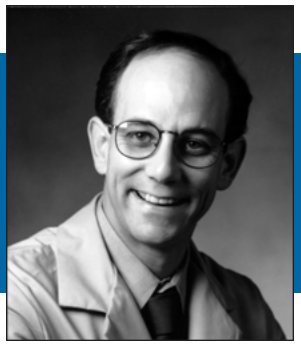
Long-Acting Opioids for Refractory Chronic Migraine

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.



By Lawrence Robbins, MD

Many patients with chronic migraine (CM) are refractory to our usual therapies.[1] Medication choices for the refractory chronic migraineur are limited and include polypharmacy with several preventives, monamine oxidase inhibitors, botulinum toxin type A and opioids, among others.[2] Each of these pharmacologic approaches helps a limited number of patients.

There have been a number of studies on long-acting opioids (LAO) as a treatment for refractory chronic daily headache.[3-5] Earlier studies focused on the use of low doses of methadone and a small minority of patients who did well long-term. Several studies reported better success rates with other opioids, such as oxycodone CR or long-acting morphine preparations.[6] 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 long-acting opioids for those who had done well with short-acting opioids (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 U.S. headache clinic. Data was collected via chart review, patient diary and patient interview. Patients who had been prescribed long-acting opioids during the six-year period 2002-2007 were assessed.

Patients kept a headache diary and used a 10-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 If adequate functioning was not maintained, the patient was usually withdrawn from the opioid.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, and
- 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 refractory chronic migraine.[7] They had longstanding daily headaches that caused significant functional impairment or decreased quality of life. Each patient had failed multiple trials of preventive medicines. In addition, they had little or no relief from abortive medications (triptans, NSAIDs, DHE, etc.) While attempts were made to minimize medication overuse headache, patients with this condition were not excluded from using the long-acting opioids. Virtually every one of these patients would qualify as refractory chronic migraine utilizing the 2008 proposed criteria for definition of refractory migraine and refractory chronic migraine.[7]

Inclusion Criteria

Long-time patients at the treating headache clinic with a diagnosis of refractory chronic migraine were included. Chronic migraine was defined according to the International Headache Society criteria.[8] All patients had been prescribed long-acting opioids, 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 quality of life on short-acting opioids. The minimum period of use of the SAOs was one 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 long-acting opioid for at least nine months and the patient consistently reported a 30% or greater

Table 1. 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 (non-bipolar)	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
Non-exercisers	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

improvement in headache frequency and/or severity over baseline. The baseline of comparison was the 3-month period prior to initiation of the long-acting opioid.

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.[9] 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 non-medical arenas; frequent ER visits for opioids; hoarding, forging or altering scripts; borrowing or stealing similar medications from family and friends; physical signs of overuse or addiction; and calls to the physician from family members with concerns about patient overuse.[10,11]

Anxiety. Patients with anxiety disorders included those with generalized anxiety disorder, panic disorder, and obsessive compulsive disorder. Anxiety was assessed via patient interviews, histories, and the initial anxiety and psychiatric assessment forms. DSM-IV criteria were utilized.[12]

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.[12]

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 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[12] In addition, the modifications to DSM-IV by Akiskal were utilized in defining bipolar disorders.[13,14]

Personality Disorders (PD). The diagnosis of PD was done in accordance with DSM-IV criteria.[12] Patients with severe personality disorders were not placed on the opioids. Only patients deemed moderate-to-severe with PD psychopathology were included.[15]

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 healthcare providers, and to exclude those with marginal PD diagnoses. Cluster A, B and C personality disorders were included.

The most prevalent were borderline, avoidant, dependent, and obsessive-compulsive.

Attention Deficit Disorder (ADD). Patients with ADHD were included along with ADD. DSM-IV criteria were utilized.[12] Assessment was done via patient interviews, histories, and the Adult Self-Report Scale (ASRS).

Exercise. Patients who exercised at least 20 minutes a day on average (140 minutes 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 hours per week or more, or worked full-time in the home, with normal functioning.

Disabled Patients. These patients were on long-term disability, or were unable to function more than minimally due to the chronic migraine.

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

Results

N=115 (87F, 28M, 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 comormid condition is summarized in Table 1. 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 nine 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:

- 3 to 15 years of headache prior to opioid: n=37, 69% positive response.
- 16 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 short-acting opioids, n=32/115 (28%). Of the latter, 91% went on to abuse the long-acting opioids as well. Information on smoking was available for 72 patients. Of the 53 identified non-smokers, 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 personality disorders. A Z-test was utilized. To be significant at the .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."

Discussion

We assessed 115 patients with refractory chronic migraine who were treated with long-acting opioids during a six-year period. This was a select group of patients who had all done well previously with short-acting opioids. 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 nine months on the opioid. The average duration of use of the opioid was 4.5 years. Forty-four percent of the patients reported adverse events. Patients with an increased chance of success included younger patients, high copers, and those without previous opioid abuse. Predicators of failure were those with personality disorders, older patients and, in particular, those with previous abuse of the short-acting opioids. In this study, anxiety, depression, bipolar depression, ADD, exercise, working, disability, fatigue or cigarette smoking did not significantly change the long-term outcome.

Previous Studies. In one of our previous studies conducted in 1999,[16] 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 short-acting opioids (SAO). Also, while 29 of these 115 (25%) patients did have a personality disorder, patients with severe personality disorders 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 short-acting opioids without overuse and in not prescribing the opioids to those with severe personality disorders or other severe psychiatric problems.

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In 1997, Saper and associates assessed refractory chronic daily headache with scheduled long-acting opioids, particularly methadone.[3] There was a small subset of patients who did well. Similar results were obtained from Rothrock[4] and from Robbins.[16] Subsequently, Saper and his associates soured on the use of the opioids. An unpublished study from Rothrock indicated that in the chronic migraine patients who were responsive at two months to the methadone treatment, over 70% continued to maintain a response at one year.[17] 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.[17]

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 over 3,000 patients resulted in the conclusion that there was no great evidence for sustained, long-term results in the majority of the patients.[18] 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.[19] 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."[20] 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 1,145 patients for chronic, non-cancer pain. Across all of the trials, the mean decrease in pain intensity was at least 30%.[21] 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%. 56% of the patients stopped the opioids due to lack of efficacy and/or side effects while 44% continued long-term. In various studies, the effects of opioids on quality of life 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.[22] 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.[24] In one study in 2002, 54% preferred the opioids versus 30% the TCAs.[25]

Short-acting (SAO) versus Long-acting (LAO) Opioids. Short-acting generally refers not only to how long a drug carries the desired effect, but the speed of the onset of the drug and how fast it drops off toward the end of the dose. Quick onsets and fast dropoffs are major determinants for abuse.[26] 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 4 tablets per day of 7.5 or 10mg 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 quality of life.[27] Self-selected groups, such as in our current study here, will report better efficacy because all patients who were chosen did well on the short-acting opioids.

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.[3-5] While success rates have been relatively low, they represent patients who have failed the usual ministrations, and who have few options available.

The advantages of long-acting opioids include:

- 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, and
- better compliance, with less psychological dependency on the drug.

Disadvantages of long-acting opioids include:

- 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 the SAOs,
- interactions with other sedating drugs or alcohol, and
- 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.[28]

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. Despite the inherent problems, there is growing acceptance of continuous slow-release preparations for chronic pain.[29]

Definitions of Substance Use and Misuse

Physical Dependence. Physical dependence occurs with many drug classes, such as the SSRI's, nitroglycerin, and insulin, as well as opioids. This is an expected outcome of long-acting opioid use and is a normal physiologic consequence. It occurs within 3 to 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.[30] 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.[31] 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.[32] 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.[31]

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.[31]

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 long-acting opioids is a complicated issue. It should be approached on a case-by-case basis and is dependent on a number of factors. Among the considerations:

- 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,[33] and
- 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.[34-36] Our current study affirms that those with personality disorders or previous abuse of short-term opioids are at increased risk.

A Proposed Classification Scheme for Prescription Opioid Abuse

It is too simplistic to view patients as "addicts vs. non-addicts." 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.[37]

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.[38] The PDUQ (Prescription Drug Use Questionnaire) 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 ORT (Opioid Risk Tool), with only 5 questions, has been validated as a simple initial screen.[39] The SOAPP-R takes 10 minutes and is comprised of 24 items; a shorter, 14-question form is now available.[40] 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%.[41] 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 personality disorders were substance abusers.[42]

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.[42] Our study indicated that those with personality disorders were at increased risk for abuse, but that other psychiatric conditions did not lead to more abuse.

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 Man-agement 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 long-acting opioids 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 short-acting opioids. We prefer to restrict use of LAOs to patients who have received SAOs for one year or more. Of course, all of these patients will have been refractory to conventional, non-opioid 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 thirty 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. Medication overuse headache (MOH) should be ruled out.

Patients with characteristics of narcissistic, antisocial, borderline, histrionic, or paranoid personality disorders are at increased risk for abuse.[43] It is best to avoid opioids in these PD patients. Patients with avoidant or dependent personality disorders, 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 long-term; however, the severe Axis I pathology does raise the risk of abuse, although this has not been absolutely proven.[3]

The Multidisciplinary Approach. Management of those with chronic migraine involves a biopsychosocial approach. Patients must not rely simply on the drug in order to function. While medications may be a mainstay of therapy, other interventions must be employed. Active coping should be strongly encouraged with each visit and may involve a variety of approaches. These may include seeing a psychotherapist, physical therapist or other practitioner, or using self-help approaches such as exercise or biofeedback. Passive coping is a major predictor of disability in chronic pain patients. 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.[44]

The intermediate phase is comprised of the diligent monitoring of the patient while on the opioid. This must include ongoing assessment of the patient's pain level and overall functioning, with a watchful eye for signs of abuse. 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.

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

Methadone may be more effective than some of the other medications, but has a litany of problems associated with it. Besides the social stigma, high protein binding is a risk which may lead to irregular drug levels, difficulty with withdrawal, and an increased risk for sudden death.[45] If methadone is used, it should be started at a very low dose of no more than 5-10mg a day, and titrated slowly. Patients placed on methadone require close monitoring, and other sedatives must be reduced or discontinued.

The usual dosing range in my practice is:

- methadone, 5 to 40mg per day
- morphine, 20 to 90mg per day
- oxycodone, 20 to 60mg per day
- fentanyl patch, 12.5 to 50mcg 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.[46]

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:

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

There are several resources on opioid agreements, such as the AAPM website, www.painmed.org, the American Pain Society website, www.ampainsoc.org, the Federation of State Medical Boards, Inc.,

www.fsmb.org, and the U.S. DEA, www.usdoj.gov/dea. In addition there is an excellent article on agreement contracts by Fishman, 1999.[47]

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 two to four weeks of a low dose, there usually will not be an adequate response.[17] With no or little response by four 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 lab error or test insensitivity, but it possible that the patient has been binging early on and has run out of drugs before the visit.[48] 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.[49] Urine panel screens should include cocaine, amphetamines, opioids, methadone, THC and benzodiazepines. Aminoassay urine screening is simple, has high sensitivity but lacks specificity. Chromatographic testing is better.[50] Combined testing techniques, such as 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 hours.[51] For patients with non-cancer breakthrough pain, such as chronic daily headache, I tend to minimize the total opioid and avoid layering pain medicines on top of each other. Prescribing short-acting medications, such as hydrocodone, for chronic headaches greatly increases the abuse rate. The occasional patient can remain on a low dose of the long-acting opioid, with one or two 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, opioid-induced hyperalgesia, and increased pain due to disease progression. While the last usually refers to cancer-type pain, it may also occur with the headache patient. Opioid-induced hyperalgesia occurs where the opioid facilitates nociceptive events; this counteracts the positive results from the opioid medication.[52] 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.

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.ampain soc.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

Conclusion

Chronic migraine remains undertreated, as only approximately 50% of patients do well 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 quality of life. 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 quality of life.

"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."

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, personality disorders 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-naive, long-acting opioids may be a successful option. ■

Acknowledgement
Patricia Goldfein, Editorial Assistance.

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