Opioids have long been used to treat intractable headache, although not every practitioner is willing to use these agents. Because of their addictive nature, opioids can be a medicolegal minefield, with the recent oxycodone controversy a current example. However, groups such as the American Pain Society and the American Academy of Pain Medicine (AAPM) have worked legislatively with the American Medical Association to garner increased funding from Congress for research and treatment. The Decade of Pain Control and Research began January 1, 2001, with passage of HR3244 (Title VI, Sec. 1603). The AAPM has also worked with the Federation of State Medical Boards to create a clinical guideline for the appropriate use of opioid medications in treating pain. AAPM is also developing an educational program for primary care professionals on pain assessment, opioid use, detection of addiction, and prevention of diversion. Organizations such as the National Committee for Quality Assurance and Joint Commission on Accreditation of Healthcare Organizations are working toward evidence-based measures of pain treatment. Indeed, pain has become the “fifth vital sign.”

The following is a summary of a roundtable discussion among 3 renowned experts on migraine and pain management. They share their clinical pearls on chronic opioid use in chronic daily headache (CDH).

Dr Saper: Many of the patients presenting to my center, the Michigan Head-Pain & Neurological Institute in Ann Arbor, are experiencing severe, intractable, daily headache, while at the same time, they are taking large amounts of opioid medication on a daily basis. Despite what is often hundreds and even thousands of milligrams of opioid medication daily, the headaches are severely painful and the patients often quite desperate. They require intense treatment in order to detoxify them and reduce their symptoms. The large number of these patients who have been referred to us over time prompted us to undertake a
5-year prospective study to assess the value and risks of continuous opioid treatment in patients with intractable headache.

A total of 385 patients were included in the 5-year prospective study. Of the 385 patients enrolled, 160 were assessed for 3 or more years. Of these 160 patients, less than half were able to be maintained on opioid therapy during their entire course in the study. Of these 70 patients, 41 experienced 50% or more improvement. These 41 patients represented only 26% of patients who were treated for 3 or more years. The remainder either did not do well or could not tolerate the drugs.

We also observed that a large percentage of those who did well reported that a significant improvement in their headache occurred by 1 to 2 months into treatment. If improvement occurred at this time, it was often sustained throughout the duration of the study. In fact, at any starting dose, with any opioid used in the study (eg, methadone, long-acting oxycodone preparations, and others), improvement during the first month was an important prognostic factor for improvement 1 to 3 years later.

Of particular interest was the comparison of the headache index assessment (determined on a visit-by-visit basis by staff) and the global patient perception, as measured by the VAS [visual analog scale]. A substantial number of patients who reported at least 50% improvement on the global VAS measurement did not demonstrate a similar improvement on the headache index measure, which we considered to be more reliable and accurate. Moreover, functional and performance assessment demonstrated that a significant percentage of those reporting 50% or more improvement on the VAS measurement remained disabled on numerous disability measures. This suggests that although some patients reported more than 50% improvement as measured by the VAS, their limitations and disabled status did not improve.

Also, although much of the pain literature suggests that noncompliance is rare when opioids are administered to patients who have chronic pain, our study demonstrates that 50% of patients had some form of significant noncompliance during the course of the study. The most common noncompliance was dose deviation, increasing their dose of medicine without approval. This and the other noncompliant behaviors occurred despite monthly visits with the medical team, monthly visits with the psychologist, a compliance contract signed at the initiation of the study, and the involvement of other family members. Patients also agreed to one dispensing pharmacist and one prescribing physician. Importantly, some noncompliance was not apparent to the medical treatment team but became evident only after chart audits and collateral data collection—activities not available in the average medical office.

Moreover, despite the improvement in headache index, the improved group (26% of the whole) did not show a significant capacity to reduce the number of preventive or abortive medications used to treat headache. Attempts to reduce these drugs were not successful despite placing strong pressure on the patient to do so.

In summary, approximately 26% of patients in our 5-year prospective study experienced significant headache control. The study also demonstrated that 50% of the total study population exhibited noncompliant behavior. Most were not able to reduce their concurrent preventive or abortive medications, and despite reporting improvement, many were unable to demonstrate improvement in functional capacity. Also demonstrated was a significant difference between global patient reports of improvement (VAS) and the documented status at visit-by-visit assessments (headache index). From this study we conclude that only a small group of patients do well on sustained opioid therapy. Most do not.\(^1\)\(^2\)

**Clinical Pearl**

The following are suggested guidelines for sustained opioid treatment in the headache population:

- Opioids should be considered in:
  - Patients with severe, convincing, daily or almost daily headache that is clearly refractory to aggressive comprehensive treatment (ie, full detoxification from drugs to address rebound headache, behavioral treatment, and aggressive medication administration); OR
  - Elderly patients, pregnant women, or those with significant medical comorbidities that would prevent the use of other migraine medications.

- Sustained opioid treatment is contraindicated in:
  - Severe Axis I diagnoses (eg, depression, schizophrenia, and bipolar disease);
  - True addictive disease (ie, excessive use with antisocial behavior, use beyond need, multisourcing or, illegal behavior);
- Cluster B personality disorders (ie, borderline, narcissistic, or antisocial).

• Opioid trials should be well monitored, structured, and contractual.

• Initial drug trials should last no longer than 1 to 2 months, at which time assessment of benefit should be undertaken. If only modest benefit occurs or there are any signs of noncompliance, the opioid should be stopped. With impressive improvement during the trial period, the drug should be continued with careful monitoring.

**Dr Rothrock:** At the University of South Alabama (USA) Headache Center, we see a high volume of patients from a multistate region and are largely restricted to outpatient management of their headache syndromes. For extensive inpatient management of our most difficult cases, we tend to rely on quaternary care facilities such as the Michigan Head-Pain & Neurological Institute, although many of our treatment-refractory patients cannot avail themselves of that option. With that group, we have turned to such 'unconventional' therapies as chronic methadone. Over the past 7 years, we have prospectively treated and followed up 70 patients with refractory chronic migraine (ie, daily or near daily headache with an International Headache Society diagnosis of migraine), who we have treated with chronic methadone or another long-acting opioid. The majority of the patients were women, and about three fourths had CDH. The remaining one fourth of patients had frequent episodic migraine (ie, at least 15 days per month but not daily). The mean duration of CDH in this group with chronic migraine was 5 years.

Of the CDH patients, about 30% were categorized as having “new daily persistent headache with migrainous features.” The remaining 70% had transformed migraine (ie, episodic migraine evolving into CDH). The number of prophylactic therapies previously used and failed ranged from 2 to 12; in all cases, a therapeutic dose had been administered for an adequate amount of time. The opioids we used were methadone, continuous-release oxycodone, and the fentanyl patch.

Our results are eerily similar to Dr Saper’s: 34% of the 70 patients had a positive response, but only 26% had a sustained positive response (mean, 2 years). An additional 10% of patients did not meet our criteria for a positive treatment response but nonetheless indicated that they were “much better.” In this last group, the patient’s subjective assessment of response typically does not match up with objective information in headache diaries or correlate with a reduction in the number or quantity of abortive medications used.

Of the 46 patients (66%), who did not respond 10 were unable to tolerate the chronic narcotics prescribed due to side effects. The remaining 36 failed to achieve a positive treatment response (ie, ≥50% reduction in headache days per month).

A surprisingly small number of patients (n = 4) developed tolerance to the opioid prescribed; therefore, few required dose escalation over the period of therapy. Only 1 of the 70 patients abused the narcotic medication in the traditional sense (ie, he sold his methadone for oxycodone, mixed that drug with whiskey, and injected it intravenously).

In all treatment responders, we tried to taper therapy after varying periods of time, but in all cases, the headache syndrome worsened almost immediately. This suggests that opioids can suppress headache clinically without modifying the underlying biology of the headache syndrome.

In summary, although prescription of chronic narcotic therapy for headache suppression is labor intensive, such treatment can be effective for a significant minority of patients with intractable chronic migraine.

**Clinical Pearl**

In a substantial minority of CDH patients, long-acting, chronic opioid therapy can be used safely and effectively. Patients involved in the study described here have reported:

“...I’ve been treated at the USA Headache Center for chronic daily migraines...We started the methadone treatment and the headaches went away, just like turning them on and off... Methadone for me has been a miracle.”

“...Over the past 5 years...my head hurt, I stayed in bed, contemplated suicide...Now it’s almost about at the ninth month [with methadone treatment] and I hold a 60-hour-a-week job. There’s a reason for me to live and this drug has given me my life back and I thank you for it.”

“...Before I was taking the oxycodone, my life was just horrible...I was in bed just about every day... unable to play with my children, not able to help my husband with the business, not able to really do the house-
work...Now that I'm taking oxycodone, it's given me my life back and I'm thankful so much that there is some type of medication out there for me and my headaches."

"...My headaches were daily, awful, and I was not able to perform my regular, daily activities in the way I wanted to...Before I started taking methadone, my husband and I rarely ever made any plans to do anything...We haven't taken a vacation in probably 15 years because I had so many headaches...I was incapacitated with headaches. But since I've been taking methadone, I'm so much better."

**Dr Rome:** At the Mayo Clinic Pain Management Program, we emphasize a rehabilitative approach to pain management, in which opioids are one part of a long continuum of care. The pain rehabilitation program at the Mayo Clinic was founded in 1974. It is a multidisciplinary, multifaceted, multimodal treatment approach with an emphasis on functional restoration and amelioration of the emotional, behavioral, and functional symptoms that accompany chronic pain disorders of all kinds. The program is a 3-week, full-time, group program that uses the typical array of methods in the care of patients with persistent pain. At any one time, there are 24 patients in the program. Follow-up is at 6 months after discharge.

By the time these patients join our program, they have failed virtually every headache treatment, including opioids. Our philosophy is to withdraw analgesics in general and opioids in particular, and emphasize a rehabilitative approach with avoidance of analgesics for a period of roughly 6 months, with hopefully, a conservative approach to analgesics to follow thereafter. I do not believe that patients with chronic refractory headache have a problem that can be resolved with more and continuous agonists at the opioid receptor. Also, it is possible that facilitation of nociception by opioids may be part of the problem.

The patients come from all over the country and are uniformly distressed and dysfunctional: 50% are clinically depressed, and 50% are drug dependent (ie, physiologically dependent on these medications). The headache patients at this center typically have persistent daily headaches rather than sporadic headache syndromes, and their headache is complicated by rebound phenomenon and injudicious use of multiple medications.

There are many factors to consider in developing a treatment plan for these patients, including the particular headache syndrome, previous treatment, the psychosocial environment, the particular opioid, and the parameters of dosing.

The general standard of care for treatment of refractory headache is not well defined. Formal guidelines or treatment algorithms on opioid use in headache patients are not yet available. The care varies according to the patient, the setting, and the physician. It varies regarding the focus of treatment: immediate pain relief or long-term gains in level of functioning and quality of life.

Treatment with opioids is an interactive process. It requires monitoring and assessing results, decisions to continue treatment, adjust dose, or add other therapies.

Of the last 1000 patients in the program, who represent about 2.5 years of activity, 15% (n = 150) of patients had a headache syndrome of some kind (excluding temporomandibular joint disorders, post-herpetic neuralgias, and uncommon eye pain problems from laser surgery). A total of 50% of the 150 headache patients were using opioids at the time of admission. Of particular importance, the duration of pain in opioid-using patients was twice that of patients not using opioids.

On admission, we use the following instruments for assessment: Multidimensional Pain Inventory, Sickness Impact Profile, Health Status Questionnaire, Center for Epidemiologic Studies Depression Scale-10, and a catastrophizing scale. There were significant differences in pain severity and pain interference with opioid-using patients compared with nonusers on admission. At discharge, the scores on the assessment scales improved across the board, with no difference between opioid-using and nonusing patients at the time of discharge in either pain severity or pain interference.

Catastrophizing has been highly correlated with functional outcomes in chronic-pain patients. Catastrophizing and depression are both worse in opioid-using patients at admission, with significant improvements at discharge in both groups.

Long-term follow-up at 6 months shows similar results. The multidimensional pain inventory shows a significant improvement in pain severity, pain interference, improvements in life control, and general activity.

Of note, among the patients who are discharged, only 2 of 16 returned to opioid use at 6-month follow-up.
CLINICAL PEARL

With regard to opioids, practitioners fall into 3 categories: the Puritans, the Zealots, and the Unitarians. The Puritans are hesitant to use an opioid for any type of pain. The Zealots feel compelled to bombard the synapse with opioids. The Unitarians are eclectic, choosing aspects of care from several sources, with no one consistent dogma.

In short, all that hurts is not opioid sensitive. Opioid use requires careful consideration of the complex patient, the variable treatment setting and plan, and disease history, as well as thorough long-term follow-up.

REFERENCES