

Chapter 2

Refractory (Difficult-to-Treat) Headache

Difficult-to-Treat Chronic Migraine: Outpatient Medication Approaches

Refractory chronic migraine often is a disabling, debilitating, and challenging illness. Patients who have medication overuse headache or psychological comorbidities require a combination of therapeutic approaches.

Patients with refractory chronic migraine (RCM) experience a great deal of disability and the loss of their quality of life (QOL). Chronic migraine (CM) occurs in approximately 2% of the population, but we do not know the epidemiology or rate of occurrence of RCM.

To provide a framework for other physicians and health care providers, the Refractory Headache Special Interest Section (RHSIS) of the American Headache Society (AHS) was formed in 2001. This committee of headache specialists seeks to define a standard of diagnosis for health practitioners and raise awareness of improved treatments for headache.

The definition of CM is outlined in Table 2.1, and the current proposed criteria for the definition of RCM is a work in progress and is summarized in Table 2.2 [95, 96]. The committee may want to add modifiers related to the degree of refractoriness (mild, moderate, or severe). In some patients, RCM improves or resolves over time, whereas in others it worsens. These differences need to be addressed in the definition [42].

Challenges of Refractory Migraine

RCM presents a number of major challenges, with each challenge necessitating a change in approach [42]. These challenges include:

- What role does disability play, and should disability help to define RCM?
- What constitutes resistance to treatment(s)?

Table 2.1 Defining chronic migraine. (Based on Refs. [95, 96])

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 five 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 two of “a” through “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)
	Has at least one of “e” or “f”	
	e.	Nausea and/or vomiting
	f.	Photophobia and phonophobia
	2. Treated and relieved by triptan(s) or ergot before the expected development of C1	
D.	No medication overuse and not attributed to another causative disorder	

Table 2.2 Proposed criteria for definition of refractory migraine and refractory chronic migraine. (Based on Ref. [95])

Criteria	Definition
Primary diagnosis	ICHD-II migraine or chronic migraine
Refractory	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
	Failed adequate trails of preventive medicines, alone or in combination, from at least two of four drug classes: Beta-blockers Anticonvulsants Tricyclics Calcium channel blockers
	Failed both a triptan and DHE intranasal or injectable formulation Failed 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 > 11

DHE dihydroergotamine, *ICHD* international classification of headache disorders, *MIDAS* migraine disability assessment

- There are no accepted, identifiable biological marker(s) for RCM. Therefore, how does one diagnose RCM?
- The degree of disease can change over time, improving or worsening. What role does the varying severity play?

- There are various subsets of RCM—posttraumatic headache, RCM with or without medication overuse headache (MOH), RCM with or without major psychiatric comorbidities, etc. How is the diagnosis and treatment affected by these subsets?
- How does the treatment differ for various ages: adolescent versus young adult versus middle age versus older ages?

Pathophysiology

We are just beginning to look beneath the surface of what causes RCM [28]. Some of the issues include:

- What is the role of genetics in drug resistance and inheritance of chronic headaches?
- What structural changes (in white matter or iron deposition) play a role?
- What role does central sensitization and neuroplasticity play?
- How much involvement is peripheral versus central nervous system (CNS)?
- How does MOH affect the structure and function of the nervous system?
- What is the physiologic impact of psychiatric comorbidities? Do depression and/or anxiety fuel the headaches?

Continuing research is critical to answer these questions.

Several risk factors are posited to drive the development of RCM. These include lifestyle issues such as medication overuse, sleep habits, caffeine overuse, and obesity [45]. While pharmacotherapy may be the cornerstone of treatment, other modalities are no less important. The patient must manage his or her triggers with regard to sleep, food, and caffeine intake. 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, and neck should be addressed.

Medication Overuse Headache

MOH is a critical issue that must be addressed early in the treatment of any form of headache [44]. The overuse of abortive migraine medication, used at the onset of a headache, 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 abortive medications is the principal cause of the headaches.

The criteria for diagnosing MOH are listed in Table 2.3. Note that the headache progresses, instead of subsiding, 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 in whom MOH is a major contributor,

Table 2.3 Medication overuse headache

Headache present on > 15 days/month
Regular overuse, > 10 days/month or 15 days/month, depending on the medication type
The overuse is for at least 3 months
Headache has developed or markedly worsened during medication overuse

we know that MOH should be one of the first considerations when a patient presents with worsening headaches.

While medication overuse is common, not all overusers suffer from increased headaches as a result of the abortive medications. The current definition of MOH conflates medication overuse with MOH, and, as a result, many patients are incorrectly labeled as having MOH.

Treatments for RCM

There is no algorithm for migraine treatment. The choices of medication will vary for each patient, depending on headache severity and comorbidities. For an RCM patient, the choice of therapy depends on a number of variables, including age, psychiatric comorbidities (for more on psychiatric comorbidities, see related article), tendency towards addiction, sleep, medical conditions, etc. Comorbidities often steer where we go with medications: Conditions such as irritable bowel syndrome (IBS), fatigue, and 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. It is also crucial to resolve medication overuse, and eliminate rebound in all RCM patients. For the remainder of this chapter, the author has highlighted a number of possible approaches (opioids, onabotulinum toxin, daily or frequent triptans, stimulants, monamine oxidase inhibitors (MAOIs), injections, and miscellaneous), some of which may be combined.

Opioids

In my practice, long-acting opioids (LAOs) are the most commonly used approach for RCM. The best candidate for LAOs is the person who has done well on short-acting opioids (SAOs) and who does not have characteristics of a personality disorder (PD).

Phases in Opioid Use

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 use, and the doctor–patient discussion and signing

of an opioid agreement. Prior to initiation of LAOs, an assessment of the following should be done: pain level, moods, social and family functioning, work status, physical functioning, and activities of daily living [27].

The intermediate phase comprises the diligent monitoring of the patient while he/she is 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. On return visits, the physical exam 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 misuse the drugs.

Patients usually respond fairly quickly to an opioid; if they have not responded by 2–4 weeks on a low dose, there usually will not be an adequate response [88]. If patients do not report an improvement in functioning, or if functioning declines, consideration should be given to withdrawal the opioid. Some patients have an improvement in pain but a decline in physical 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. Higher doses place the patient at an increased risk for addiction and abuse as well as 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 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 [64]. 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, 5–40 mg per day
- Morphine, 20–90 mg per day
- Oxycodone, 20–60 mg per day
- Hydrocodone, 15–40 mg 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 (www.painmed.org; www.ampainsoc.org; www.fsmb.org; www.usdoj.gov/dea). In addition, there is an excellent article on agreement contracts by Fishman [25].

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 h [111]. For patients with noncancer 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 for chronic headaches greatly increases the abuse rate. The occasional patient can remain on a low dose of the LAO, with one or two SAOs per day, but, in general, clinicians should try to avoid SAOs.

Long-Acting Opioids

The following summarizes certain LAO studies and describes guidelines for using LAOs in chronic migraineurs.

In 1997, Saper and associates assessed refractory chronic daily headache with scheduled LAOs, particularly methadone [91]. There was a small subset of patients who did well. Subsequently, Saper and his associates soured on the use of the opioids.

Similar results were obtained from Rothrock [87]. An unpublished study from Rothrock indicated that of the CM patients who were responsive at 2 months to methadone treatment, more than 70% continued to maintain a response at 1 year [88]. Rothrock found that patients tend to either respond to relatively low doses or not at all. His studies also indicated that virtually all of the positive responders, when tapered off of the methadone, relapsed into their frequent headache patterns [88].

In 2007, our group evaluated 115 patients with RCM who were treated with LAOs during a 6-year period. This was a select group of patients who previously had all done well on SAOs. Avoidance of opioid-induced hyperalgesia (OIH) is important in patients taking opioids in the long term; however, all of the patients in this study already had been on SAOs for at least 1 year [76].

Sixty-five percent of the patients did well for at least 9 months on the opioid. This was a significantly higher rate of success than that found in a previous study (13%) that used a different standard of success [65]. 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, patients with high coping skills, and those without a history of opioid abuse. Predictors of failure were comorbid PDs, older age, and, in particular, previous abuse of the SAOs. In this study, anxiety, depression, bipolar depression, attention deficit disorder (ADD), exercise, work status, disability, fatigue, and cigarette smoking did not significantly change the long-term outcome.

SAOs Versus LAOs

The term SAO generally refers not only to how long a drug carries the desired effect but also the speed of onset of the drug and how fast it drops off toward the end of the dose. Quick onsets and fast drop-offs are major determinants for abuse [36].

Table 2.4 The pros and cons of long-acting opioids

<i>The advantages of long-acting opioids include</i>
Avoidance of the “end-of-the-dose” phenomenon, with mini-withdrawals throughout the day
Consistent dosing one or two times daily, which decreases the obsession with the next dose
Maintenance of stable blood levels
Avoidance of acetaminophen, aspirin, and NSAIDs that are included in many short-acting preparations
Probable diminished risk of significant abuse
Better compliance, with less psychological dependency on the drug
<i>The disadvantages of long-acting opioids include</i>
Social stigma
Fatigue and constipation
Difficulty in obtaining scripts, with no refills available
Need for frequent office visits and monitoring
Risk of opioid-induced hyperalgesia
Risk of abuse, although probably less than with short-acting opioids
Interactions with other sedating drugs and alcohol
Risk for overdose
<i>NSAID</i> nonsteroidal anti-inflammatory drug

SAOs 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 SAOs lead to more abuse than LAOs. Although certain long-acting drugs have been 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 [63, 87, 91]. While success rates have been relatively low, they represent patients who have failed the usual ministrations, and who have few options available. Table 2.4 outlines the advantages and disadvantages of LAOs.

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, using 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 nonmedical arenas, frequent emergency room (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 [11, 110].

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 tablets 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 already has 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 often are overlooked. It is not as if any one aberrant behavior warrants immediate discontinuation of an opioid, but most of the serious overuse situations follow a number of previous 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: To identify other substances that are present but should not be and to measure the levels of the prescribed substance for compliance. When there is no opioid present, there sometimes is laboratory error or test insensitivity, but it may be that the patient has been bingeing early on and has run out of drugs before the visit [30]. 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 followed by a tranquil period. Chemical coping is all too common, but is poorly understood and under-researched [62]. All addicts are chemical copers to some degree, but not all people who cope chemically are addicts. The person who uses 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 its procurement, and they have few coping skills outside of using the drug [56]. 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 [37]. 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 [56]. Men may use the drugs for anxiety and depression, but they 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 [56].

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 LAOs is a complicated issue. It should be approached on a case-by-case basis and depends on a number of factors. Among the considerations:

- What substances were abused?
- How many years has the patient been clean?
- Has the patient successfully completed treatment for addiction?
- What is the quality of the patient's support system?
- Does the patient have any comorbid psychiatric conditions [110]?
- What are the patient's 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 [6, 22, 94].

A National Institute of Mental Health (NIMH) analysis identified certain problems that carried an increased risk for substance abuse [54]. Of patients with anxiety, 25% had a substance use problem, as did 33% of those with obsessive-compulsive disorder (OCD), and 61% in the bipolar I category. Unipolar depression also carried a higher risk, but not as much as bipolar disorder. Among PD patients, Webster found that 84% of those with antisocial PDs were substance abusers [110]. Also, patients with somatization are probably at a higher risk. In a study by Biederman et al., untreated attention-deficit hyperactivity disorder (ADHD) in older adolescent boys carried a 75% risk for substance abuse, whereas those with treated ADHD in this age group had a 25% risk. The boys without ADHD had an 18% overall abuse rate [7].

As noted, our study indicated that those with PDs were at an increased risk for abuse but that other psychiatric conditions did not lead to more abuse [76].

Successful Management of LAOs

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 LAOs—after the physician can establish that there has been little or no previous abuse.

In our practice, patients must have demonstrated an adequate response to SAOs. To avoid OIH, we restrict use to patients who have received SAOs for 1 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 from this treatment approach. In this author's view,

previous abuse of SAOs almost always leads to abuse of the LAOs. Pseudoaddiction certainly is encountered, but it seems to be rare in headache patients. Be wary of the patient who claims he or she can tolerate almost no medications except for opioids.

In older patients, particularly those over age 65, the brain has lost the ability to do the “neuronal gymnastics” necessary for the development of tolerance to the analgesic effect. Therefore, older patients may remain on the same low dose for a number of years. In contrast, the use of opioids in patients under 30 years of age should be restricted because younger patients are more likely to develop tolerance to the analgesic effects. If a younger patient fulfills all the requirements, such as truly being refractory, is normal psychologically, and is at low risk for addiction, he or she may be the exception to the age rule.

Management of those with CM involves a biopsychosocial approach. Patients must not rely on the drug 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, including seeing a psychotherapist, physical therapist, or other practitioners, or using self-help approaches such as exercise or biofeedback. Passive coping is a major predictor of disability in chronic pain patients. Patients who rely only on opioids have less of a chance of sustaining long-term relief. Even though pharmacotherapy is the cornerstone of treatment, it is only part of a more comprehensive plan.

Botulinum Toxin Injections

Onabotulinum toxin type A (Botox, Xeomin, and Dysport) has been used as a migraine and chronic daily headache preventive since the 1990s [5]. Botox is the only brand that is Food and Drug Administration (FDA) indicated for CM.

The results of studies have varied widely. Two phase III studies (Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and 2) with 1384 CM patients found onabotulinum toxin (specifically the brand Botox) useful for improving functioning and reducing disability. One of the studies was very positive in reducing headache days [58]. The preponderance of evidence points to onabotulinum toxin as being safe and efficacious, and this author concurs.

There are a number of possible explanations as to why onabotulinum toxin may alleviate pain. One of its mechanisms of action is that it is anti-inflammatory at the neuronal level. Onabotulinum toxin may block the release of substance P. More importantly, it may also inhibit the level of secretion of calcitonin gene-related peptide (CGRP) [5]. CGRP has 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. Onabotulinum toxin also may block the release of certain other neuropeptides that contribute to the “inflammatory soup.” This neuropeptide blockade and onabotulinum toxin’s inhibitory effects on the excitatory neurotransmitter glutamate result in a lessening of peripheral sensitization.

With the use of onabotulinum toxin, there is also a decrease in central sensitization [55]. Relatively few other compounds have an effect on central sensitization, which is so vital to the pathophysiology of CM.

As with a number of migraine treatments, the results of onabotulinum toxin studies vary. A number of variables may explain some of the differences, including [5]:

- Headache severity, chronicity, and degree of refractoriness
- Medication overuse
- Different types of pain (“imploding” vs. “exploding”)
- Different methods of assessing outcomes

Different numbers of units of onabotulinum toxin used and different locations of injections.

In a number of onabotulinum toxin studies, the high placebo response rate has been difficult to overcome in proving efficacy. The optimal mechanics of onabotulinum toxin administration are still a work in progress [14, 97]. The FDA’s indicated dose for Botox is 155 units, administered in 31 injections about the head. Some patients do well with much less, which is off-label.

For some patients, we “chase the pain” and administer additional injections around the area of pain, which is also off-label. 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 onabotulinum toxin at least once more. Onabotulinum toxin is expensive but relatively safe. It may be combined with various medication approaches.

Side effects to onabotulinum toxin 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 a short time.

Daily or Frequent Triptans

It has been over 20 years since triptans were first introduced, and they appear to be much safer than was originally thought. Very few serious adverse events have been reported, considering that more than 100 million patients have taken triptans. Several studies have described the use of daily triptans for the preventive treatment of chronic daily headache [76, 73]. Some patients respond only to triptan medications—sumatriptan (Imitrex, Alsuma, others), naratriptan (Amerge, others), rizatriptan (Maxalt, others), almotriptan (Axert), zolmitriptan (Zomig, others), frovatriptan (Frova), and eletriptan (Relpax). Zecuity is a sumatriptan skin patch.

Short-lasting adverse events are often encountered with triptan use. These include paresthesias, fatigue, chest heaviness, and jaw or neck discomfort [15]. Chest symptoms are, with rare exceptions, not of cardiovascular origin. Echocardiography and electrocardiography generally have been normal after triptan use, 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. Chronic ischemic changes, valvular abnormalities, and fibrosis are theoretical considerations. Cardiac ischemia due to triptan use is rare [15], and, despite widespread triptan use, the number of adverse cardiac events has been limited. These risks have not been systematically studied, however. The number of patients throughout the world who have used 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.

To study the cardiac safety of frequent triptan use, we studied patient who “on their own” had discovered that daily use of a triptan would alleviate headaches for most or all of the day [73]. Most patients in the study had a long history of headaches that were refractory to usual medications. Most of the patients had been using frequent triptans, prescribed by their primary care physician. A minority of our patients had increased the amount of triptans they used on their own.

Patients were withdrawn from triptans to determine if rebound headache was present. The only patients who continued on triptans were those who had been determined truly to be refractory to other approaches, experienced no or minimal side effects, had rebound headaches excluded, and signed a “Frequent Triptan Informed Consent” form. A summary of patient dose and usage can be found in Table 2.5.

Routine laboratory (hematologic) tests, including complete blood counts and chemistries, were done, and no abnormalities were felt to be due to triptans. Electrocardiograms (ECGs) were performed on all of the 118 patients, and 8 patients (7%) had abnormal findings that were determined not to be from the triptan. Echocardiograms (with Doppler) were done on 57 of the 118 patients (48%), and 10 of those patients (17%) had abnormal findings. 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 [73].

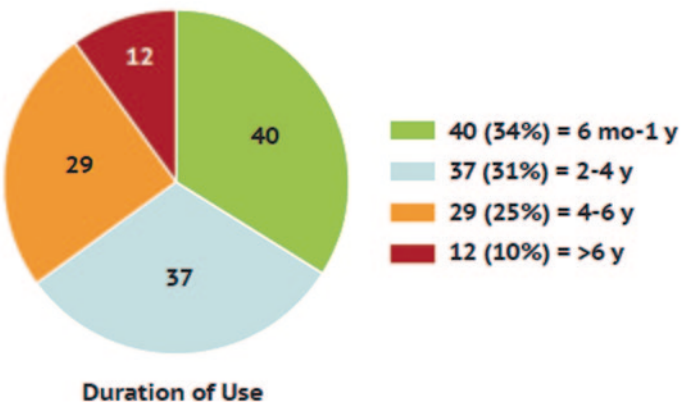
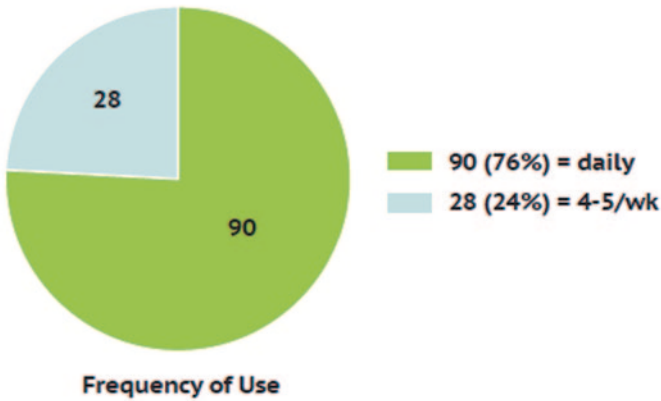
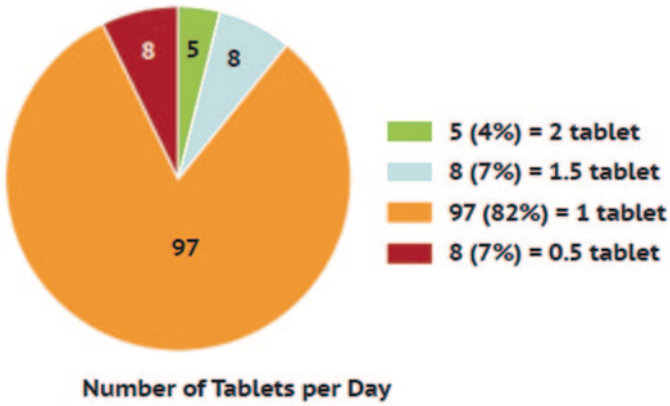
Of the 118 patients, 9 felt that the triptans contributed to fatigue; 5 had mild chest tightness at times that was possibly due to the triptans, but cardiac disease was ruled out; and 3 felt that the triptans contributed to nausea [73].

Because the patients in the study decided to use triptans on a daily basis on their own, 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. So, frequent triptan use is not ideal, but may actually be safer than some other approaches. Of course, patients must accept the possibility of the (rare) serious side effect.

Stimulants

When prescribed for headache patients, stimulants may be beneficial for various comorbidities, such as ADHD, depression, and fatigue. In addition, stimulants do not cause the weight gain that is seen with a number of other headache preventive

Table 2.5 Characteristics of daily triptan use among 118 patients



medications. Amphetamines have been shown to possess intrinsic analgesic properties, primarily through brain catecholamine activity. They also intensify the analgesic effects of certain opioids [21]. Stimulants have been used to counteract the sedation encountered by opioids. An excellent review article on stimulants as adjuncts for opioids concluded that “evidence suggests that amphetamine drugs may enhance the effect of opioids and, at the same time, decrease somnolence and increase cognitive performance [17].”

As a group, CNS stimulants cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity [24]. Caffeine, the most widely consumed stimulant in the world, is believed to have several mechanisms of action in the prefrontal 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 [24].

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 [24]. 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 peripheral nervous system (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 monoamine oxidase (MAO) [24]. The major cause of the behavioral effects of amphetamines is thought to be due more to release of dopamine than norepinephrine [24]. This, ultimately, results in increased alertness, decreased fatigue, decreased appetite, and insomnia, as well as the usual “fight or flight” response that is 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. As noted, stimulants may potentiate the analgesic actions of opioids [17]. The most commonly studied combination has been dextroamphetamine and morphine. Methylphenidate also has 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 [32]. In another case report, a man was successfully treated with methylphenidate for his refractory episodic cluster headaches [52].

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; 34% of the patients both remained on the stimulants and reported positive efficacy with regard to headache; 41% of the patients suffered at least 1 adverse event, whereas only 2 patients abused the stimulant [86].

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 certainly may occur, but it is uncommon in adults. Stimulants should be considered in patients with certain comorbidities. The few studies conducted 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

For those with RCM and unipolar depression, monoamine oxidase inhibitors (MAOIs) may be of help. MAOIs sometimes are effective for treatment-resistant depression [40]. They are also effective for alleviating anxiety. MAOIs were commonly prescribed in the 1980s, but with the advent of selective serotonin reuptake inhibitors (SSRIs) and triptans, they fell out of favor. The available literature on MAOIs for headache treatment dates to the 1970s and 1980s. For a select group of RCM patients, the MAOIs greatly enhance QOL. At this point, I believe that MAOIs are underused.

The traditional, classical MAOIs form an irreversible complex with the enzyme monoamine oxidase. Monoamine oxidase is located in a number of tissues, including the brain. The mechanism of action is most likely receptor-mediated pre- and postsynaptic events, not simply an increase in serotonin [40]. The traditional MAOI phenelzine has been the one most commonly used for headache.

The transdermal selegiline patch (Emsam) is a selective MAO-B inhibitor that does not require patients to eat a tyramine-restricted diet, at least in the lowest (6-mg) dose. Another nontraditional reversible MAOI is moclobemide, which is not available in the USA. Moclobemide has fewer dietary and medication restrictions than the classic MAOIs. The efficacy of these nontraditional MAOIs is not as clearly established as the more traditional MAOIs (phenelzine) [41].

Careful patient selection is crucial when using the MAOIs. Patients need to carefully observe the restrictions on diet and medications. I usually prescribe low doses of phenelzine and start patients with 15 mg at night, increasing after 1 week to 30 mg at night. If no response is noted after 3–4 weeks, I usually increase the dose to 45 mg at night; 75 mg is the usual maximum dose. By always taking the MAOI at night, the patient is less likely to encounter a food interaction. Side effects include insomnia, weight gain, sedation, and orthostatic hypotension. The MAOIs have a reputation as being somewhat dangerous and difficult to use, but they usually are well tolerated.

The previous MAOI diets were overly restrictive. The risk of most foods was based on anecdotal cases. Newer evidence-based diets are easier to follow (Table 2.6) [60]. 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 phenelzine at night in low doses and avoid the major tyramine-rich foods, interactions are less likely.

Table 2.6 Sunnybrook health center MAOI diet

Food group	Food to avoid	Food allowed
<i>Cheese</i>	Mature or aged cheese, casseroles made with these cheeses; all others except listed in “allowed” column	Fresh cottage, cream, and ricotta cheese and processed cheese slices; all fresh milk products
<i>Meat, fish, poultry</i>	Fermented/dry sausage, pepperoni, salami, mortadella, improperly stored meat, fish, and poultry	All fresh packaged or processed meat, fish, and poultry, stored in refrigerator and eaten as soon as possible
<i>Fruits and vegetables</i>	Fava or broad bean pods, banana peel	Banana pulp, all others, except those listed in “avoid” column
<i>Alcoholic beverages</i>	All tap beer	Alcohol: no more than two domestic or canned beers or four oz. wine a day
<i>Miscellaneous foods</i>	Marmite yeast concentrate, sauerkraut, soy sauce, and soy condiments	Other yeast extracts, soy milk

MAOI monoamine oxidase inhibitor

Serotonin syndrome may occur due to the administration of serotonergic drugs (i.e., SSRIs) and MAOIs. Other drugs that should be avoided include amphetamines, sympathomimetics, pseudoephedrine, certain opioids (meperidine), dextromethorphan, and others. Most triptans are not combined with MAOIs, but low doses of triptans (frovatriptan and several others) may be used with caution.

For patients suffering from both refractory chronic headache and treatment-resistant depression, MAOIs may offer some measure of hope and are not as dangerous as their reputation might imply.

Injections and Nerve Blocks

Various injections and blocks are used for refractory headache. For frontal headaches, sphenopalatine ganglion (SPG) blocks may be useful. Posteriorly, occipital injections are used. For cervical and occipital pain, various cervical blocks or injections may be helpful.

SPG Blocks

For frontal headache, blocking the SPG can be helpful. This has been done for 100 years, but three newer devices make it easy to do. These are the SphenoCath, the Tx360, and the Allevio SPG device. Each of these shrinks the time required from 1 h to a few minutes. SPG blocks, usually performed with bupivacaine, are safe, with few reported adverse events. For (frontal) CMs, the blocks are helpful if done 2 (or 3) days per week for several weeks.

Cervical Blocks/Injections

Various cervical procedures may be helpful, particularly if cervicogenic headache is present. When the pain is primarily in the posterior occipital area, and/or the neck, these procedures may be beneficial. Cervical epidurals may provide temporary relief. Facet injections often are useful as well. If the temporary blocks help, then procedures that are longer lasting might be more beneficial.

Occipital Nerve Blocks

For posterior head pain, blocking one or both occipital nerves may help, at least for a period of time. Occipital blocks are the treatment of choice when occipital neuralgia is present. If the pain is anterior and posterior, combining SPG and occipital blocks may provide relief.

Polypharmacy

Rational polypharmacy is commonly used for RCM. Comorbidities influence medications selection. Two (or more) preventives may be more effective than one. However, we also strive to minimize the number of medications used. If a patient is hypertensive and depressed, an angiotensin-receptor blocker plus an antidepressant might lessen the headache. Weight gain often is a concern, and with these patients, we avoid certain medications (valproate, amitriptyline, propranolol, etc.). Many RCM patients complain of being chronically tired. A number of headache medications may exacerbate fatigue. For patients with IBS, we would attempt to choose medications that may help treat the IBS and the headache. Some medications may help the diarrhea of IBS, but constipation tends to be a difficult problem in patients with IBS and headache because a number of headache drugs exacerbate constipation. Unfortunately, there are no algorithms that apply to complicated RCM patients. Each patient, with their comorbidities, is unique.

Miscellaneous

Methylergonovine (Methergine) is a smooth muscle constrictor that primarily is used to stop bleeding after childbirth. Methylergonovine is useful for a small number of RCM patients. The usual dose is one tablet three times daily. Triptans usually are not used concurrently. Availability has been a problem.

Muscle relaxants occasionally help those with RCM. We usually stick with non-addicting muscle relaxants, such as baclofen (Lioresal) or cyclobenzaprine (Flexeril, Amrix). Fatigue is a common side effect. Another muscle relaxant, metaxalone (Skelaxin), minimizes fatigue. These agents may be beneficial for treating insomnia as well. Many patients use low doses of these (half a tablet at a time).

Memantine (Namenda) is a drug used for the treatment of Alzheimer's disease and dementia. Memantine is an *N*-methyl-D-aspartate receptor antagonist that may be helpful for pain management. Memantine is a safe, well-tolerated drug. The usual dose of memantine is 14–21 mg per day.

New Developments

New approaches, such as transcranial magnetic stimulation (TMS), are becoming available. In December 2013, the US FDA approved the first TMS device specifically for the management of migraine (Cerena, eNeura TMS). According to the FDA, nearly 38% of subjects who used the Cerena (eNeura) TMS when they had migraine pain were pain-free 2 h after using the device compared to about 17% of patients in the control group. After 24 h, nearly 34% of the Cerena (eNeura) TMS users were pain-free compared to 10% in the control group [26]. TMS has few side effects and has been in testing for 10 years. Patients can have a unit at home that delivers several quick, magnetic pulses to the occipital cortex in the brain. Over time, we will see how effective TMS is for severe headaches. Studies are very promising.

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. While it is invasive, expensive, and associated with frequent side effects, nerve stimulation is viable for a small number of patients. Other nerves (such as the supraorbital) have also been the target of nerve stimulation.

In pharmacotherapy, there are a number of emerging compounds that may eventually come to market. These include newer preventive techniques, such as a monthly injection of a CGRP antibody. CGRP preventives are very promising.

Conclusion

RCM often is 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, a search for biomarkers, psychological comorbidities, nonmedication approaches, and pharmacotherapy.

Patients with RCM who have MOH 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, a number of approaches are presented in this chapter. However, we desperately need breakthrough medications and technologies that can prevent headache pain. Note this is an updated version of an article that appeared in the September 2014 issue of *Practical Pain Management*.

RCM: The Use of LAOs

Study results for a group of difficult-to-treat migraineurs provide a basis for determining efficacy and guidelines for the use of long-term opioids in this population.

Many patients with CM are refractory to our usual therapies [83]. Medication choices for the refractory chronic migraineur are limited and include polypharmacy with several preventives, MAOIs, botulinum toxin type A (Botox) and opioids, among others [67]. Each of these pharmacologic approaches helps a limited number of patients.

There have been a number of studies on LAOs as a treatment for refractory chronic daily headache [63, 87, 91]. Earlier studies focused on the use of low doses of methadone and a small minority of patients who did well in the long term. Several studies reported better success rates with other opioids, such as oxycodone CR or long-acting morphine preparations [66]. This suggested that, for the difficult-to-treat patient, this approach may be worthwhile, despite the difficulties in prescribing daily opioids.

The current study evaluated LAOs for those who had done well with SAOs for an extended period. These patients had been prescribed SAOs for significant periods in the past. Certain comorbidities were evaluated to assess if they could have predictive value as to who would do well with the opioid and who would fail. These comorbidities were also used to assess risk for abuse.

Study Design

This retrospective study was conducted at a single US headache clinic. Data were collected via chart review, patient diary, and patient interview. Patients who had been prescribed LAOs during the 6-year period 2002–2007 were assessed.

Patients kept a headache diary and used a ten-point visual analog scale to measure severity. Functional status was assessed with each visit. If adequate functioning was not maintained, the patient was usually withdrawn from the opioid. During each visit, the following were assessed in addition to functioning:

- Pain level
- Brief physical exam
- Side effects of the opioid
- Overuse/abuse behaviors

Patient Characteristics

For the study 115 patients were evaluated (87 female, 28 male, age range 23–77). All patients had been diagnosed as having RCM [96]. They had longstanding daily headaches that caused significant functional impairment or decreased QOL. Each

patient had failed multiple trials of preventive medicines. In addition, they had little or no relief from abortive medications (triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), dihydroergotamine (DHE), etc.) While attempts were made to minimize MOH, patients with this condition were not excluded from using the LAOs. Virtually every one of these patients would qualify as RCM utilizing the 2008 proposed criteria for definition of refractory migraine and RCM [96].

Inclusion Criteria

Long-time patients at the treating headache clinic with a diagnosis of RCM were included. CM was defined according to the International Headache Society (HIS) criteria [100]. All patients had been prescribed LAOs, including methadone, long-acting forms of morphine or oxycodone, or the fentanyl patch during the years 2002–2007. All patients had previously shown improved functioning and QOL on SAOs. The minimum period of use of the SAOs was 1 year. Thirty-two (28%) of the patients had abused the SAOs to some degree.

Primary Outcome Measure: Efficacy

The primary outcome measure was efficacy of the opioid. Efficacy was determined to be positive (+) if the patient continued on the LAO for at least 9 months and the patient consistently reported a 30% or greater improvement in headache frequency and/or severity over baseline. The baseline of comparison was the 3-month period prior to initiation of the LAO.

Secondary Outcome Measures: Definitions and Criteria

Opioid Abuse

The term “opioid abuse” is not well-defined in the literature and is rather imprecise. However, we use this term for the study because it encompasses not only true addiction but lesser forms of overuse as well—such as chemical coping [56]. In our current study, patients were labeled as abusers if certain behaviors were severe, persistent, or pervasive. Some of the criteria were felt to be more significant than others. 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; repeatedly missing, canceling, or refusing

appointments; selling the drugs; obtaining opioids from nonmedical 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 [141, 110].

Anxiety

Patients with anxiety disorders included those with generalized anxiety disorder, panic disorder, and OCD. Anxiety was assessed via patient interviews, histories, and the initial anxiety and psychiatric assessment forms. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria were utilized [4].

Depression

Unipolar depression and dysthymia were evaluated according to DSM-IV criteria. Patient interviews, histories, psychiatric assessment forms, Beck Depression Inventory, and the PHQ-9 (Patient Health Questionnaire Depression Module) were utilized [4].

The Bipolar Spectrum

Evaluation was accomplished by the following: (1) chart review, (2) Mood Disorder Questionnaire, (3) PHQ-9 (Patient Health Questionnaire Depression Module), and (4) interviews with patients and families.

The lifetime prevalence of bipolar, including the milder end of the spectrum, was assessed. Bipolar illness was defined according to the criteria established by the DSM-IV [4]. In addition, the modifications to DSM-IV by Akiskal were utilized in defining bipolar disorders [1, 74].

Personality Disorders

The diagnosis of PD was done in accordance with DSM-IV criteria [4]. Patients with severe PDs were not placed on the opioids. Only patients deemed moderate to severe with PD psychopathology were included [78].

The PD characteristics were pervasive, longstanding, and influential in social and work functioning. The purpose of this was twofold: to identify patients at risk to themselves and their health care providers, and to exclude those with marginal PD diagnoses. Cluster A, B, and C PDs were included. The most prevalent were borderline, avoidant, dependent, and obsessive–compulsive.

Attention Deficit Disorder

Patients with ADHD were included along with ADD. DSM-IV criteria were utilized [4]. Assessment was done via patient interviews, histories, and the Adult Self-Report Scale (ASRS).

Exercise

Patients who exercised at least 20 min a day on average (140 min per week) were considered to be exercisers.

Coping

Patients were assessed by the treating neurologist as to coping skills. Patients on disability due to headache were regarded as low copers. Medium to high copers were active and continued to work or go to school despite the presence of refractory pain.

Working Patients

These patients continued to be employed 15 h per week or more, or worked full-time at home, with normal functioning.

Disabled Patients

These patients were on long-term disability, or were unable to function more than minimally due to the CM.

Fatigue

These patients had longstanding (greater than 6 months) chronic fatigue, or excessive daytime sleepiness. Other than the headache, fatigue and/or tiredness were a primary complaint.

Statistical Analysis

Descriptive statistics (percentages) were used to summarize demographics and outcomes. A Z-test for proportion analysis was utilized. To be significant at the 0.05

level, the Z had to be > 1.96 . The Z -test was applied to groups with specific psychiatric diagnoses.

Results

$n = 115$ (87 female, 28 male, age range 23–77).

Overall Efficacy and Number of Years on the Opioid

Sixty-five percent of patients were positive responders and response rates by type of patient or comorbid condition is summarized in Table 2.7. At the time of the study, the average number of years on the opioid for the positive responders was 4.5 years. The range was 9 months to 13 years. Seventy-three percent of patients reported at least one adverse event due to the opioid. The most common adverse events noted were: constipation (54%), fatigue or somnolence (29%), and nausea (21%). Efficacy with regard to number of years of headache prior to starting the opioid was as follows:

- Three to fifteen years of headache prior to opioid: $n = 37$, 69% positive response.
- Sixteen or more years of headache prior to opioid: $n = 78$, 61% positive response.
- Overall rate of opioid abuse (as defined above) was $n = 30/115$ (26% of patients) as compared with previous abuse of SAOs, $n = 32/115$ (28%). Of the latter, 91%

Table 2.7 Summary of results by patient type or comorbidity (n/r =not reported)

Group by patient type or comorbidity	% of total sample	% of group showing long-term positive results from opioids	% of group that qualified as opioid abusers
Anxiety (including generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder)	67/115 (58)	44/67 (66)	19/67 (28)
Depression (nonbipolar)	76/115 (66)	52/76 (68)	21/76 (28)
Bipolar depression	16/115 (14)	10/16 (63)	5/16 (31)
Personality disorders (PD)	29/115 (25)	10/29 (34)	13/29 (45)
Attention deficit disorder (ADD)	20/115 (17)	13/20 (65)	6/20 (30)
Exercisers	43/115 (37)	26/43 (60)	n/r
Nonexercisers	72/115 (63)	42/72 (58)	n/r
Low copers	32/115 (27)	16/32 (50)	9/32 (28)
Medium to high copers	83/115 (72)	63/83 (76)	21/83 (25)
Working patients	75/115 (65)	45/75 (60)	20/75 (27)
Disabled patients	19/115 (17)	12/19 (63)	4/19 (21)
Fatigue	15/115 (13)	10/15 (67)	n/r

went on to abuse the LAOs as well. Information on smoking was available for 72 patients. Of the 53 identified nonsmokers, the abuse rate was 9/53 (17%) while for the 19 who had smoked at some point, the abuse rate was 4/19 (21%).

Statistical Analysis of Efficacy Rates

The rate of “positive efficacy” was compared to the rate of “no efficacy” for each of the following groups: those with anxiety, depression, bipolar depression, and PDs. A Z-test was utilized. To be significant at the 0.05 level, the Z had to be > 1.96 . There were no significant differences for any of the above diagnoses between those who had a “positive efficacy” outcome versus those with “no efficacy.”

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.

Discussion

We assessed 115 patients with RCM who were treated with LAOs during a 6-year period. This was a select group of patients who had all done well previously with SAOs. All of the patients in this study had already been on SAOs for at least a year.

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 PDs, older patients and, in particular, those with previous abuse of the SAOs. In this study, anxiety, depression, bipolar depression, ADD, exercise, working, disability, fatigue, or cigarette smoking did not significantly change the long-term outcome.

Previous Studies

In one of our previous studies conducted in 1999 [65], a significantly lower rate of success (13%) was obtained compared to the current study (65%). This was, in part, due to an altered standard of success utilized in the current study. The current study defined success as a 30% or more improvement in headache, compared to the 50% in the previous study. In addition, patient selection has been greatly improved. For this study, every patient selected had demonstrated a favorable response to SAOs. Also, while 29 of these 115 (25%) patients did have a PD, patients with severe PDs were not placed on opioids during this study period. This study ran from 2002 through 2007. I believe that our patient selection has steadily improved over the years, particularly in selecting those who have had success from SAOs without

overuse and in not prescribing the opioids to those with severe PDs or other severe psychiatric problems.

In 1997, Saper and associates assessed refractory chronic daily headache with scheduled LAOs, particularly methadone [91]. There was a small subset of patients who did well. Similar results were obtained from Rothrock [87] and from Robbins [65]. Subsequently, Saper and his associates soured on the use of the opioids. An unpublished study from Rothrock indicated that in the CM patients who were responsive at 2 months to the methadone treatment, more than 70% continued to maintain a response at 1 year [88]. 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 [88].

Saper found that only 10–15% of initially enrolled patients experienced sustained, long-term, and meaningful improvement. Another meta-analysis of long-term efficacy with the opioids in more than 3000 patients resulted in the conclusion that there was no great evidence for sustained, long-term results in the majority of the patients [102]. In this, as in the majority of studies, there has been a high dropout rate due to adverse events and lack of pain relief.

Since 1870, opioids have gone through cycles of being overprescribed and underprescribed [36]. A balanced approach is probably best. Portenoy has stated that “There appears to be a select subpopulation of patients with chronic pain that can achieve sustained partial analgesia from opioid therapy without the occurrence of intolerable side effects or the development of aberrant drug-related behaviors [57].” In general, at least half of the patients who are prescribed opioids abandon them due to side effects or lack of efficacy.

Kalso analyzed 15 placebo-controlled studies involving 1145 patients for chronic, noncancer pain. Across all of the trials, the mean decrease in pain intensity was at least 30% [38]. The vast majority (80% of patients) suffered at least one adverse event. Constipation occurred in 41% of patients, nausea in 32%, and somnolence in 29%. Fifty-six percent of the patients stopped the opioids due to lack of efficacy and/or side effects while 44% continued in the long term. In various studies, the effects of opioids on QOL are inconsistent. Long-term, large, multicenter trials have not been done.

In one neurology office, Watson assessed 102 patients and concluded that opioids prescribed by the neurologist for chronic pain did lead to acceptable pain relief and decreased disability [108]. In a review of multiple randomized clinical trials, Farrar concluded that approximately a 30% decrease in pain is the demarcation where most patients feel that it is relevant clinically [23]. Opioids have been tested versus tricyclic antidepressants (TCA) in several trials, and have generally proven somewhat more effective [102]. In one study in 2002, 54% preferred the opioids versus 30% the TCAs [59].

SAOs Versus LAOs

Short acting generally refers to not only how long a drug carries the desired effect but also the speed of the onset of the drug and how fast it drops off toward the end

of the dose. Quick onsets and fast drop-offs are major determinants for abuse [36]. SAOs 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 and overuse may occur. However, it has not been proven conclusively in studies that SAOs lead to less or more abuse or are more dangerous than LAOs.

In a previous study by Doley, 81% of self-selected patients on SAOs had continued good efficacy with the same dose, averaging four tablets per day of 7.5 or 10 mg hydrocodone. Eighty-one percent did say that the opioid was just as effective as in the previous month, and stable dosing was noted in these patients for an average of 31 months. Seventy percent of the patients remained free of any overuse violations or infractions. In addition, the patients on the SAOs had an increased QOL [20]. Self-selected groups, such as in our current study here, will report better efficacy because all patients who were chosen did well on the SAOs.

Although certain drugs—such as oxycodone CR—are more easily abused, 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.

Advantages and Disadvantages of LAOs

Several previous studies have evaluated daily opioids for severe chronic daily headache [63, 87, 91]. 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 LAOs include:

Avoidance of the “end-of-the-dose” phenomenon, with mini-withdrawals throughout the day

Consistent dosing one or two times daily, which decreases obsession with the next dose

Maintenance of stable blood levels

Avoidance of the acetaminophen, aspirin and NSAIDs that are included in many short-acting preparations

Probable diminished risk of significant abuse

Better compliance, with less psychological dependency on the drug

Disadvantages of LAOs include:

Social stigma

Fatigue and constipation

Difficulty in obtaining scripts, with no refills available

Need for frequent office visits and monitoring

Risk of OIH

Risk of abuse, although probably less than the SAOs

Interactions with other sedating drugs or alcohol

Risk of overdose

LAOs and Abuse

Most opioid abuse is secondary to immediate-acting opioids or the longer-acting ones that are easily convertible to short-acting ones. An example of this would be oxycodone CR. Younger people, particularly older adolescents, are the most frequent abusers [110].

Since their introduction in 1982, the LAOs have not been shown to be widely abused. The transdermal fentanyl has been available since 1991, and has only been minimally abused. It does not have a quick onset of action. Oxycodone CR (Oxycontin) has greatly increased the abuse rate, possibly owing to its hydrophilic nature where crushing it leads to a very quick onset. The newer abuse-deterrent preparations have been of some (limited) help in curbing abuse. Most of the abuse of LAOs is ingesting multiple oral tablets, often along with alcohol. Crushing and snorting or shooting the opioids is not as prevalent as oral ingestion. Despite the inherent problems, there has been an increasing use of continuous slow-release preparations for chronic pain [2].

Definitions of Substance Use and Misuse

Physical Dependence

Physical dependence occurs with many drug classes, such as the SSRIs, nitroglycerin, and insulin, as well as opioids. This is an expected outcome of LAO use and is a normal physiologic consequence. It occurs within 3–10 days after initiation of the opioid, but the degree varies widely between patients. In physically dependent patients, the abstinence (withdrawal) syndrome will occur if the drug is suddenly discontinued. Unfortunately, physical dependence is too often confused with addiction.

Opioid Abuse

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

Patients in the study were assessed for behaviors typical of opioid abuse or overuse as described earlier. 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 should not 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—for example, 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.

Chemical Coping

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 [62]. 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 chemical coping 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 [56]. 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 [37]. 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 [56].

Men may utilize the drugs for anxiety and depression, but also use them out of boredom and for sensation seeking. In particular, when men are disabled by their pain, they often chemically cope out of boredom. For some men, there is a strong relationship between substance abuse and sensation seeking [56].

Tolerance

With opioid use, tolerance is a natural biological consequence. Tolerance means requiring increasing doses of the opioid in order to maintain the same response. Tolerance rates vary widely among patients, and younger people do develop tolerance more quickly than older individuals. As people age, their neurons lose some of the ability to develop tolerance. Many patients do not become tolerant to the analgesic effects and the same dose may be maintained for years. The tolerance to sedation is beneficial. Tolerance to constipation rarely occurs.

When tolerance to the analgesic effect does occur and the patient is at the upper limit of our comfort zone in prescribing, there are three options: adding a short-acting analgesic, switching opioids, or discontinuing opioids for a period of time. I believe it is a mistake to continuously increase the dose in the face of analgesic tolerance. For headache patients with nonmalignant chronic pain, I believe it is crucial to maintain low to medium doses of the opioid.

Addiction

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 LAOs 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:

- What substances were abused
- How many years the patient has been clean
- Whether the patient successfully completed treatment
- The quality of the support system
- Any comorbid psychiatric conditions [110]
- Assessment of risk factors

Previous studies have indicated that risk factors for opioid abuse include the following: 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 [6, 22, 94]. Our current study affirms that those with PDs or previous abuse of short-term opioids are at an increased risk.

A Proposed Classification Scheme for Prescription Opioid Abuse

It is too simplistic to view patients as “addicts versus nonaddicts.” Dr. Sidney Schnoll, MD, PhD, has proposed a potentially useful classification system which describes subtypes of potential abusers. These include the following:

- Health care professionals,
- Illicit opioid addicts,
- Prescription opioid addicts,
- Polydrug abusers,
- Rave abusers,
- Casual abusers,
- Patient abusers,
- Patient diverters, and
- Sham-patient diverters [39].

This scheme recognizes the variability among abusers; the subtypes represent differing levels and types of abuse. Many of our patient abusers may not be easily classified.

Screening for Abuse

There are a number of diagnostic tools available for screening [13]. The Prescription Drug Use Questionnaire (PDUQ) is a long interview that is fairly predictive of substance abuse and liability. However, with 42 questions, it does take a fair amount of time. The shorter Opioid Risk Tool (ORT), with only five questions, has been validated as a simple initial screen [109]. The Screener and Opioid Assessment for Patients with Pain (SOAPP)[®] takes 10 min and is comprised of 24 items; a shorter, 14-question form is now available [9]. Each of these tools varies as far as sensitivity and specificity. While the SOAPT is highly sensitive (90%) in picking up patients who will abuse the opioids, it also has a fairly high false-positive rate of about 30% [8]. For patients new to a practice, assessment tools can quickly identify possible risks. However, risk assessment should be an ongoing process. Even for established patients, the screening tools are helpful. The best screen for abuse is a long and established relationship between the doctor and patient.

Specific Psychiatric Problems and Risk of Abuse

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 PDs were substance abusers [7].

Untreated ADHD in older adolescent boys had 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 [7]. Our study indicated that those with PDs were at an increased risk for abuse, but that other psychiatric conditions did not lead to more abuse.

Somatization is a complex syndrome, where the person has physical complaints with no demonstrable cause. Distress is turned into physical complaints. Somatizing patients are probably at an increased risk for opioid abuse. However, the risk of abuse in somatizing patients has not been adequately studied.

Guidelines for the Successful Management of LAOs in Headache Patients

Patient Selection

The patient has to be reliable, and well-known to the practitioner. Many of the problems occur with new patients. It is usually prudent to wait several visits before prescribing the LAOs and after the physician can establish that there has been little

or no previous abuse. Also, the physician must have knowledge and experience in the use of these drugs.

Patients must have demonstrated an adequate response to SAOs. We prefer to restrict use of LAOs to patients who have received SAOs for 1 year or more. Of course, all of these patients will have been refractory to conventional, nonopioid therapies. The patient must truly be refractory to the usual ministrations, with multiple adequate trials of the usual preventive medications. In this author's view, previous abuse of opioids should exclude patients, inasmuch as the current study demonstrates that previous abuse of SAOs almost always leads to abuse of the LAOs. 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 opioids.

The use of opioids in patients under 30 should be restricted. Younger patients are more likely to develop tolerance; the older patients, particularly after age 65–70, have lost the ability to do the “neuronal gymnastics” that are 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 psychologically normal, and at low risk for addiction, he or she may be the exception to the age rule. MOH should be ruled out.

Patients with characteristics of narcissistic, antisocial, borderline, histrionic, or paranoid PDs are at increased risk for abuse [85]. It is best to avoid opioids in these PD patients. Patients with avoidant or dependent PDs, however, may not be at an increased risk for these drugs. Note that there is a spectrum of severity with PD patients; those with a mild PD are at lower risk than those with a more severe PD.

It is also best to avoid the opioids in patients with severe axis I pathology, particularly severe depression and anxiety. Some of these patients may do well in the long term; however, the severe axis I pathology does raise the risk of abuse, although this has not been absolutely proven [91].

The Multidisciplinary Approach

Management of those with CM 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. Beware of the patient who says, “Doctor, when you give me enough drugs to stop the pain, then I will go back to work.” Those patients who rely only on opioids have less chance of sustaining long-term relief.

Mental health professionals are invaluable in caring for the severe pain patient and they can help in risk assessment. Physical therapy is a powerful tool that may

help us minimize the use of drugs. Biofeedback has consistently proved helpful in motivated patients and chiropractic treatment, yoga, acupuncture, and massage are helpful for selected patients. Even though pharmacotherapy is the cornerstone of treatment, it is only part of a more comprehensive plan.

Three Phases of Treatment

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 LAOs, an assessment of the following should be done: pain level, moods, social and family functioning, work status, physical functioning, and activities of daily living [23].

The intermediate phase comprises 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. 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.

The guidelines for initiation and maintenance of the opioids cannot be absolute, as that would inhibit the utilization of these drugs in appropriate patients. Requiring that every patient has multiple visits with the prescribing physician, sees a primary care doctor, and consults a psychologist prior to administration of the opioids is simply not practical. The above steps are helpful and necessary for certain patients but, in others, opioids may be initiated using less rigid guidelines. We do not want to make the requirements for the initiation and maintenance of opioids so onerous as to render them impractical. Note this is an updated version of an article that originally appeared in *Practical Pain Management*, Issue 6, July 2009.

It is helpful to involve family members or significant others, other health care practitioners, and to review previous medical records. Spouses or other significant people in the patient's life often give a more accurate depiction of functioning and moods than the patient himself can. Speaking with the other health practitioners who are involved with the patient, and reviewing previous medical records may be invaluable in assessing the appropriateness of the opioids and the risk for abuse.

Dosing and Titration for Migraineurs

In my experience with migraineurs, higher doses of the opioid rarely work out in the long term. They place the patient at an 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 [64]. 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 for LAOs in my practice is:

Methadone, 5–40 mg per day
Hydrocodone, 15–50 mg per day
Morphine, 20–90 mg per day
Oxycodone, 20–60 mg per day
Buprenorphine patch, 10–20 mg per day

The Opioid Agreement

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.

An agreement sets limits, educates the patient, deals with patient responsibilities, discusses termination criteria, and should include mention of urine testing for drugs. It is a bilateral agreement; the physician can be held accountable for its contents. For instance, there was a case where the patient violated the agreement, yet the physician continued to prescribe. When the patient overdosed and died, the physician was held liable in court [12].

Probably the best evidence of the benefits of the opioid agreement is seen in patients with known addiction histories. The agreement in this situation may improve compliance. Considerations for the agreement should include the following:

- Do not label it as a contract, but rather as a patient–physician agreement.
- Carefully word the agreement so as to minimize risk to the physician.
- Do not word it punitively toward the patient.
- Use the agreement primarily as education and to outline limits.
- Consider having the patients’ primary care physician also sign the agreement.

There are several resources on opioid agreements, such as the American Association of Physicists in Medicine (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 Drug Enforcement Administration (DEA), www.usdoj.gov/dea. In addition, there is an excellent article on agreement contracts by Fishman [25].

Ongoing Assessment

Every visit after the initial one should include an assessment of function, mood, pain level, abuse, adverse events, and a brief physical exam. The physical exam on a return visit needs to primarily assess for slurring of words, abnormal gait, and pupillary abnormalities. Patients usually respond fairly quickly to an opioid. If they have not responded by 2–4 weeks of a low dose, there usually will not be an adequate response [88]. With no or little response by 4 weeks, the consideration should be for switching or discontinuing the opioid.

Urine Testing

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.

There are two purposes to testing. One is to identify other substances that may be present though they should not be. Another is to detect the levels of the prescribed substance for compliance. When there is no opioid present, there is sometimes a laboratory error or test insensitivity, but it is possible that the patient has been bingeing early on and has run out of drugs before the visit [30]. Another possibility is that the patient is selling the drugs.

In my experience, the pain patients who raise objections and do not grant urine test requests usually have a drug problem. Specimen collections should be random and not scheduled. Most of the illegal drugs and metabolites last in the urine for 1–3 days [106]. Urine panel screens should include cocaine, amphetamines, opioids, methadone, tetrahydrocannabinol (THC), and benzodiazepines. Immunoassay urine screening is simple and has high sensitivity but lacks specificity. Chromatographic testing is better [10]. Combined testing techniques, such as gas chromatography/mass spectrometry (GC/MS), are even more accurate.

Breakthrough Pain

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 h [111]. For patients with noncancer 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 LAO, with one or two SAOs such as hydrocodone per day but, in general, try to avoid these SAOs.

When Tolerance Occurs

There are three components to tolerance: pharmacologic tolerance, OIH, and increased pain due to disease progression. While the last usually refers to cancer-type pain, it may also occur with the headache patient. OIH occurs where the opioid facilitates nociceptive events; this counteracts the positive results from the opioid medication [48]. When patients become tolerant to the positive effect of the opioids, a switch in opioids may be more beneficial than increasing the dose. Cross-tolerance of opioids is often incomplete, so that rotating the opioids may be of benefit. To change opioids, we generally start at 40–70% of the equivalent dose of the old medication. Actively managing the accompanying constipation is crucial in order to improve compliance:

With careful patient selection and close monitoring, certain patients may do well for many years on opioids and may significantly improve pain and quality of life.

Heed red flags! If a relatively new patient calls with a tale such as, “the tablets fell down the sink,” we need to be careful about giving the patient the benefit of the doubt. How often are stories like this true? Of course, a situation from a long-term patient who has never shown signs of abuse may be more believable than a new patient with the same story.

It is not always clear how serious the abuse is. The discovery that a patient received six tablets of hydrocodone from a dentist is probably innocuous, although it would be better if the patient had informed your office. However, finding that a patient that you have on morphine is also receiving 30 tablets of hydrocodone from an internist warrants serious consideration for discontinuation.

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.

A number of national organizations have published guidelines and standards for opioid prescribing. The consensus is that opioids are appropriate for certain legitimate pain patients, but the practitioner needs to observe state and federal guidelines. More information is available through their websites, including: American Pain Society, www.ampainsoc.org; American Society of Addiction Medicine, www.asam.org; American Academy of Pain Medicine, www.painmed.org; American Academy of Pain Management, www.aapainmanage.org. The excellent site www.legalsideofpain.com is a terrific source for the practitioner.

Conclusion

CM remains undertreated, as only approximately 50% of patients do well in the long term with preventatives. The other half remains at a loss. Untreated, chronic pain has an enormous impact on a patient's economic situation and QOL. When these patients are successfully treated, many will demonstrate significant functional improvement. With careful patient selection and close monitoring, certain patients may do well for many years on opioids and may significantly improve pain and QOL.

Patient selection is key, and monitoring of opioid use must be continual and vigilant. While use of opioids does carry risks for migraineurs, all of the other medication choices for these refractory patients have side effects. Patients more likely to do well include younger patients, high copers, and those without previous opioid abuse. Predictors of failure are older patients, PDs and, in particular, those who previously abused opioids. Patients with anxiety, depression, bipolar disorder, or ADD did as well as those without these comorbidities. Cigarette smoking was not a predictor for abuse. For a limited number of carefully selected patients who are not opioid-naïve LAOs may be a successful option. Note this is an updated version of an article that originally appeared in *Practical Pain Management*.

Stimulant Use in Migraineurs

Stimulants may be beneficial for chronic migraine patients presenting with various comorbidities such as attention deficit hyperactivity disorder (ADHD), depression and fatigue.

Amphetamines have been shown to possess intrinsic analgesic properties, primarily through brain catecholamine activity. They also intensify the analgesic effects of certain opioids [21]. When prescribed for headache patients, stimulants may be beneficial for various comorbidities such as ADHD, depression, and fatigue. In addition, stimulants do not cause the weight gain that is seen with a number of other current headache preventives.

This chapter reviews our experience with stimulants in CM patients over a period of 6 years.

Methods

Study Design

This retrospective study was conducted at a single US headache clinic. Data were collected via chart review, patient diary, and patient interview. Patients who had been prescribed stimulants during the 6-year period of 2002–2007 were assessed.

Patients kept a headache diary and used a ten-point visual analog scale to measure the severity of the pain.

Patient Characteristics: Seventy-three patients (57 female, 16 male) were evaluated. The patients had been diagnosed previously as having CM. With a few exceptions, the stimulants were prescribed primarily for the associated comorbidities. The comorbidities (some patients had more than one) included: ADHD ($n=28$), unipolar depression ($n=28$), fatigue/sleepiness ($n=17$), bipolar depression ($n=14$), and narcolepsy ($n=3$).

Inclusion Criteria: Long-time patients at the treating headache clinic with the diagnosis of CM were included. CM was defined according to the International Headache Society criteria [100]. All patients had been prescribed stimulants, including amphetamine/ dextroamphetamine, dextroamphetamine, and methylphenidate.

Primary Outcome Measure: The primary outcome measure was efficacy of the stimulant with regard to headache. Efficacy was determined to be positive if the patient continued on the stimulant for at least 9 months and consistently reported a 30% or more improvement in headache frequency and/or severity over a 3-month baseline.

Results

Efficacy: Of the 73 patients, 55 (75%) continued on the stimulant for at least 9 months. Of the 55 patients, 26 (47%) met the standard of efficacy of at least a 30% decrease in headache frequency and/or severity. Of the original 73 patients, 34% remained on the stimulant and reported positive headache efficacy.

Efficacy in Relation to Comorbidity: The positive headache response allocated by comorbidity is presented in Table 2.8.

Adverse Events: Of 73, 30 (41%) of the patients experienced at least one side effect. The side effects are presented in Table 2.9 (note that some patients reported multiple side effects).

Abuse or addiction: Two patients (3%) abused the stimulant.

Discussion

Psychopharmacology of Stimulants: Common stimulants include nicotine, caffeine, amphetamine, and amphetamine derivatives. As a group, CNS stimulants cause

Table 2.8 Efficacy in relation to comorbidity

Comorbidity	No. of patients with comorbidity	No. of patients with positive efficacy	% of patients with positive efficacy
ADHD	28	7	25
Unipolar depression	28	8	29
Fatigue/sleepiness	17	6	35
Bipolar depression	14	3	21
Narcolepsy	3	2	66

ADHD attention-deficit hyperactivity disorder

Table 2.9 Summary of adverse events

Side effect	No	%
Anxiety	9	12
Increased headache	9	12
Insomnia	7	10
Decreased appetite	6	8
Nausea	6	8
Dry mouth	5	7
Tachycardia	4	5
Depression	4	5
Hypertension	2	3
Diarrhea	2	3

excitement and euphoria, decrease feelings of fatigue, and increase motor activity [24]. Caffeine, the most widely consumed stimulant in the world, is believed to act by several mechanisms of action in the prefrontal 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 [24].

Nicotine, the active ingredient in tobacco, specifically stimulates nicotinic receptors in the autonomic ganglia, resulting in euphoria, arousal, relaxation, improved attention, learning, problem solving, and reaction time [24]. However, in very high doses, nicotine causes blockade of autonomic ganglia, resulting in respiratory depression and severe hypotension.

Cocaine acts to stimulate the CNS in a more indirect manner by blocking reuptake of norepinephrine, serotonin, and dopamine into the presynaptic terminal from which they are released [24]. This reuptake antagonism serves to potentiate and prolong the CNS and PNS effects of these catecholamines. In the CNS, this results in intense euphoria, acutely increased mental awareness and increased motor activity. At high doses, these effects manifest as hallucinations, delusions, paranoia, tremors, and convulsions. Peripherally, the effects of cocaine include tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction [24].

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 MAO [24]. The major cause of the behavioral effects of amphetamines is thought to be due more to release of dopamine rather than norepinephrine [24]. 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.

Stimulants and Headache: Our study 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 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 two patients abused the stimulant.

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 [17]. 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 [32]. In another case report, a man was successfully treated with methylphenidate for his refractory episodic cluster headaches [52].

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 [17]."

Which headache patients should receive stimulants? Those with ADHD certainly warrant consideration. For refractory headache, where little has helped, occasionally stimulants help both pain and energy. Many of our patients are overweight and tired, with poor concentration, and stimulants may help these comorbidities. Stimulants are occasionally helpful for depression, as adjunctive medication. By themselves they are not very effective antidepressants. Keeping doses low is a key. Many patients do well for months or years, as long as they are able to stick to lower doses of stimulants.

Conclusion

Stimulants have proven utility for certain conditions such as ADHD. This study demonstrates that for patients with these comorbidities, the stimulants may also be beneficial for a minority of patients with CM.

Advantages of stimulants include enhanced cognition and alertness but 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. Note this is an updated version of an article originally published in *Practical Pain Management*, Vol. 9, Sept. 2009.

Brief Communication

Frequent Triptan Use: Observations on Safety Issues

L. Robbins MD

Note this article was previously published in *Headache* (2004).

Objective: To examine the safety of frequent triptan use over extended periods. For a small group of patients with refractory migraine plus chronic daily headache, triptans are effective.

Methods: This retrospective study primarily evaluated the cardiac safety of daily triptan use in 118 patients and, in addition, hematologic tests were assessed. Each patient had utilized a triptan for a minimum of 4 days per week for at least 6 months. Patients with rebound headache had been withdrawn from the triptans. Most patients (97 of 118) averaged one tablet daily; most would occasionally go for several days without a triptan. Forty patients had taken a triptan for 6 months to 2 years, 37 patients from 2 to 4 years, and 41 for 4 or more years.

Results: Routine hematologic tests were performed periodically on all patients, and no abnormalities were attributable to triptans. Almost all patients had an electrocardiogram (ECG), and no abnormal ECGs were felt to be related to triptans. Cardiac echocardiography was performed in 57 patients. The ten abnormal echocardiograms were not due to triptans. All 20 cardiac stress tests revealed normal findings. Adverse events were minimal; nine patients described fatigue due to triptans, and five had mild chest tightness.

Conclusion: This long-term study of 118 patients indicates that frequent triptan use may be relatively safe.

Keywords: triptan, chronic daily headache, migraine

Abbreviations: CDH chronic daily headache

(*Headache* 2004;44:178–182)

Many patients' migraine and chronic daily headache (CDH) are refractory to the usual preventive medications. One previous study of patients with CDH indicated that, over the long term, only 46% would respond to preventives [83]. The usual preventives include: antidepressants, anticonvulsants, beta-adrenergic blocking agents, calcium channel antagonists, and muscle relaxants [68]. For those who continue to experience moderate or severe headache on a frequent basis, medication choices are limited. These include (among others) opioids [63], monoamine oxidase inhibitors (MAOIs) [19], botulinum toxin injections [29], or a combination of preventives.

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 [61, 84, 98]. The patients in this study were never instructed to use triptans on a daily basis. They "self-discovered" that a dose of triptan 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 triptan 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 criterion, 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.

Patients and Methods

Patients

A total of 118 patients (27 men and 91 women), aged 27–73 years (mean, 52), were evaluated. Inclusion criteria were: (1) the patient had used a triptan for a minimum of 4 days weekly, for at least 6 months and (2) all patients would occasionally go days without a triptan. Exclusion criteria included: (1) the presence of rebound headache (patients were withdrawn from the triptan before 6 months), (2) not utilizing a triptan at least 4 days weekly on a consistent basis, and (3) had not had adequate trials of standard preventive approaches. All patients had signed a “Frequent Triptan Informed Consent” form.

Previous Medications

All study participants were long-term patients at the Robbins Headache Clinic. Each patient’s headache had been refractory to at least three of the usual preventive medications. These included: beta-adrenergic blocking agents, calcium channel antagonists, antidepressants, anticonvulsants, methysergide, nonsteroidal anti-inflammatory drugs (NSAIDs), and muscle relaxants. Most patients’ headaches had been refractory to five or more daily preventives. During the study, besides the triptan, most patients continued on at least one preventive medication, the most common of which were antidepressants. Some patients also used NSAIDs or other analgesics.

Rebound Headache

Patients were carefully screened for the presence of rebound headache. If the history was possibly consistent with rebound headache, the patient was withdrawn from the triptan. All patients were withdrawn from the triptan for a period, to help exclude the possibility of rebound headache.

Patient Assessment

The treating neurologist at Robbins Headache Clinic performed the interviews and chart reviews. Hematologic, electrocardiographic, and echocardiographic findings were assessed via retrospective chart reviews. In patients on daily triptans, as a

matter of routine (at this clinic), hematologic tests were regularly done, as were ECGs. Cardiac echocardiography with Doppler flow studies was accomplished in 57 (almost half) patients.

Type of Headache

Headache classification was based on International Headache Society (IHS) revisions proposed by Silberstein et al. [99]. Of 118 patients, 107 were diagnosed with migraine plus CDH, 2 patients with CDH alone, and 9 patients had chronic cluster headache.

Type of Triptan

During the course of treatment, most patients switched from one triptan to another, and often reverted to the original one. Reasons for this included tolerance and insurance issues.

Patients had taken the stated triptan for at least 2 months: 85 patients used sumatriptan, 68 naratriptan, 37 rizatriptan, 30 zolmitriptan, and 6 almotriptan.

Amount of Triptan

For most of the treatment course, most patients (97 of 118) averaged one tablet daily (50 mg sumatriptan, 2.5 mg naratriptan, 10 mg rizatriptan, 5 mg zolmitriptan). Eight patients used only half a tablet daily, while eight used 0.5 tablets on a daily basis. Five patients consumed two tablets daily. Ninety patients used the triptan every day, while 28 patients averaged 4–5 days per week. All of the patients would occasionally go for several days without a triptan (or occasionally take a drug holiday for weeks).

Forty patients had taken a triptan for 6 months to 2 years, 37 for 2–4 years, 29 for 4–6 years, and 12 patients took a triptan for more than 6 years. Forty-one patients had taken daily triptans for 4 or more years (Table 2.10).

Results

Laboratory (Hematologic) Tests

Routine blood tests including complete blood counts and complete chemistries (liver and kidney functions, as well as cholesterol levels) were performed regularly, usually every 6–9 months, on all patients. Thirty-two patients had an increased cholesterol level, 12 patients had increased liver enzymes, and 3 had anemia. Two

Table 2.10 Duration of triptan use in study participants

Triptan use, no. of months	No. (%) of patients (<i>n</i> =118)
6–12	18 (15)
13–18	9 (8)
19–24	13 (11)
25–30	9 (8)
31–36	11 (9)
37–42	11 (9)
43–47	6 (5)
48–53	10 (8)
54–60	9 (8)
61–66	3 (3)
67–72	7 (6)
73–78	12 (10)

patients had an increased blood urea nitrogen, and 1 had a decrease in platelets. None of the laboratory abnormalities were felt to be due to triptans.

Cardiac Stress Test

Twenty patients had cardiac stress tests; all were normal. The stress tests were done for various reasons, unrelated to the triptans. One patient had a cardiac catheterization which was normal.

Adverse Events

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.

Electrocardiograms

The study participants were not at high risk for cardiac disease; the ECGs were performed prospectively due to the nature of the medication, after a minimum of 6 months of daily triptan use. Most patients had an ECG during 2001 or 2002, which was toward the end of the study. A cardiologist evaluated the ECGs. No abnormalities were felt to be related to triptans. One hundred three patients had an ECG, 95 tracings were normal. The following abnormal ECG findings were apparent in eight patients: atrial fibrillation, *n*=1; tachycardia, *n*=2; bradycardia, *n*=1; inverted T

waves, $n=1$; nonspecific ST-T wave changes, $n=2$; and rare premature atrial contractions, $n=1$.

Echocardiogram with Doppler

Fifty-seven patients underwent echocardiography with Doppler flow studies. The echocardiograms were performed a minimum of 9 months after the onset of daily triptan use to screen for cardiac abnormalities that may have occurred during the course of treatment. Most patients had an echocardiogram during the past 1.5 years of the study.

The attending cardiologist or internist saw the ten patients with an abnormal echocardiogram. None of the abnormalities were felt to be due to use of triptans. Six patients had mitral valve prolapse, and mitral regurgitation, enlarged aorta, mild right ventral enlargement, and aortic regurgitation were each found in one patient.

Comments

In this current study, there were no adverse consequences from frequent use of triptans over a prolonged period. A total of 118 patients (primarily with migraine plus CDH) had “self-selected” triptans as the only beneficial treatment for their daily headaches. These patients had been refractory to the usual CDH and migraine preventives.

ECG, echocardiography with Doppler, and laboratory blood tests were performed. There may be adverse consequences of daily triptan use that were not detected in this study.

Our previous study assessed 59 patients with migraine plus CDH [84]. As in the current study, the patients had taken a daily (or near-daily) dose of a triptan for a minimum of 6 months. These patients had found daily triptans to be beneficial after years of failing various preventive regimens.

In our previous study, 23 patients (39%) had been on triptans for 6–12 months, while 36 (61%) had been on them for more than 1 year [84]. The patients had previously failed multiple first- and second-line preventive medications. Forty-one patients (69%) were currently on preventive medications, the most common being sodium valproate and antidepressants. Forty-five patients (76%) used abortive medications, in addition to the daily triptans. While 39 patients (66%) had previously overused abortives, they were not overusing them since being on daily triptans. Side effects were minimal in this patient population. As in the current study, however, since the patients self-selected daily triptan use, side effects would be expected to be low. All patients had been carefully screened for rebound headache. Blood tests were done on all patients. Results were within the reference range in 47 of the 59 patients. None of the abnormal test results were felt to be due to triptans. ECGs revealed normal tracings in 19 of the 23 patients who had this procedure, while

4 patients had abnormal findings. The abnormal ECG results were not felt to be due to triptans. Echocardiography was done on five patients with no abnormalities [84].

Short-lasting adverse events are often encountered with triptan use. These include paresthesias, fatigue, chest heaviness, jaw or neck discomfort, etc. [46, 107].

Chest symptoms are, with rare exceptions, not of cardiovascular origin. Cardiac ischemia due to triptan use is rare [15, 104]. 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 [103]. Echocardiography and electrocardiography generally have been normal after triptan use, even in the presence of chest symptoms [16, 35].

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 frequent 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 near-daily triptans is unknown. Until these patients have been studied, it is reasonable and prudent to do cardiac monitoring, as well as hematologic tests.

While adverse effects from long-term triptan use are unknown, the alternatives have potential problems. Many patients with CDH are overusing analgesics, which have well-known adverse events [50]. These include liver dysfunction, gastrointestinal bleeding, renal insufficiency, and addiction.

Many patients' headaches have been refractory to daily preventive medications. The use of frequent triptans may help a limited number of these patients. We will need further studies to evaluate the safety of frequent triptan use. Note this originally appeared in *Headache*, Vol. 44, 2004.

Migraine Headache Surgery (Letter; February, 2014 Headache)

The excellent article by Mathew, "A Critical Evaluation of Migraine Trigger Site Deactivation Surgery," casts doubt on the data supporting migraine surgery [31, 49]. Migraine surgery is being promoted by plastic surgeons. A common statement on certain surgery sites states that "of the 60–80% of patients who respond to Botox, 90% will benefit from migraine surgery." The word "cure" appears all too often.

The following are observations about migraine surgery:

1. Migraine is a complex syndrome involving genetics, brain chemistry, neuroinflammation, behavioral aspects, etc., and it is unlikely that a simple surgery would fix all of these factors.
2. Response to Botox (which most of the surgeons use as a guideline) should not necessarily predict a successful surgery; the mechanism of action of Botox

for migraines probably involves, among other factors, an anti-inflammatory response, not simply via muscle relaxation.

3. The surgery is supposed to be primarily for refractory migraine patients but is being done for those with new onset daily persistent headache (NDPH), post-traumatic headache, occipital neuralgia, and other varied headache syndromes.
4. Migraine and NDPH patients who have not had trials of medications are being operated upon, some of whom have had headaches for less than 1 year, and the patients have not necessarily been under the care of a neurologist or headache specialist.
5. Surgery about the head is not new: migraine patients who have undergone various cosmetic procedures (which are similar to the surgery being promoted) have not reported (in my experience) an improvement in headaches.
6. The disappointment after failed surgery cannot be underestimated. A young man in my practice had NDPH and was 50% improved over 6 months. We could not dissuade him from undergoing the surgery (he was enthralled by the website claims), and after the surgery failed, this patient committed suicide. He was severely depressed, but the disappointment may have been a contributing factor.
7. Adverse events from the surgery should not be minimized; these are sensitized patients, often with allodynia, and cutting structures about the headache may lead to increased headaches or new neuralgia pains.
8. My “anecdotal scorecard” for the surgery results in about a 10% success rate, not the 90% often stated on the surgery websites.
9. We need multicenter trials to evaluate migraine surgery. Without adequate studies, the surgery remains an unproven and experimental procedure. Note this letter originally appeared in *Headache*, Vol. 54, Feb. 2014.

In Defense of Butalbital

The article on butalbital-containing medicines (BCMs) by Tfelt-Hansen and Diener [105] accurately summarizes the literature. They appropriately call for a limit on BCM. However, the authors oversimplify an important and complex topic. There are significant advantages to BCM that should also be acknowledged.

Why use BCM? We use BCM partly because our alternatives often fall short. Triptans and dihydroergotamine do not work for many patients, may not be appropriate for others, or may be limited because of finances and insurance. Many patients take their triptan, and later, they also utilize an analgesic, such as a BCM. Ergots are rarely appropriate. Nonsteroidal anti-inflammatory drugs and aspirin are only mildly effective and have significant side effects, particularly with advancing age. Over-the-counter combinations (usually containing caffeine) are only modestly effective. They may cause MOH and may cause other adverse effects. Isometheptene-containing compounds have limited efficacy, may not be well-tolerated, and often are unavailable. Opioids create the same problems as BCM, with overuse, addiction, and adverse effects being commonplace.

To minimize the use of BCM (and other abortives), preventives are utilized. However, the available preventives often fail over the long term [69]. Previously, I evaluated preventives in 540 chronic headache patients over a 6-month time period. Only 46% of patients remained on any preventive for at least 6 months. Fifty-four percent of patients dropped off of the preventives because of declining efficacy and/or adverse reactions [83].

The use of onabotulinumtoxinA (Botox) has improved our success with preventives. Many patients, however, cannot afford the injections or find that the Botox is ineffective. Even those who do find some success with preventives still require abortive medications, such as BCM.

The positive attributes of BCM include: (1) reasonable efficacy (primarily anecdotal); (2) low cost; (3) minimal cardiac and other side effects (except for sedation); (4) relatively few drug interactions, they may be used with most other abortives, such as triptans; (5) reasonably well-tolerated at older age ranges; (6) versatility, available with acetaminophen or aspirin, with or without caffeine, and with or without codeine; (7) BCM may alleviate both migraine and tension-type headaches; (8) antianxiety effects (though we would not specifically prescribe BCM to treat anxiety or moods); (9) BCM will produce a mild euphoria or act as a mood enhancer in some individuals; while this is not our intent on prescribing BCM, in certain patients, this is not an undesirable side effect, improving QOL; (10) in some patients, BCM will alleviate certain other painful conditions, such as fibromyalgia, neck or back pain, or arthritis; while we would not specifically prescribe BCM for those conditions, the relief of other painful conditions may enhance QOL; and (11) refractory headache patients usually require analgesics, and BCMs are one of our available choices [82].

The downsides of BCM include the milder side effects (such as fatigue), the tendency of these drugs to contribute to MOH, and most importantly, the risk of addiction. Medication overuse (MO) is common among those with CM, but MO does not always lead to MOH. BCM, along with opioids and high-caffeine-containing analgesics, are more likely to cause MOH than most abortives, such as triptans. Dependence upon BCM is occasionally encountered, with the dose remaining stable for months or years. Dependence may be justified in some patients with chronic pain. True addiction also occurs with the use of BCM, where patients cross the line into a set of addictive behaviors. Addiction and MOH are the two serious consequences from the use of BCM.

A previous study described ten trials of BCM, but none was a well-done, randomized, controlled trial (RCT) [51]. A recent RCT was fairly negative for BCM [18]. The lack of RCTs for BCM reflects the era during which they were introduced. The paucity of trial evidence does not mean that BCM are not efficacious. We rely on anecdotal evidence for many of our older therapies. Although funding could be difficult, as these drugs are generic, it would be worthwhile to pursue at least one additional well-done RCT of BCM.

To minimize the risks of BCM, patient selection is crucial. I have found that the highest risk lies with those who have certain personality disorders, along with patients who previously overused addicting medications [80]. Patients with severe

anxiety and/or depression may also be at risk for overuse. Reasonable limits on BCM might be: use restricted to 2 days per week and a limit of 20 tablets per month. There are outliers who do very well on 30–60 tablets of BCM per month, without MOH or addiction.

In an ideal world, BCM would not be necessary: preventive approaches would work well for a high percentage of patients, and our abortives would be headache specific, nonaddicting, and safe for all ages. We are a long way away from this ideal situation. If we eliminate BCM, many patients are left without effective options. We would not have BCM-mediated MOH, but many of these patients would subsequently overuse opioids, along with other analgesics. BCM have well-known downsides, but they also provide significant benefits. Note this letter originally appeared in *Headache*, Vol. 52, Sept. 2012.

Medication Overuse Headache: Inaccurate and Overdiagnosed L. Robbins, M.D.

The article “Medication Overuse Headache” [53] is an excellent review. However, the entity “medication overuse headache” (MOH), as defined in the article, is misleading and inaccurate. Current diagnostic criteria for MOH only require abortive medication use on 10 or 15 days/month (depending upon the drug) [34]. What is not needed is any evidence that the abortive actually causes an increase in headache. Medication Overuse (MO) often occurs among people with frequent headaches. However, MO does not necessarily lead to increased headache. Diagnosing MOH is not an easy task. MOH diagnosis must require an individualized assessment of the patient’s medication and headache history. The epidemiologic studies of MOH are not valid, as they do not differentiate MO from MOH.

A number of years ago all abortives, including nonsteroidal anti-inflammatory drugs (NSAIDs), were implicated in MOH. We now realize that certain drugs (NSAIDs and triptans) are less likely to cause MOH than others. Opioids and butalbital compounds are the worst offenders. Although simple NSAIDs usually do not contribute to MOH, they continue to be included in the MOH criteria.

Patients often are given the label of MOH simply because they admit to regularly consuming over-the-counter analgesics or a triptan. Many patients who frequently use these medications do not suffer from MOH. There are a number of variables, including genetics, age, type of drug, etc. that help to explain why one patient suffers from MOH, while the next does not.

For many patients with frequent headaches, behavioral techniques and preventive medications (including Botox) are inadequate. Our current preventives often provide little relief, and frequently cause unacceptable side effects. We do not have any preventives that were initially developed for headache. One long-term study indicated that only about half of migraineurs found any preventive helpful for longer than 6 months [65, 69]. Declining efficacy and increased side effects often lead to discontinuation of the preventive. Many physicians are quick to blame the patient for causing MOH. The patients are told that they are suffering from MOH due to a

particular medication, even though: (1) they have only been taking that drug for a short time, (2) the headaches did not increase once they began the medication, or (3) drug withdrawal did not lead to a lessening of the headaches.

Physicians often instruct the patient to only use the abortive 2 days per week. The patient usually responds, “that is fine, but what do I do the other 5 days? I have to function.” Many headache specialists and neurologists maintain a rigid posture, refusing to allow more than a bare minimum of abortive medication. The patient either suffers or drifts elsewhere.

Much of what is written about MO and MOH is confusing, with little basis in fact. These are arbitrary terms, without scientific validation. Of course, we must try to minimize abortives. Patients on frequent abortive medication should be withdrawn for a period of time, which is easier said than done. However, many refractory patients would have zero QOL without their (frequently used) abortives.

The current criteria conflate MO with MOH. As a result, MOH is wildly overdiagnosed. An inaccurate label of MOH may harm the patient. Patients with the MOH diagnosis often are denied the only medication that is helpful. We could redefine MOH, using scientifically validated criteria. Alternatively, we could drop the term MOH altogether. Note this letter originally appeared in the journal *Headache*, Nov/Dec, 2014.

Difficult to Treat Headache: Patient Version

Refractory (difficult to treat headaches), which occur frequently, usually are CM. CM is defined as a headache occurring 15 (or more) days per month, of which at least 8 of the headaches are migraine. For those with CM, preventive medications often help. However, approximately one-half of patients with CM continue to suffer frequent pain, with little relief from medications. This condition is termed RCM.

RCM is described as frequent migraines that have failed adequate trials of various preventive and/or “as needed” medications. A person must have failed to obtain relief from at least two categories of preventive medications. In addition, the person with RCM usually has not found adequate help from the usual migraine “as needed” medications, such as sumatriptan, naproxen, etc. Those with RCM also find that their functioning and QOL is impaired by the frequent headaches. RCM affects millions of individuals.

A small minority of those with refractory headaches do not suffer from migraine. Instead, they may experience refractory cluster headaches or another headache syndrome.

Many questions involve RCM, such as:

What role does disability play, and should disability help define RCM?

How resistant to the myriad of available treatments qualifies the patient to be considered refractory?

Treatments may differ depending upon the age of the person; medications prescribed for a 16 year old may not be used at the age of 80. The resistance demonstrated by

some patients may be due to genetics (genetics often plays a huge role), structural changes in the brain (particularly the white matter), and medication overuse.

Various subsets of RCM have been identified. These include posttraumatic headache, headaches exacerbated by medication overuse, headaches in a person with severe psychiatric illness, etc.

Outside of Medication

The headache sufferer should not rely solely on medicine for relief. Lifestyle changes are important too. It is crucial to avoid caffeine overuse and to encourage “active coping,” through exercise, physical therapy, yoga, psychotherapy, etc.

Exercise (at least, on average, 20 min daily) and weight control may improve headache and QOL. Yoga or Pilates may be beneficial. Physical therapy is often useful, and is primarily aimed at associated neck pain. Although stress may be a major trigger for the headaches, managing stress is difficult to achieve. For those with anxiety and/or depression, psychotherapy is helpful for improving QOL. Biofeedback and other relaxation techniques are also underutilized and should be considered.

Medication overuse headache (MOH) is a critical issue that must be addressed. It is important to try to limit “as needed” medications. If a patient is consuming pain medications or triptans for 10 or more days per month, he or she may be suffering from some degree of MOH. However, these analgesics often are the only effective treatment for that person. Withdrawal from the analgesics may be very difficult to accomplish. MOH tends to be overdiagnosed. Many patients overuse the pain or triptan medications. However, overuse of the “as needed” medicines does not necessarily mean that the drugs are increasing the headache.

Medication: Selected Outpatient Options

When migraineurs have failed three or more of the “usual” preventive regimens (for example, topiramate, amitriptyline, beta blockers, etc), the physician should consider other treatment approaches. Most medications used for refractory headaches are considered “off-label:” they were initially developed for another purpose. How is a medication selected that is best suited for the individual? Comorbidities must be identified. These include the psychiatric and medical conditions, other than headaches, that occur in the individual. If someone has anxiety/depression, antidepressants may be prescribed. If weight gain is a major issue, drugs associated with weight gain must be avoided. With hypertension, medications used to lower the blood pressure are prescribed.

Each patient is unique, and our medication choices vary widely between patients. The following is a discussion of various treatment options for RCM.

Botulinum Toxin (Botox)

Botulinum toxin type A (specifically Botox), is the only FDA-approved medication for CM. This treatment may be used once the diagnosis of CM has been established. Due to insurance or financial restrictions, Botox is usually injected after a number of other standard medications have failed. For CM, Botox is the most effective migraine preventive with the least side effects. Since 1996, over 3 million patients have received Botox for headaches. Botox is effective in 60–65% of the patients, and the effects usually last for 2.5–3 months. Short-term side effects include eye drooping, headache, and neck pain. Long-term side effects have not been reported. The injections are minimally painful because Botox does not sting.

The FDA indication recommends Botox injections every 3 months. This totals 31 injections (155 units). Many patients do well with a lesser dose (60–100 units). Some physicians “chase the pain,” injecting more Botox at the sites where the pain is located. If the Botox wears off after 2 months, it is generally safe to reinject before the 3-month interval.

Many insurance policies cover Botox injections, particularly with “prior authorization” obtained by the physician’s office. An increasing number of physicians have received training in Botox injections for CM.

Most physicians, concurrently with Botox, also prescribe other preventive and “as needed” medications. For those patients with severe RCM, a multipronged approach is necessary, which includes nonmedication treatments, Botox, preventive agents, and “as needed” drugs.

Polypharmacy: Using Two (or More) Preventives

Most patients with refractory headaches require more than one medication. Comorbidities “drive” the preventive approach. For example, topiramate which is an antiseizure drug approved for use in migraine prevention, is commonly used with the antihypertensive beta blocking agents (propranolol, timolol), which are also approved for migraine prevention. These drugs may be prescribed with other preventives, including the antidepressant amitriptyline. It is vital to minimize the drugs and to avoid side effects. For instance, if a person has constipation, we would avoid using the older antidepressants (such as amitriptyline). If weight gain is a problem, we may use topiramate instead of valproate. If a person cannot afford to have any memory problems (such as an accountant), topiramate may not be the best choice. For each migraineur, the “top ten” list of appropriate medications varies.

Concurrently with preventive therapy, almost all patients utilize “as needed” medications. The idea is to minimize the use of these drugs, trying not to “chase the headache” every 4 h. Most patients with RCM utilize one or two preventive agents, and three or four “as needed” drugs, from their medicine cabinet.

Daily (or Near-Daily) Triptans

Some patients with migraine only respond to the triptans (sumatriptan, naratriptan, rizatriptan, etc.). Triptans have been available since 1991, and are relatively safe. Over the past 20+ years, several hundred million individuals have used triptans for their migraine attacks. Short-lasting side effects are often experienced, such as chest or neck pressure, tingling, fatigue, etc. Almost all patients who frequently utilize triptans (4 or more days per week), “self-select” this approach. Their physicians did not recommend daily use of triptan. The major issue with frequent triptan use is MOH. Although triptans may cause MOH, they are less likely to do so than analgesics containing caffeine, butalbital compounds, or opioids.

In addition to the risk of MOH, the major challenge of triptan use is cardiac effects. However, over the past 20 or more years, very few reports of cardiac problems have emerged. We are not certain of all the long-term risks of these drugs, but they may be safer than many alternatives. For example, one triptan per day is less harmful to the body than six aspirin with caffeine (or ibuprofen or naproxen) tablets. Many of the long-term side effects seen in headache patients are related to daily anti-inflammatory use. Most patients using triptans on a daily basis also have other “as needed” drugs to alternate with the triptan.

The ideal patient for triptan therapy experiences no triptan-related side effects and has minimal cardiac risk factors. Also, it is important to wean a patient from the triptan for a period of time, to ensure that MOH is not occurring due to triptan use. Cost and insurance reimbursements were previously a barrier to this approach. However, inexpensive generic triptans are now available.

Long-Acting Opioids (LAO)

For a minority of RCM patients, LAO may provide the most effective relief. SAOs (Vicodin/Norco/Tylenol with codeine) only provide relief for 2–4 h, and have a high risk for MOH. The ideal LAO patient is one who has had excellent pain relief from SAOs, without overuse, and without tolerance to the analgesic effects. Tolerance occurs when a person requires constantly increasing doses in order to achieve the same effect. A person with a personality disorder (borderline, antisocial, narcissistic) is a poor candidate for LAO. Previous abuse of opioids or other addicting drugs increases the risk of MOH with LAO.

The use of opioids in patients under the age of 30 should be very restrictive. We rarely use LAO in younger patients. If a person has not used opioids on a daily basis, we are very hesitant to institute these drugs. It is important to avoid creating more headaches through the use of opioids. However, if an RCM sufferer has been using opioids for a prolonged time and fulfills the above criteria, they may respond well to an LAO. The “ideal” RCM patient for LAO would be: middle aged or older patient, the one who has tried many approaches, who no personality disorder, and has responded well to SAOs (good effectiveness with no overuse and no tolerance).

One key to using LAO is to minimize the dose; if high doses are required, the LAO will not be effective. Patients usually respond quickly to the LAO, enabling the physician to make an assessment after 4 weeks of treatment regarding effectiveness and side effects. If tolerance develops, whereby higher and higher doses are required, the LAO approach will not work for the long term.

A number of downsides to LAO have been identified, including: the risk for abuse or addiction, side effects such as fatigue or constipation, the stigma of taking daily opioids, difficulty obtaining the prescription, and dependence on the LAO (withdrawal may be difficult). However, for a small number of RCM patients, LAO greatly enhances their QOL. LAO may be safer over the long-term than the SAOs, because acetaminophen contained in the short-acting preparations may cause liver or kidney problems.

A number of LAO are available and usually do not contain acetaminophen, unlike the SAOs. Some patients respond well with buprenorphine (Butrans—a 7-day patch), while others prefer extended release morphine (Kadian—an excellent type of delivery system). Methadone has certain advantages (effective, can split tablets, inexpensive) and disadvantages (difficult withdrawal, more dangerous if overused). Oxycodone controlled-release (Oxycontin) carries a higher risk of abuse, and is much shorter acting than Butrans or Kadian. Zohydro is an excellent “pure” hydrocodone, without acetaminophen. Whichever type of LAO is used, it is crucial to only prescribe low doses.

Nerve Blocks

Sphenopalatine ganglion (SPG) nerve blocks have been used for over 100 years. Several new devices are available that facilitate completing an SPG block in the physician’s office. The SPG is a nerve center near the top of the nose, between the eyes. The block is accomplished easily, and takes only a minute. No pain has been reported. A type of novocaine is sprayed up the nose via the Tx360 or Sphe-noCath device. SPG blocks are safe, and most effective if done two or three times a week for several weeks. If effective, these blocks may provide relief for days or weeks (occasionally longer). Some neurologists and pain specialists perform the SPG blocks in their office.

Occipital nerve blocks involve injecting under the skin in the back of the head. Some type of novocaine is used, sometimes with cortisone. Although somewhat painful, occipital blocks are fairly safe. These injections may help for weeks (usually not more than one month). Some neurologists, and almost all pain specialists, perform occipital nerve blocks.

Trigger point injections are usually undertaken with a type of novocaine, injected into the neck or upper back areas. The effects of these injections may last from days to weeks, and are performed by some neurologists and pain specialists.

Deeper neck (cervical) injections may help some patients with RCM, particularly when the neck is involved. For those with neck and “back of the head” pain,

these injections should be considered. These include steroid epidural injections, and “facet” nerve blocks which are performed by a pain specialist on an outpatient basis. Although generally safe, these injections carry slightly more risk than the superficial injections, and are costly.

Miscellaneous Medication Approaches

Monoamine oxidase inhibitors (MAOI) are powerful antidepressants that may be effective for refractory headaches. For those with moderate or severe depression, the MAOIs may be beneficial.

Weight gain and insomnia are common side effects. With the traditional MAOI, such as phenelzine (Nardil), a low-tyramine diet must be followed, and certain medications may not be used concurrently. At this time, MAOIs, are probably underutilized. There is a milder MAOI patch available (selegiline, or Ensam) with less side effects.

Stimulants (methylphenidate or mixed amphetamine salts) may help pain as well as some comorbidities (fatigue, weight, attention). For some patients, these agents greatly enhance QOL. Fatigue is commonly encountered in headache patients, and stimulants may help offset the fatigue. Stimulants are primarily used for ADHD, which is a common condition. Many patients with RCM struggle with their weight, and the stimulants help in weight loss (at least for a period of time).

Methylergonovine (Methergine) is a medication used following childbirth, and is occasionally helpful for headaches. Methylergonovine is usually dosed 2 to 3 times daily. However, a number of medication interactions have been reported. Cost and availability have been issues.

Memantine (Namenda XR) is a drug used for memory problems (Alzheimer’s syndrome). Memantine is fairly safe and well tolerated. Memantine (used in the XR form, once per day) is effective for some headache patients with very few drug interactions.

Muscle relaxants are occasionally effective for RCM. The nonaddicting agents are preferred, such as lioresal (Baclofen), cyclobenzaprine (Flexeril), or tizanidine (Zanaflex). Although generally safe, associated fatigue may limit their use. For those with insomnia, using a muscle relaxant at night may help both sleep and headache.

Conclusion

For many chronic headache sufferers, the “usual” approaches are not effective. It is important to utilize nonmedication approaches while minimizing medicine. This article presents various treatment approaches for patients who have been unsuccessful with the standard headache therapies. Hopefully, in the near future, more effective

therapies for pain will be available. It should be noted that most of the treatments discussed are not FDA approved for the indication of headache treatment. The therapies presented are this author’s approach, and are not intended to represent “mainstream” treatment. This discussion is not prescriptive; the risks and benefits of any treatment should be discussed with your treating physician. Note that this article originally appeared in the patient journal *Headwise*; Vol. 4, Issue 2, 2014.

Refractory Chronic Migraine: Long-Term Follow-up Using a Refractory Rating Scale

Introduction

Refractory chronic migraine (RCM) is often a debilitating illness, with an enormous impact on QOL. The RHSIS of the AHS has provided a forum for physicians on this crucial topic. CM occurs in approximately 2% of the population [81]; the prevalence of RCM is unknown.

A lot of work has been accomplished on the definition of RCM [42]. A summary of the current proposed criteria are listed (see Table 2.11). The definition is a continuous work in progress [96]. Long-term outcomes for those with RCM have not been investigated. In addition, there is a range of severity among the RCM patients. For clinical and research purposes, it is important to categorize the RCM patients according to severity.

This study assessed pain and QOL in RCM patients over a 10 year period. A novel RCM “severity rating scale” was used for the evaluation of these patients.

Table 2.11 Refractory chronic migraine criteria (Proposed) [96]

1. Patient has diagnosis of chronic migraine (or migraine)
2. Patient has failed adequate trial of at least two out of four drug classes
a. Anticonvulsants
b. Beta blockers
c. Tricyclics
d. Calcium channel blockers
3. Patient has modified lifestyle and eliminated triggers
4. Patient has failed abortive medications, including:
a. Triptans and DHE
b. NSAIDs and combination analgesics
5. There may be modifiers:
a. With or without medication overuse
b. With significant disability

DHE dihydroergotamine, *NSAID* nonsteroidal anti-inflammatory drug

Methods

Design and Patient Selection

This was a retrospective chart review of 129 RCM patients. RCM was diagnosed according to criteria suggested by the RHSIS of the AHS (Table 2.11).

Inclusion Criteria RCM patients older than 18 years as of the year 2000. The patients were followed at our headache center during the years 2000–2010, and must have remained at the clinic for that time. One hundred and twenty nine patients, with an average age of 49 (108 Females, ages 19–72 and 21 Males, ages 31–69), were assessed.

Refractory Scale

A refractory scale of this author's design was utilized for assessment. The scale ranges from 2 (least severe) to 10 (most severe). See Table 2.12.

The patients were assigned a number (2–10) for severity as of the year 2000, and this assignment of severity was not reassessed after the initial date.

The severity groupings were as follows: score of 2, 3, or 4: mild RCM, score of 5, 6, 7: moderate RCM, score of 8, 9, 10: severe RCM.

Table 2.12 Refractory scale (2–10, 10= most severe)

1. Refractory to preventives =2 points (refractory to preventives is determined by RHSIS ^a and Silberstein [101] criteria)
2. Refractory to abortives =2 points (determined by RHSIS ^a and Silberstein ^b criteria)
3. Greater than 10 years of chronic migraine = 1 point (chronic migraine defined according to International Headache Society (IHS) criteria [33])
4. Twenty five or more days of headache per month (on average) = 1 point
5. Two of the following associated medical conditions: irritable bowel syndrome (IBS), fibromyalgia, temporal mandibular dysfunction (TMD), chronic pelvic pain, painful bladder syndrome, and chronic fatigue = 1 point. These syndromes were defined according to guidelines established by the various specialty organizations. Patients had to have been diagnosed using the standard criteria [47]
6. Psychiatric comorbidities of the following types: severe Axis I (affective disorder), or any Axis II (personality disorder) = 1 point. These were diagnosed utilizing guidelines established in DSM-IV [3]
7. Disability (work and/or home) = 1 point. The patient had to demonstrate moderate to severe disability with poor functioning for at least 6 months. Disability was assessed by various means, including interviews with the patient and family. A VAS functioning scale was utilized
8. Medication overuse headache = 1 point. Criteria established by the IHS were utilized [33]

DSM-IV Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, *RHSIS* Refractory Headache Special Interest Section *VAS* visual analog scale

Outcome Measures

Quality of Life (QOL): QOL was measured by adding pain, functioning, and mood scores (each on a 1–10 scale, with 1 = best, 10 = worst). The QOL rating scale ranged from 3 (best) to 30 (worst). Pain was assessed via a visual analog scale (VAS) of 1–10, (10 = worst). Functioning was determined by the level of the work and/or home activities. Mood determinates included depression, anxiety, and insomnia. These were assessed using DSM-IV criteria.

Pain Level: Pain was assessed using a visual analog scale, 1–10 (10=worst).

Statistics

Statistical package for social sciences (SPSS) v17 for Windows was used for the statistical analyses. Difference scores for QOL1–QOL2 and pain ratings time1–time2 were calculated. In order to analyze if these pre-post scores differed across the three pain severity groups (mild, moderate, severe), a one-way analysis of variance (ANOVA) was conducted. To determine if the treatment was significantly effective in decreasing level of pain and improving QOL, pre-post paired samples *t*-tests were calculated for each severity group. Finally, Cohen's effect size formula $[(\text{mean1} - \text{mean2}) / (\text{the average of standard deviation1} + \text{standard deviation2})]$ was used for paired samples *t*-tests.

Results

N = 129 patients (108 F, ages 19–72, 21 M, ages 31–69, average age 49). The patients were initially categorized according to the refractory scale (2–10, 10 = most refractory). QOL (Table 2.13) and pain level (Table 2.14) were assessed as of the year 2000, and also as of the year 2010.

For the mild patients, 66% improved by 30% or more in QOL during these 10 years. In the moderate group, 57% improved by 30% or more, and in the severe group 61% improved by 30% or more.

QOL over 10 years was the same, or worse, in 4% of mild patients, 16% moderate, and in 18% of severe patients.

ANOVA revealed significant mean change score (time1–time2) differences for QOL ratings between severity groups, $F(2|126) = 4.31, p = 0.02$. Bonferroni post hoc results showed that improvements in QOL after treatment were significantly larger for the severe group compared to the mild group ($p = 0.045$) and for the severe group relative to the moderate group ($p = 0.03$). Change scores for the mild to moderate group did not significantly differ.

In the mild group, 80% of the patients had a decline of 30% or more in pain levels over the 10 years. In the moderate group, 72% had a decline of 30% or more

Table 2.13 Quality of life: Year 2000 versus 2010

Initial degree of refractoriness	Initial QOL in 2000 (3–30, 30 = worst)	Final QOL in 2010	% Improvement in QOL, 2000–2010
Mild (2–4 on refractory scale) <i>N</i> =24: average # = 3.79	13.2	8.6	35% <i>p</i> <0.001, Effect Size(ES)=2.07
Moderate(5–7) <i>N</i> =67: average # = 6.04	15.8	10.8	32% <i>p</i> <0.001, ES = 1.30
Severe(8–10) <i>N</i> =38: average # = 9.02	21.6	14.4	33% <i>p</i> <0.001, ES = 1.50

Table 2.14 Pain level: Year 2000 versus 2010

Initial degree of refractoriness	Initial pain level (2000) (1–10, 10 = worst)	Final pain level (2010)	Change (%) from 2000–2010
Mild (2–4) <i>N</i> =24	7.8	4.3	–45% <i>P</i> ·0.001, Effect Size (ES)=2.55
Moderate (5–7) <i>N</i> =67	7.7	4.5	–42% <i>P</i> ·0.001, ES = 1.30
Severe (8–10) <i>N</i> =38	8.6	5.5	–36% <i>P</i> ·0.001, ES = 2.16

Table 2.15 Overall results (Across all Groups) *N*=129

Initial QOL(2000)=17 (3–30 scale, 30 = worst)	Final QOL(2010)=11.4 (33% improvement)
Initial pain level(2000)=7.96 (1–10 scale, 10 = worst)	Final pain level(2010)=4.76 (40% improvement)

in pain levels. The severe group had 71% of patients reported a decline of 30% or more in pain over these 10 years.

Pain levels were the same, or worse, over the 10 years in only 4% of mild patients, 15% of moderate, and in 18% of the severe patients. ANOVA findings for the change scores in pain ratings failed to yield any correlation between severity group differences (Table 2.15).

Sixty percent of patients had an improvement in QOL by 30% or more (over the 10 years)

Fifteen percent of patients saw no change, or suffered a decrease, in QOL

Seventy three percent of patients had pain levels decrease by 30% or more

Fourteen percent of patients reported no improvement, or an increase, in pain levels over the 10 years

Paired samples *t*-tests were conducted for each severity group between assessment periods. In case of the mild group, QOL ratings significantly improved after treatment, $t(23)=11.88$, $p<0.001$, *ES* (Cohen's *d*)=2.07, and pain ratings significantly decreased, $t(23)=10.15$, $p<0.001$, *ES*=2.55.

Table 2.16 Medications. The following medications were reported to be beneficial by the refractory patients. To be listed, the patient must have found the medication helpful for their pain, and to have continued on the medication for at least 6 months

	Opioid	Frequent triptans, 4+ per week	Butalbital	Onabotulinum- toxinA	Stimulant	Other
Mild N=24	10 42 %	11 46 %	3 13 %	6 25 %	4 17 %	2 8 %
Moderate N=67	44 66 %	23 34 %	11 16 %	9 13 %	5 7 %	6 9 %
Severe N=38	27 71 %	6 16 %	8 21 %	6 16 %	6 16 %	4 11 %
Total N=129	81 63 %	40 31 %	22 17 %	21 16 %	15 12 %	12 9 %

In the moderate group, QOL significantly increased, $t(66)=9.95$, $p<0.001$, $ES=1.30$, and pain levels significantly decreased, $t(66)=13.36$, $p<0.001$, $ES=2.26$. Finally, results for the severe group revealed a statistically significant increase in QOL after treatment, $t(37)=9.51$, $p<0.001$, $ES=1.50$, and a significant decrease in pain levels, $t(37)=10.42$, $p<0.001$, $ES=2.16$. Overall, the results suggested that the treatment was effective in improving QOL, and reducing level of pain for all severity groups (Table 2.16).

Overall, the medications that helped the most over the 10 years included: opioids (63%), frequent triptans (31%), butalbital compounds (17%), and onabotulinum-toxinA (16%).

Discussion

This study categorized RCM patients according to a unique refractory rating scale. The patients were evaluated as of the year 2000, and again 10 years later. Most (60%) of the patients had at least a 30% improvement in QOL, while 73% also experienced a 30% (or more) improvement in pain levels. While the severe patients also improved over 10 years, they still had significantly lower QOL, and higher pain scores than the mild or moderate patients. In this refractory group, opioids and frequent triptans were the most commonly used medications.

The refractory rating scale presented here is an initial attempt to classify RCM patients according to severity. A refractory scale may be beneficial for both clinical and study purposes. Patients with mild RCM will generally be easier to treat than those with severe RCM. Therapeutic studies on those with RCM may be less likely to succeed if the patients have severe RCM versus milder RCM. The individual components of the scale reflect various elements of refractoriness, including comorbidities. This author awarded more weight to “refractory to preventives” (2 points) or “refractory to abortives” (2 points) than to the other components (1 point

each), primarily because refractory to preventives or abortives are central hallmarks of RCM.

As the plasticity of the brain may be an important factor in refractoriness, it is important to include the length of time of the headache (selected for this study at > 10 years). The average number of headache days per month is important, with 25+ days probably being more refractory than 15–24. Associated medical comorbidities often occurring in those with CM were included. These conditions may complicate treatment, and add to refractoriness. For this study, we included the following: IBS, fibromyalgia, TMD, chronic pelvic pain, painful bladder syndrome, and chronic fatigue.

Psychiatric comorbidities, commonly seen in RCM patients, certainly complicate treatment. Significant abuse in childhood may predispose one to RCM. Important comorbidities include anxiety, depression, the bipolar spectrum, personality disorders, somatization, and posttraumatic stress disorder [75, 78]. For this study, severe DSM-IV Axis I (affective disorders), or any Axis II (personality disorders) were considered important in refractoriness [3].

Disability should be a part of a refractory scale. Those who function at a low level, at work or at home, often are more resistant to treatment. Patients exhibit a wide range of coping and resilience. Resilience is a combination of nature and nurture; one can almost predict resilience based upon the shape of the serotonin transporter gene. This author believes that disability, or a chronically low level of functioning, renders it less likely that the RCM will improve. The level of functioning should factor into a refractory rating scale.

Medication overuse headache (MOH) is a remarkably complicated concept; MOH must be distinguished from medication overuse without resulting headache. It can be exceedingly difficult to determine who has MOH [33]. For this study, we used IHS guidelines as to MOH. MOH does add to refractoriness and resistance to treatment, and should be included in a refractory scale [33].

The medications utilized by patients in this study included: opioids (usually LAO), frequent triptans, butalbital, onabotulinumtoxinA, and stimulants. The author has published on most of these subjects [71, 72, 77, 79]. For RCM patients, it often takes a combination of medications to achieve even minimal benefits. Many of the patients in the study took two or more of the listed medications.

RCM constitutes a small but important subset of migraine patients. For clinical and study purposes, it is helpful to categorize RCM patients as to the degree of refractoriness. After 10 years, the severe patients remained behind the other groups regarding QOL and level of pain. However, over the 10 years, all of the groups (mild, moderate, severe) improved regarding QOL and level of pain. This initial attempt to create a refractory rating scale should be refined and improved with further study and research. Note this article originally appeared in *The Journal of Headache and Pain*, Vol. 13, 2012.

Comment Observation and Rebuttal

Long-Acting Opioids and Headache

The article by Morris Levin, MD, “Opioids in Headache,” [43] is an excellent review of the subject. I agree that LAO may be beneficial for a small number of refractory patients with CM. In addition, those with severe, refractory posttraumatic headache, as well as new-onset daily persistent headache may be good candidates. Over time I have developed guidelines for patient selection for LAO, which include:

1. The patient must truly be refractory to multiple other approaches.
2. We should not use these medications under the age of 30, with rare exceptions.
3. Exclude certain personality disorders, particularly borderline, antisocial, and paranoid. (I have not found anxiety, depression, or bipolar to be a substantial risk factor for LAO.)
4. There must have been a good response to shortacting opioids, without escalation of dose and lacking significant side effects.
5. Patients should be excluded if they previously overused/abused short-acting opioids.
6. Use low doses; if patients need escalation they are probably not good candidates.
7. Heed red flags, particularly early in treatment; early problems with abusive behaviors rarely lead to successful long-term treatment.

My long-term success with LAO improved from 22% during the 1990s to 42% from 2000 to 2008, and is now 48% (currently 46 patients total) [70, 76]. This primarily reflects a 20-year learning curve as to patient selection. In addition to improved selection, we now have more choices of LAO (particularly the buprenorphine patch).

Dr. Levin discusses MOH from opioids; while MOH is certainly a major problem, the patients selected for LAO should have successfully been taking short-acting opioids, without increased headache. Dr. Levin also raises the possibility of OIH; OIH is certainly encountered, but not everyone develops OIH, and these candidates must have had a significant decrease in head pain from opioids, not an increase.

Dr. Levin states that “tolerance to the analgesic, euphoric and relaxing effects seems to be inevitable for most patients taking opioids chronically.” This is true, but for those who do not develop analgesic tolerance, the LAO may be a good choice. I have treated a number of patients who have remained on the same low opioid doses for up to 20 years. In virtually all of the successfully treated LAO patients, tolerance to the euphoric effects wanes over time.

The patients who are candidates for LAO tend to be in the “severe” RCM group [82]. QOL is abysmal for these people. The treatment choices (polypharmacy, intravenous treatments, MAO inhibitors, stimulants, nerve stimulation, nerve blocks, etc.) often are ineffective or are poorly tolerated. Certainly LAO is only appropriate

for a small minority of refractory patients, and often is not successful for a long term [92, 93]. In a number of years, we will have significantly improved treatments for these patients. Until then, we should consider LAO for the occasional refractory patient who fits our guidelines.

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