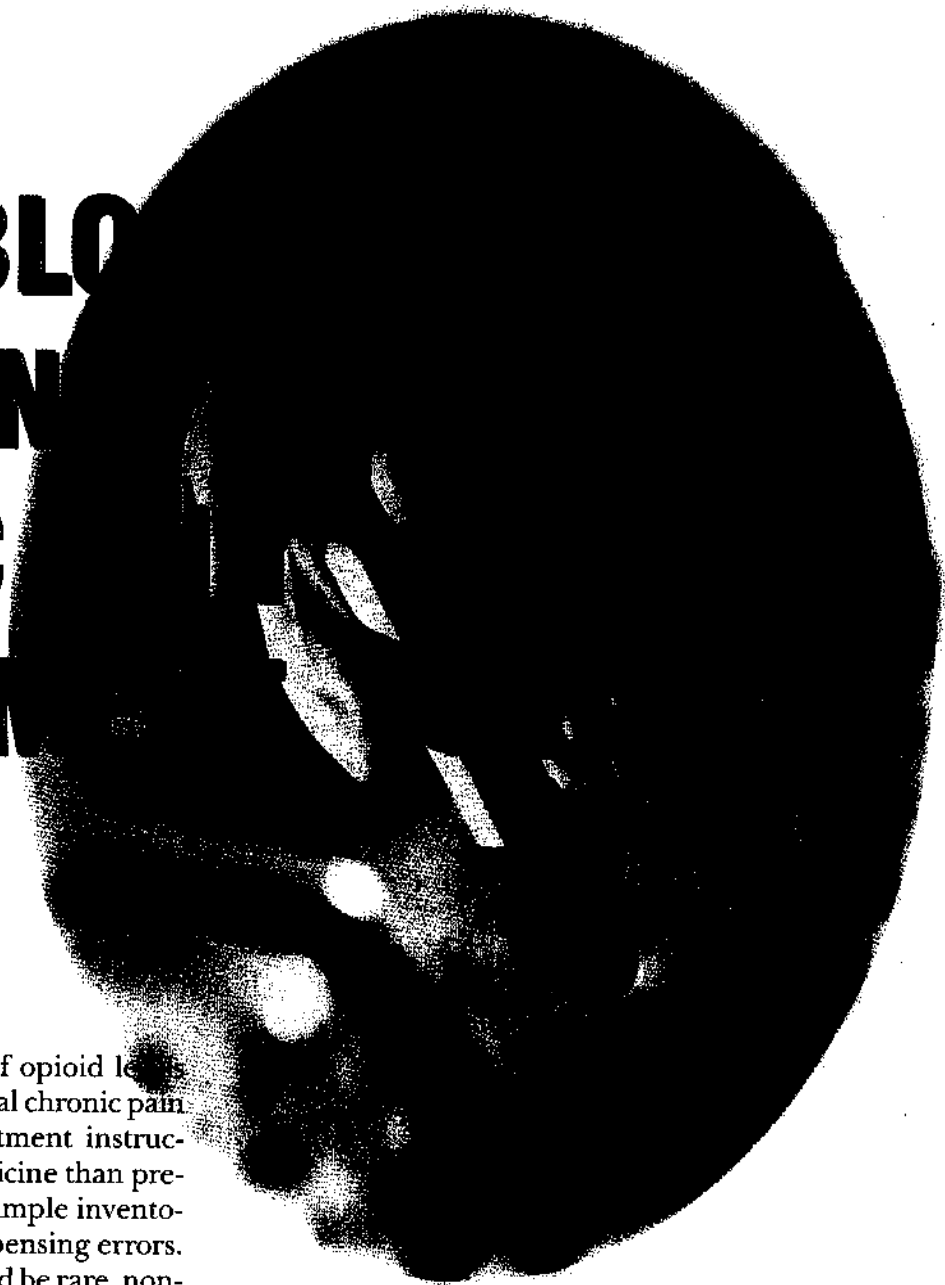


# OPIOID BLOOD LEVELS IN CHRONIC MANAGEMENT



By Lawrence M. Probes, M.D.

In an ideal world, measurement of opioid levels rarely would be necessary. The ideal chronic pain patient always would follow treatment instructions exactly and never use more medicine than prescribed. Pharmacies would maintain ample inventories of all opioids and never make dispensing errors. Addiction and pseudoaddiction would be rare, non-existent, or someone else's problem. No patients would have personality disorders or create angry and unpleasant situations with office staff and clinicians. The fear of lawsuits over any possible adverse event would not cast a shadow over daily practice, and defensive medicine would not be necessary. Patients would have textbook pharmacokinetics without problems of swallowing, absorption, digestion, drug-drug interactions, enzyme inhibition or induction. Allergic reactions to medications would be rare. Insurance companies would approve of first-choice and brand-name medication without prior authorizations. Since these conditions do not exist, clinicians should take advantage of opioid blood levels to complement other forms of monitoring in our "real-world" patients.

Determination of opioid levels in the blood is emerging as an important tool for ensuring the safety, effectiveness and integrity of opioid analgesic therapy in the treatment of chronic pain.

## Safety of Treatment

Safety at the start of treatment relies principally on clinical evaluation and patient selection, and measurement of blood opioid levels is not a routine need when starting opioid therapy. However, in the elderly, the young, the debilitated, and those at higher risk for misuse, abuse and diversion of drugs, opioid blood level monitoring early in treatment might be indicated.

The most immediate safety concerns with opioids are ventilatory depression and hypotension, which primarily are acute risks upon initiating the drugs or raising the dose. They are managed by careful evaluation of the patient before starting the opioids, education of the patient and family about the side effects and risks of treatment, and clinical monitoring.

When evaluating a patient with chronic pain for opioid therapy, it is important to consider cardiopulmonary functioning and any disorders that might increase the risk of ventilatory suppression. Patients with diagnosed or suspected sleep apnea might require evaluation in a sleep disorders clinic and/or overnight polysomnography, and — if indicated — treatment with continuous positive airway pressure (CPAP) or other interventions. One approach is to prescribe lower doses of short-acting drugs for use only during the daytime when the patient is awake and active. This reduces the risk of a long-acting drug suppressing respiration and ventilation during sleep at night, when the risks are greater. Around-the-clock opioid therapy and treatment with controlled-release and long-acting opioids can be delayed until the patient is evaluated more completely and any indicated treatment started. Patients with chronic obstructive pulmonary disease (COPD) and asthma may require consultation with a pulmonologist to optimize respiratory management prior to initiating chronic opioids.

Fortunately, tolerance to most of the undesired effects of opioids develops rapidly after reaching a stable dose, including effects on respiration and blood pressure — which usually return to normal levels. The only two effects to which tolerance does not develop routinely are constipation and analgesia itself. Most patients on chronic opioids require bowel management plans. True tolerance to analgesia in long-term therapy is uncommon, and a much more likely explanation

for loss of analgesia is pseudotolerance: increased pain caused by disease progression or pharmacokinetic factors of ingestion, absorption and metabolism that lower blood levels.

In order to minimize the risk of hypotension, patients should be advised to maintain good hydration, eat regular meals and carefully manage treatment for diabetes, hypertension and other problems. In patients at increased risk for hypotension, the prescribing physician should consider additional cardiovascular evaluation (electrocardiogram, cardiology consultation).

Sedation may occur with opioids both acutely and during chronic administration. All patients should be cautioned about drowsiness, cognitive dulling and motor slowing, and they should be instructed not to drive, operate machinery,

text of chronic pain management. A more useful term is “intoxication.” When opioids reach a dose that is too high or when the blood levels are rising very quickly upon acute administration, the most reliable signs of excessive medication are the behaviors of intoxication. Signs of intoxication due to alcohol, sedative-hypnotics and opiates are familiar to clinicians and the public alike and include slurred speech (dysarthria), unsteady gait with staggering or swaying (ataxia), rambling speech, decreased coordination, and drowsiness (appearing sleepy or actually falling asleep).

Intoxication cannot be implied by a particular blood level. It is a clinical term based on clinical criteria that may be observed and described objectively. There are legal definitions of intoxication, such as a certain blood alcohol level, but for

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or engage in any other potentially hazardous activities if they do not feel fully alert and awake. Considering the prevalence of medical disorders (especially sleep apnea) and social situations (sleep deprivation, shift work sleep disorder) that cause excessive daytime sleepiness (EDS), all patients — even those not taking opioids or other sedating drugs — should be evaluated for possible disorders of arousal.

Opioids have a narrow therapeutic index upon acute administration, which means that blood levels progress from safe and therapeutic to potentially intoxicating and dangerous over a relatively narrow range. However, upon chronic administration, the therapeutic range widens, so that some patients require levels two to four times greater than patients treated for acute trauma or postoperative pain. Individuals with chronic chemical dependence disorders may have blood levels of various drugs five times greater or more than the laboratory reference range and yet show minimal or no clinical evidence of sedation or intoxication.

The terms “toxic” and “detoxification” often are applied incorrectly in the con-

clinical purposes these are not very useful. It is possible for a person to be intoxicated and grossly impaired with relatively low blood levels of an opioid after acute administration. Likewise, patients who take opioids chronically may have blood levels well above what the laboratory reports as a “toxic” level and yet show no signs of intoxication or impairment. Unfortunately, pain patients — experiencing opioid withdrawal after being unable to obtain their medication — are sometimes sent to a recovery program for “detox,” when in fact they show no signs of intoxication whatsoever. These patients need totally excellent pain and psychiatric treatment, possibly in a doctor’s office or perhaps in a pain program or inpatient psychiatric dual-diagnosis unit.

It is important at each office visit to document the overall behavior and mental status of opioid patients. Consider this excerpt from an office progress note:

“The patient appeared punctually, casually and neatly dressed and groomed, fully awake and alert with no signs of agitation, affective lability, irritability, depression, drowsiness or intoxication. Attention and concentration were normal

with no signs of cognitive dysfunction. Speech was clear, coherent, well-articulated, logical and spontaneous without slurring, rambling or pressure. Gait was steady without staggering or swaying. Posture was erect with good eye contact, well-modulated facial affective expression, good coordination and no adventitious movements."

If this same patient has a 2-hour serum oxycodone level of 219 ng/ml and reports good to excellent pain control and side-effect management on OxyContin 80 mg t.i.d., then despite a laboratory report indicating "toxic >200 ng/ml," the clinician may conclude that the patient shows no clinical evidence of intoxication and continue the same dose of medication.

For patients with major risk factors, the "start low, go slow" approach is best. Consider establishing baseline levels early in the course of treatment. Although the titration may be gentle, it is no less important to reach and maintain a therapeutic level that corresponds to good pain control.

### Effectiveness of Treatment

Despite reference ranges for analgesia printed on laboratory reports for blood opioid levels, the true analgesic range for any opioid is not known. This is not because of limitations in laboratory assay methods but rather due to the subjective nature of pain assessment. Also, analgesic ranges mostly have been studied in patients with acute and postoperative pain, not studied in chronic pain patients with neuropathic pain and psychiatric illnesses. Therefore, the reference ranges provided by laboratories and textbooks should be used as broad guidelines in chronic pain patients.

Consider each opioid patient to represent a clinical investigation with an "N" of one. In each patient, the blood opioid levels establish a benchmark, a "ballpark" figure that supports (or casts doubt on) the safety, effectiveness and integrity of treatment. With continued treatment and monitoring, subsequent opioid levels can be interpreted primarily in the light of previous levels and patient reports of pain relief with a given medication and dosage. We can study and determine the therapeutic range for an individual patient.

In routine treatment settings, "standard" laboratory reference ranges should not be the sole reason or even a major reason for restricting treatment. If anything,

monitoring of blood opioid levels tend to lead to an increase in the dose of pain medications. Patients with a low risk profile who do well early in treatment probably do not need opioid level monitoring at all, although one still might order them simply to establish a baseline, in case some unexpected changes in their medical condition or adverse circumstances emerge.

One of the most common reasons to measure opioid levels is when a patient who has been titrated up to a robust dose of an opioid reports partial pain control and asks for an increase in the dose. For example, a patient with chronic low-back pain, a low-risk profile for aberrant behavior, and no history of substance abuse (except nicotine dependence) has been titrated on controlled-release oxycodone (OxyContin) up to 80 mg every 12 hours. Serum oxycodone levels collected 2 hours and 8 hours after the first morning dose of OxyContin 80 mg come back in the medium or low range, 50 nanograms per milliliter (ng/ml) and 25 ng/ml respectively. Some laboratories have reported a therapeutic oxycodone range of 10-40 ng/ml (Medtox Laboratories, St. Paul, MN; Spectrum Health, Grand Rapids, MI) with "toxic" levels >100. However, the therapeutic reference range that is becoming more widely reported is 10-100 ng/ml (National Medical Services, Willow Grove, PA; San Diego Reference Laboratory, San Diego, CA) and "toxic" >200.

Patients in the author's psychiatric chronic pain practice generally report the best relief of pain at levels greater than 40 ng/ml, and supports the view that 75 ng/ml as a threshold for "doing business with the CNS" in chronic pain patients, especially those with psychiatric comorbidities such as major depression, bipolar disorder and post-traumatic stress disorder.

Take, for example, a patient with chronic pain who reports partial pain control for 6, maybe up to 8 hours after the first morning dose of OxyContin 80 mg. Pain intensity falls from a 9 to a 6 on a 0-10 scale, but then pain is poorly controlled for 4-6 hours until after the next dose. Collections at 2 and 8 hours show that blood levels dropped by 50%, from 70 to 35 ng/ml. It is likely that this patient will respond better to q.8-hour dosing, rather than q.12-hour dosing as recommended in the package insert. A reasonable pre-

scription would be to add OxyContin 20-40 mg as one of the 3 daily doses for 3 to 7 days then, if desired and well-tolerated, increase by another 20-40 mg up to a new target dose of 80 mg t.i.d. (q.8 hours).

### Treat the Patient, Not the Blood Level

When valproate (Depakote) was approved only for treatment of seizure disorders, the therapeutic range was considered 50-100 ng/ml. For the first few years after Depakote was approved for the treatment of Bipolar Disorder, it was assumed that the therapeutic range for mood disorders would be the same. However, experience showed that some patients required levels much higher, up to 150 ng/ml. Clinical experience led the way, but until the higher reference range was accepted nationally, clinicians would receive calls from the laboratory with a "critical" serum valproic acid level of 125 ng/ml.

Based on the upward revision of therapeutic levels for Depakote for mood disorders, it could be hypothesized that bipolar disorder is a "higher-demand" central nervous system diathesis compared to epilepsy. By way of analogy, the author's experience in treating chronic pain in psychiatric patients with major mood and anxiety disorders (especially major depression, bipolar disorder and post-traumatic stress disorder) suggests that comorbid psychiatric disorders intensify the experience and perception of pain. "Time after time after time" these dual-diagnosis pain-psychiatric patients have required higher blood opioid levels and a wider range of co-analgesic drugs. It is noteworthy that most classes of co-analgesic drugs are psychotropics, namely antidepressants, anticonvulsant mood stabilizers, psychostimulants, and antipsychotics.

The limbic system governs the experience and expression of emotional states, but it also processes the hedonic aspects of pain perception. Experience with dual-diagnosis chronic pain-psychiatric patients suggests that they suffer from a mutually-reinforcing set of negative conditions: emotional dysphoria (depression, irritability, fear) and psychiatric disorders create or intensify the perception of pain, while chronic pain originating in the periphery or the CNS tends to induce dysphoria, creating secondary psychiatric syndromes and exacerbating primary mental illness that preceded the pain disorder.

## Leading Questions

Could it be that latent or expressed psychiatric disorders and neurotransmitter dysregulation predispose a person to chronic pain disorders? Why do some individuals with injuries and surgery recover completely with no residual pain disorder while others go on to develop chronic pain? Why do so many patients with mood and anxiety disorders so often develop a wide range of somatic as well as psychic complaints, even in the absence of any objective pain generators? Could it be that "wind-up" at the spinal cord level is more likely to develop in persons with dysregulation of the descending bulbospinal tracts that modulate dorsal horn neurons and interneurons through release of serotonin and norepinephrine? Can intense and chronic pain sensitize limbic system neurons and create a type of "wind-up" phenomenon at the central level? Is "central sensitization" a limbic as

treatment monitoring, including blood opioid levels.

## How to Order Blood Levels

For outpatients without chemical abuse and dependency disorders, opioid blood levels can be collected routinely in plain red top tubes at clinical laboratories or medical offices. After oral administration, immediate-release opioids generally reach peak blood levels in about one hour. The half-life ( $T_{1/2}$ ) of most opioids is 2-7 hours, with the notable exception of methadone, which is quite variable and may exhibit a  $T_{1/2}$  of >100 hours.

In order to build confidence in the integrity of blood opioid level measurement, the author has developed the following protocol. Patients are instructed to come to the office at 8:30 or 9:00 a.m. and to bring all medications in their original prescription bottles. Staff compares prescription bottles with chart records and

into the specimen container. In such cases, patients are instructed to return to the office for the urine drug test right after having their blood drawn. A staff member accompanies the patient to the restroom to observe urine specimen collection directly.

## The Intoxicated Patient

When a patient presents to the office with signs of intoxication, a cross-sectional urine drug screen and blood levels of suspected intoxicants are invaluable, although a direct history from the patient and a collateral history from a friend or family member often will point to the cause(s). Clinicians should be cautious about attributing intoxication to opioid analgesics merely because they are being prescribed. Intoxication may be due to several causes, of which opioids may be only a minor factor. For example, if a patient on opioids who previously has been fully awake and alert presents unexpectedly with drowsiness and mildly slurred speech and no known change in opioid medication, look for other explanations. Undiagnosed sleep disorders and general medical conditions may be overlooked. Oxygen saturation may be decreased or benzodiazepines and similarly-acting sedative-hypnotics may be the culprits. Perhaps another clinician added a new drug or changed existing medicines. Fluid and electrolyte status should be evaluated. Consider many other causes and contributing factors to intoxication and encephalopathy, especially in older adults, debilitated patients, and those with a history of traumatic brain injury. Having a baseline opioid level on file in this instance can be useful in determining the most proximate cause of the intoxication.

## Is the patient actually taking the prescribed drugs?

An unannounced, surprise urine drug screen is among the most commonly used ways to verify that a patient is taking what is prescribed and not taking what isn't. However, two commonly prescribed opioids, oxycodone and fentanyl, typically are not detected in a standard urine drug test. To identify oxycodone in the urine, it may be necessary to order a no-cutoff screen and/or gas chromatography confirmation to document the presence of oxycodone. Fentanyl will not be detected as an "opiate," but it can be identified by

A typical laboratory order might read, "Serum oxycodone levels 2 hours and 8 hours after the first morning dose of OxyContin 80 mg administered in my office under direct supervision."

well as a spinal cord phenomenon? Could it be that central, limbic, affective pain is the highest expression of neuropathic pain in the neuraxis?

Among the most challenging patients with chronic pain are those with major psychiatric and chemical abuse disorders. Measurement of opioid blood levels suggests that these dual- and triple-diagnosis patients may require higher doses and higher blood levels than chronic pain patients without neuropathic transformation or comorbid mood and anxiety disorders. Knowing this gives clinicians greater confidence when increasing the dose of opioids in difficult cases.

## Integrity of Treatment

When blood levels are measured to strengthen the integrity of treatment, they are no more reliable than the integrity of the testing procedure. Substance abusers and drug diverters can be shrewd and creative in outwitting the system of monitoring. Not every abuser or diverter will be detected, but most eventually can be identified with systematic application of the wide range or

counts residual medication. Then patients are told to take the first morning dose of the drug(s) to be tested. After being observed to swallow the medication, they immediately are given a glass of water to drink and asked to remain seated under continued observation. Thirty minutes later they are dismissed from the office and told to report to a nearby clinical laboratory for collection of blood specimens 2 hours after taking medications. In the case of a controlled-release opioid, a second level 6 or 8 hours is optional. A typical laboratory order might read, "Serum oxycodone levels 2 hours and 8 hours after the first morning dose of OxyContin 80 mg administered in my office under direct supervision."

The closest correlation between blood levels and urine drug screen results can be achieved by collecting the urine drug screen specimen at the same time as the blood levels. However, few laboratories provide staff observation of urine specimen collection, and it is much easier for drug abusers and diverters to substitute other liquids for their urine if they are not observed directly while urinating

requesting gas chromatography. Laboratories generally retain specimens for up to 2 weeks, so after reviewing the initial drug screen results, additional gas chromatography confirmations and assays at lower cutoff levels can be ordered on the same specimen.

An unannounced blood opioid level also can be ordered. Unfortunately, drug abusers and diverters who may not be taking their prescribed opioid (or who may take it intermittently and divert the rest) may carry at all times one or two doses in their pocket just in case they are required to submit for unannounced testing. If a person is being prescribed OxyContin 80 mg t.i.d. and a blood level collected at any time shows no oxycodone, then it is unlikely that the OxyContin is being taken, and it greatly increases the index of suspicion of drug diversion or other aberrant drug-related behavior or some form of non-compliance.

**The Methadone Patient**

Serum methadone monitoring already was underway before widespread accept-

ance and use of the full range of opioids for treatment of non-malignant chronic pain. The trend over time has been to recognize that many patients on methadone maintenance for treatment of opioid dependence require higher blood levels than what originally was thought. Levels of 200-400 ng/ml once were believed to be sufficient, and clinicians might be inclined to lower the dose of methadone if levels were too high, even if there were no signs of intoxication or relapse of drug abuse. Now laboratories report therapeutic methadone levels up to 1000 ng/ml.

Methadone is a dual-purpose agent: a maintenance drug to prevent withdrawal symptoms in heroin addicts and an analgesic drug widely used to treat chronic pain. If methadone is prescribed solely to maintain a state of opiate dependency in addiction, it only can be prescribed by physicians in special, federally-licensed clinics, often referred to simply as "The Methadone Clinic." However, any physician with a Drug Enforcement Administration license (DEA number) can prescribe methadone legally for treatment of

pain. One study found that 37% of patients in methadone maintenance treatment programs (MMTPs) and 24% of patients in residential treatment facilities (RTFs) experience chronic severe pain, and up to half (48.8% in MMTPs and 41.8% in RTFs) report pain as the reason for first using drugs and alcohol. General physicians may use methadone to treat patients with opioid dependence, as long it is incidental to the use of methadone for treatment of pain.

Some laboratories report three different ranges for methadone. In 2003 Warde Medical Laboratory (Ann Arbor, MI) reported:

- Serum therapeutic range (Analgesic): 100-400 ng/ml
- Serum methadone (Addiction therapy): 100-1000 ng/ml
- Serum methadone toxic range: >1000 ng/ml

In 2004 National Medical Services (Willow Grove, PA) provided the following description after the serum methadone level:


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The author's own experience suggests that severe, chronic pain, especially non-malignant pain, is a higher-demand central nervous system diathesis. These patients require methadone levels at least as high, if not higher, than patients being treated for primary opioid dependence.

## Legal Defense

If a patient on opioids and possible other pain and psychotropic medications experiences a serious adverse event, such as a car accident while driving, baseline blood levels of opioids and other drugs may be helpful in determining what, if any, effects medications may have contributed. Take, for example, Bill, a chronic pain patient who is stable on OxyContin 80 mg q.8 hours. Bill has made numerous monthly visits to the office, and each of Bill's progress notes, similar to the one above, documents an alert mental status and no signs of intoxication. The most recent 2-hour and 8-hour serum oxycodone levels after the first morning dose of OxyContin 80 mg were 210 ng/ml and 105 ng/ml respectively.

Then Bill was involved in a car accident at a busy intersection. He was distracted while tuning the car stereo and rear-ended the car in front of him. Although both drivers sustained only minor injuries, they were taken to a hospital emergency department for evaluation. While giving his medical history, Bill explains to the emergency physician that he is on OxyContin 80 mg t.i.d. for chronic pain. The doctor considers this to be a "high" dose, and although Bill's mental and physical examination showed no signs of intoxication, a urine drug screen and serum oxycodone levels were ordered. The urine drug screen comes back negative for opiates, but the serum oxycodone level is 203 ng/ml, and the laboratory report specifies the therapeutic range for oxycodone as 10-40 ng/ml. Unfortunately, a lawsuit develops, Bill's medical and psychiatric records are subpoenaed, and the plaintiff's lawyer plans to show that Bill was driving while "toxic" on OxyContin.

A very strong defense for the physician prescribing OxyContin is the well-documented history of multiple office visits with alert mental status, no signs of intoxication and baseline oxycodone levels up to 210 ng/ml that correspond both to

good pain control and to alert and non-impaired behavior. Bill's attorney and treating physician argue persuasively in a deposition that although he may have been distracted by tuning the car stereo, there was no evidence that he was mentally or physically impaired or intoxicated due to therapeutic pain medicine. The case is settled routinely, and no medical malpractice action is initiated against Bill's doctor.

## Author's Experience

This author is a board-certified psychiatrist, having completed residency training in 1982. After 11 years of hospital and office-based practice in the 1980s and serving as medical director of a county psychiatric hospital, the author started a private, fee-for-service practice of general psychiatry in 1993. In the mid-1990s (1995-2000) — while prescribing methadone for treatment of chronic pain, then transdermal fentanyl (Duragesic), controlled-release morphine (MS Contin) and OxyContin — referrals mostly were free of addiction disease. Patients were not "drug-seeking" or involved (to the author's knowledge) in drug diversion. Then in 2000, as the author's clinical skills in opioid management developed, many more complicated and high-risk patients were being referred.

Presently, the author has some 450 active patients. About 100 of them are on chronic opioid regimens for treatment of severe, non-malignant pain. The most common classes of medications are antidepressants, anticonvulsants, psychostimulants and second-generation antipsychotic mood-stabilizers. Most of them undergo psychotherapy with a psychologist for a period of time. (Psychotherapy has "co-analgesic" properties.) A few patients have a history of heroin or other opioid abuse or dependence, but treatment of their chronic pain with methadone or other opioids under close supervision has been effective. Most of the opioid patients never were treated at a federally-licensed methadone maintenance clinic, but those who were have turned out to have the greatest risk of relapse into substance abuse. Opioid chronic pain patients represent almost one-fourth of the author's patient load, but they occupy more than half of every office day. Opioid patients with behavioral health problems are time- and labor-intensive.

## Conclusion

There is a large population of complex chronic pain patients in the "real world," the ones that we see every day in Everyville, USA, and usually excluded from most controlled studies. The same individuals may suffer from severe chronic pain with multiple pain generators, one or more major psychiatric disorders, drug addiction, and a variety of general medical conditions. In the absence of controlled studies, clinicians must rely on case reports and guidance from experienced clinicians, focusing on a qualitative, rather than quantitative approach to patient care. Measurement of blood opioid levels is a confidence-building measure that strengthens the resolve to treat patients, move toward higher doses and higher blood levels when clinically indicated, raise the bar by seeking not only good but better and best results, support the integrity of treatment, and strengthen the legal position of prescribing physicians. ■

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