. For patients with these comorbidities the stimulants may also be beneficial for a minority of patients with chronic migraine.

Advantages of stimulants include enhanced cognition and alertness, with no weight gain. Disadvantages primarily revolve around the side effects, such as anxiety or insomnia. Abuse may certainly occur, but it is uncommon in adults. Stimulants should be considered in patients with certain comorbidities. The few studies to date have indicated a positive role for stimulants, but further studies on stimulants for headache would help to clarify that role.

Monoamine Oxidase Inhibitors (MAOI's)

For those with RCM and unipolar depression, MAOI's may be of help. MAOI's are sometimes effective for treatment-resistant depression.[55] They are also effective for alleviating anxiety. MAOI's were commonly prescribed in the 1980's, but with the advent of SSRI's and triptans, they fell out of favor. The available literature on MAOI's for headache treatment dates to the 1970's and 80's. For a select group of RCM patients, the MAOI's greatly enhance quality of life. At this point, I believe that MAOI's are underutilized.

The traditional, classical MAOI's form an irreversible complex with the enzyme monamine oxidase. Monamine oxidase is located in a number of tissues, including the brain. The mechanism of action is most likely receptor-mediated pre- and post-synaptic events, not simply an increase in serotonin.[55] Phenelzine, a traditional MAOI, has been the one most commonly used for headache.

One non-traditional reversible MAOI is moclobemide, which is not available in the USA. Moclobemide has fewer dietary and medication restriction than the classic MAOI's. The transdermal selegiline patch is a selective MAO-B inhibitor that does not require the tyramine-restricted diet. The efficacy of these non-traditional MAOI's is not as clearly established as the more traditional MAOI's (phenelzine).[56]

Careful patient selection is crucial when using the MAOI's. Patients need to carefully observe the restrictions on diet and medications. I usually prescribe low doses of phenelzine, 15 mg. tablets, and start with one tablet at night, increasing after one week to two at night. If no response is noted after three to four weeks, I usually push the dose to 3 tablets at night. By always using the MAOI at night, the patient is less likely to encounter a food interaction. Five tablets a day (75 mg.) is the usual maximum. Side effects include insomnia, weight gain, sedation, and orthostatic hypotension. The MAOI's have a reputation as being somewhat dangerous and difficult to use. Despite this reputation, MAOI's are usually well-tolerated.

The previous MAOI diets were overly restrictive. The listed risk of most foods was based on anecdotal cases. Newer evidence-based diets are easier to follow. See table 4 for the MAOI diet.

Table 4. Sunnybrook Health Center MAOI Diet [57]

Food Group	Food to Avoid	Food Allowed
Cheese	Mature or aged cheese, casseroles made with these cheeses; all except the opposite	Fresh cottage, cream, and ricotta cheese and processed cheese slices; all fresh milk products
Meat, fish, poultry	Fermented/ dry sausage, pepperoni, salami, mortadella, improperly stored meat, fish or	All fresh packaged or processed meat, fish or poultry; stored in refrigerator and eaten as soon as

	poultry	as possible
Fruits and vegetables	Fava or broad bean pods, banana peel	Banana pulp, all others except listed opposite
Alcoholic beverages	All tap beer	Alcohol: no more than 2 domestic or canned beers or 4 oz. wine a day
Miscellaneous foods	Marmite yeast concentrate, sauerkraut, soy sauce and soy condiments	Other yeast extracts, soy milk

The hypertensive crisis that may occur with a food interaction is due to a number of factors, primarily the amount of tyramine absorbed into the bloodstream. The tyramine content of food has been difficult to accurately establish. When patients consume the phenelzine at night, in low doses, while avoiding the major tyramine-rich foods, interactions are less likely. The reversible MAOI moclobemide is much less likely to trigger any adverse reaction.

The serotonin syndrome may occur due to the administration of serotonergic drugs and MAOI's. SSRI's should not be concurrently used. Other drugs that should be avoided include amphetamines, sympathomimetics, pseudoephedrine, certain opioids (meperidine), dextromethorphan, and others. Most triptans are not utilized with MAOI's, but low doses of frovatriptan may be used with caution.

For those patients suffering from both refractory chronic headache and treatment-resistant depression, MAOI's may offer some measure of hope. They also alleviate anxiety. When cautiously used, the MAOI's are not as dangerous as their reputation might imply.

Conclusion

Refractory chronic migraine is often a disabling and debilitating illness. We face major challenges in attempting to define RCM. The definition must allow for severity of illness; also, degrees of refractoriness may change over time.

Other major areas of study within RCM include pathophysiologic mechanisms, the role of medication overuse, search for biomarkers, psychological comorbidities, non-medication approaches, and pharmacotherapy.

Patients with RCM who have medication overuse headache or psychological comorbidities require a combination of approaches. It "takes a village" to help those with severe, refractory headaches, and we need to guide the patient into comprehensive treatments. There are a number of viable therapeutic approaches, five of which are presented in this article. However, we desperately need breakthrough medications and technologies that can prevent headache pain.

Disclaimer: Dr. Robbins is a partner in Brain Stimulation Chicago North Shore, which provides TMS therapy for depression.

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