

PATIENTS WHO REQUIRE ULTRA-HIGH OPIOID DOSES

The goal of ultra-high dosage therapy is to relieve pain and improve function in those chronic pain patients that are profoundly ill, impaired, and/or bed- or house-bound—without producing sedation.

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Great controversy exists about chronic non-cancer pain patients who seemingly require very high opioid dosages. Persons and parties who surround these individuals may label them as “addicts” or “abusers,” and some may resent the high cost of high dose opioid treatment.

To compound the controversy, some observers have claimed there is no evidence that opioid doses over 200mg morphine equivalents are effective for non-cancer pain. Recent guidelines have attempted to establish morphine equivalent dosages over 200mg a day as being “high.”¹ Such guidelines, however, are not supported by any high-quality published clinical trials but, rather, represent the opinion of their authors.

Despite such claims and guidelines, pain practitioners routinely observe that some chronic pain patients require morphine equivalent doses well above

200mg and may range from 1000mg to as much as 2000mg, or even more, per day. The necessity of high opioid doses has been accepted for years in the treatment of some cancer patients but is considered controversial for non-cancer pain.

This article classifies these patients as users of “ultra-high” opioid doses and makes recommendations on their management. The impetus for this paper is driven not only by clinical needs of the patient but also to clearly and succinctly bring to light these cases so that all concerned parties can better identify, treat, accept and understand the reality of these patients.

Classification of the Patient Who Requires Ultra-High Opioid Doses

Pain specialists understand that there is no maximal safe dose of opioids and that there is wide variation in the dose required to achieve maximal comfort and function in the patient without causing sedation or physical impairment. Dosage can vary 40-fold for the same clinical condition.² A small minority of patients require massive doses of opioids for chronic pain. We propose classifying opioid doses as follows: A dose of less than 200mg/day of morphine equivalents is a standard or low dose; 201-1,000mg/day is a high dose and over 1,000mg/day of

morphine equivalent constitutes an ultra-high dose (see Table 1). Those physicians who choose to treat the ultra-high dose opioid patient should at least recognize that the patient qualifies for this classification and label. In addition, we recommend that all parties use the “ultra-high dose” label to impart to all concerned parties that this is a special patient who requires special management, concerns and understanding. Patients taking ultra-high doses require extra care in ongoing assessment of needs, benefits and monitoring of adherence and safety.

Calculation of Morphine Equivalents

Since many patients are treated with opioids other than morphine and more than one opioid, it’s useful to be able to convert the patient’s medication regimen to its equivalent in milligrams of morphine. Table 2 is provided to simplify the calculation from other opioids to morphine. Be advised that methadone does not have a linear equivalence to morphine and the equivalence table should not be used to convert patients from one opioid to another.

Who Requires Ultra-High Opioid Dosages?

Fundamentally, this is a chronic pain patient who has attempted considerable trials with low and high opioid dosages

TABLE 1. Opioid Classification of Dosage

Class	Criteria by daily morphine equivalents
Low or standard	0 to 200mg
High	200 to 1000mg
Ultra-high	over 1000mg

and continues to have significant pain and diminished quality of life as demonstrated by a bed- or house-bound state and failure to work, eat, sleep, and socially interact—among other activities of daily living. They may also demonstrate some biologic indicators such as elevated pulse and blood pressure related to undertreated pain.³ The physician who treats the patient who requires ultra-high doses of opioids must clearly document in the patient’s chart that trials with low and high dosages have not been adequate to control pain and promote function.

In addition to documentation that low and high opioid doses have not been successful, an attempt should be made to determine the presence of some physical, x-ray and/or biochemical evidence that is commonly associated with severe chronic pain.⁴

Case Reports

Case 1: Patient who was stable on ultra-high doses. Mr. M, aged 67, was referred for ongoing care when he moved from another state. He was born with myelomeningocele and spina bifida and, in young adulthood, twice had surgery because of pain related to a tethered spinal cord. Nonetheless, he had been employed until he suffered a work-related back injury 19 years prior to the first visit. He was seen at several pain clinics and it was determined that additional surgery would not help, so he was begun on opioids. At the time of his first visit, he was on sustained-release morphine, 1200mg/day plus hydromorphone 8mg up to 6 per day for breakthrough pain (total of 1392mg morphine equivalents/day). He walked using a brace and cane, but did not drive. Mr. M was continued on exactly the same regimen for the 23 months that he was seen at the clinic. His pain varied but was often as low as 4/10. He was compliant and there were no abuse or misuse issues.

Case 2: Patient who required several dosage increases. Mr. D was 47-years-old when he was first seen at this clinic for chronic back pain related to a motor vehicle accident he experienced at age 15. He had recently been seen at a university pain clinic, which recommended that his current medication regimen be continued. This consisted of sustained-release oxycodone (OxyContin®) 320mg tid (equivalent to 1440mg of morphine/day), along with temazepam 30mg qhs for insomnia, celecoxib 400mg/day for pain

and inflammation, baclofen 10mg qid for muscle spasm, and fluoxetine 40mg/day for depression. He had already received several courses of epidural and facet injections. He was ambulatory and drove his car. He had recently been accepted for Social Security Disability after a career as a school administrator. He was a divorced single father who was raising his two small children. The patient was continued on the same dose of OxyContin, 960mg/day for the entire time he saw the lead author—83 months (6.9 years)—but, because of increasing pain, he was subsequently also prescribed methadone, as well as hydromorphone for breakthrough pain. During his last 20 months of care at this clinic, he was on a combination of 960mg/day OxyContin, methadone 180mg/day, plus Dilaudid 96mg/day (total of 2004 morphine equivalents/day). He continued to have significant pain, but obtained sufficient relief that he could function. On his last visit, he was still driving and he was still raising his two children. Mr. D was compliant throughout, with no abuse or misuse issues.

Family Involvement

A patient who requires over 1000mg of morphine equivalents a day should involve the family in the management process, if at all possible. To help document the need and insure compliance with taking ultra-high doses, the closest family members (preferably spouse and/or children) of the

patient should meet the prescribing physician. Family members need to know the cause of pain and reason for the high dosage. Oftentimes the family is the agent that demands the patient take an ultra-high dose because they recognize the suffering and impairment of the patient and want “something done.” Families may also question the necessity of an ultra-high dose and need to be educated on the need for it. Further, family reporting is essential to help assess and evaluate the treatment process.

Dosage Regimen

Patients whose pain requires ultra-high opioid doses generally require more than one opioid. A sustained-release (SR) opioid (such as sustained-release morphine, oxycodone, or oxymorphone or a fentanyl patch) or an opioid with a long-half life (methadone) is required for baseline, constant or persistent pain, while short-acting or immediate-release opioids are required for flares or episodes of breakthrough pain. The long-acting or SR opioid is given on a fixed, around-the-clock schedule in order to attain a smooth and consistent blood level of the drug. For breakthrough pain, a second, rapidly acting opioid is given, to be taken on an as-needed basis. If the patient has breakthrough pain episodes that reach maximal intensity within minutes, he/she additionally require a prescription for an ultra-rapid-acting opioid (e.g., fentanyl in

TABLE 2. Calculation of Morphine Equivalents

Opioid	Mg Dosage Per Day		Calculation Multiplier		Total Morphine Each Day (mg)
Morphine		x	1	=	
Hydromorphone		x	4	=	
Oxymorphone		x	10	=	
Levorphanol		x	5	=	
Methadone		x	1	=	
Fentanyl patch		x	mcg/hr fentanyl x 2.5 = mg morphine/day	=	
Codeine		x	.08	=	
Hydrocodone		x	2	=	
Oxycodone		x	1.5	=	
Meperidine		x	.13	=	

Total daily morphine equivalents _____ mgs

Caution: This is not a conversion table. Conversion must be extremely conservative and not assume full cross-tolerance between opioids. Also, morphine and methadone are equivalent only at very low doses.

the form of lollipops [Actiq®] or lozenges [Fentora®], sublingual liquid oxycodone, or morphine suppository). If a patient requires more than one long-acting and/or more than one short-acting opioid, it's essential to document the reason for this in the patient's chart.

Body Fluid Testing

Urine drug testing (UDT) is currently recommended for most patients being treated with opioids for chronic pain. Urine testing is used to detect drugs of abuse including cocaine, methamphetamine and cannabinoids. It may also give a clue as to whether the patient is complying with prescription instructions. The absence or very low concentrations of opioids in urine may suggest diversion of prescribed drugs. It is crucial, however, for the physician to understand (1) the limitations of urine drug testing and (2) the metabolic pathways of prescribed opioids. Urine drug screens typically screen only for natural opioids (e.g., morphine, codeine and hydrocodone) but will fail to detect synthetic and semi-synthetic opioids (e.g., oxycodone and fentanyl). The outcome for a patient who is taking oxycodone or fentanyl as prescribed will be a false-negative urine drug screen which, unfortunately, has resulted in patients being unjustly discharged. To avoid this possibility, it is important to ask the laboratory to specifically test for every opioid that the patient has been prescribed. Another situation that often leads to undeserved problems for the patient is when the patient is being prescribed a short-acting opioid to be taken as needed for breakthrough pain. The serum half-life of oxycodone (e.g., Percocet®) or hydrocodone (e.g., Vicodin®) is about four hours so, if several half-lives have elapsed since the patient last took the pill, the amount remaining in the urine may be below the limit of detection. It is crucial, therefore, at the time that the patient provides the urine specimen, to ask exactly when each opioid was last taken and record this in the chart.

When comprehensive urine drug tests are ordered, it's common to find an opioid in the urine that was not prescribed. Before concluding that the patient obtained that drug on the street or from another physician, it is crucial to find out from the clinical laboratory whether the unexpected drug could be a legitimate finding of a metabolite. For example,

codeine is metabolized to morphine, hydrocodone to hydromorphone, and oxycodone to oxymorphone. Thus, a patient who is taking Percocet (oxycodone) is very likely to have oxymorphone in the urine and the quantity might be even greater than the amount of oxycodone.⁷⁵ The bottom line is, if you order a UDT, be prepared to follow-up with the lab on any unexpected finding.

Finally, it is a mistake to draw conclusions about the patient's prescription compliance on the basis of quantitative levels of the opioid in the urine. There is tremendous variation in the way different people metabolize different drugs—not to mention that the time between when the drug was taken and the urine collected varies. UDTs should not be used to determine how much of the prescribed drug the patient is taking.

Blood levels of opioids are not generally used in a clinical setting but they have value in two situations. One is when there is a significant discrepancy between the prescribed dose and the effect of the drug, suggesting the possibility of variation in the metabolism of the drug.⁶ This has proven especially helpful regarding methadone, whose metabolism varies significantly from patient to patient. The following case report illustrates this:

Mrs. J, a 32-year-old woman, was prescribed methadone for severe headaches that resulted from a head injury sustained in a motor vehicle accident. Despite multiple increases in the dose, up to 200mg/day, she said the pain was barely diminished. Finally, a specialist ordered a serum methadone level, which came back extremely low. Further evaluation revealed that Mrs. J was also taking Tegretol for a seizure disorder that had also resulted from the head injury. Tegretol is known to markedly increase the metabolism of methadone and explained the low serum methadone level. The patient was switched to a different opioid that proved to be much more effective.

A second reason to obtain a serum opioid level in patients on ultra high-dose opioids is to establish baseline serum levels that can be compared to future tests. It is unfortunate that when a patient who is on high-dose opioids suddenly dies and the cause of death is not immediately apparent, a medical examiner who finds high levels of opioids in the blood may conclude that the patient died of a drug overdose. Some physicians have found

TABLE 3. Some Basic Management Recommendations

- Physical examination on admission and periodically thereafter
- Review records of previous treatments
- Family education
- Monthly visits until stable
- Screening for hormone abnormalities
- Normalize blood pressure and pulse rate
- Titrate dosage upward to maximize function without sedation
- Urine screening for compliance, abuse or drugs

themselves accused of causing the patient's death. A strong defense is a similar high opioid blood level documented in the patient's record at a time when the patient was ambulatory and doing well. Serum opioid levels in patients on high-dose opioids have been published and have been used successfully in the defense of physicians.⁷

Hazards of Non-Opioid Drugs

We highly recommend that patients who require ultra-high opioid dosage be restricted in their use of benzodiazepines, muscle relaxants and other sedatives. Although some use of these drugs may be necessary, they may produce drug interactions that may be hazardous. It is unclear as to why some patients require ultra-high opioid dosages but some, if not the majority, may have a cytochrome P450 or other genetic abnormality. This enhances the probability of drug interactions with opioids.⁸

Management Recommendations

The initial evaluation must include a medical history, queries about the patient's prior and present use of alcohol and other drugs, previous addiction history, physical exam, and baseline laboratory studies, among others (see Table 3). It is essential to obtain relevant old records. Goals and objectives should be established along with a discussion of what constitutes a realistic goal or objective for the specific patient. Some might include 30-50% pain relief, the elimination of bed- or house-bound days, cessation of emergency room visits, or resumption of regular eating and sleeping habits. There should be some emphasis and motivation to improve social interaction

since many such patients have been house-bound for extended time periods. Part of this discussion should be to clarify to the patient that improved function is as important a goal as is pain relief. The patient needs to be actively committed to following through on the physician's recommendations regarding physical therapy, exercise, and other measures to improve function. A regular monthly visit is highly recommended until the patient is stable. After that, some physicians are comfortable seeing the patient only every two, or even three, months as long as they remain stable. Family attendance is highly desirable in the first few visits. It is recognized that not everyone has a family, and not everyone with a family has a member who agrees to accompany the patient.

At each follow-up visit, at a minimum, the 4A's as advocated by Passik and colleagues, should be assessed and documented in the patient's chart.⁹ These comprise:

- **Analgesia.** Ask about pain relief using a scale such as 1 to 10 or the Faces scale.
- **Activities.** Assessment of the patient's function, level of exercise, etc.
- **Adverse effects.** Constipation and their bowel program; possible sedation; subnormal testosterone level and its treatment.
- **Aberrant.** Drug-related behaviors such as early refills, evidence of non-compliance.

In addition, it's desirable to include a fifth A for 'Affect' which comprises the patient's mood. Chronic pain patients are often depressed since depression and pain reinforce each other. Depression may need to be treated with an antidepressant and possible referral for counseling, if indicated.

Ancillary Measures

We recommend a great emphasis be placed on movement and physical exercises. Other additions may include electrical measures (electric, microelectric, radio frequency, etc.), topical analgesics (e.g., lidocaine patch), hormone replacement, and resocialization counseling. Invariably, patients who require ultra-high opioid dosages have been too ill to carry on normal social or family functions. They usually have to be guided and motivated to resocialize and begin a new quality of life.

Successful surgery, such as total knee replacement or back fusion, significantly

reduces pain and typically results in a decreased opioid dosage requirement. In general, however, there is no necessity to ever lower or cease opioid treatment if the patient's pain and function are significantly improved and the patient is tolerating the medication well. A trial of gradual dose reduction may be attempted, but should not be a primary goal. As with other chronic diseases such as diabetes or schizophrenia, treatment may extend for the patient's lifetime.

Search For Cause

It is unclear as to why some patients with seemingly no worse underlying cause of pain need an ultra-high dose while others don't.^{2,6,8} We recommend physicians attempt to determine a possible reason for the ultra-high dose requirement. One of the authors has found that a good place to start is opioid serum levels.⁵ Very low levels relative to the dosage may indicate malabsorption or a genetic liver enzyme defect, while very high opioid serum levels may indicate a liver enzyme defect or some resistance at the blood brain barrier or opioid receptor sites. Malabsorption is common in patients with a gastrointestinal disorder, diabetes or abdominal surgery. One of the authors, as well as other researchers, have begun testing ultra-high dose opioid patients for cytochrome P450 abnormalities, and early evidence suggest that as many as one-third of ultra-high dose patients may have an abnormal genotype. Early testing suggests that high opioid serum levels may be required to make a "lazy" genotype do its job and metabolize opioids.^{8,10}

Tolerance

Tolerance is defined as the need for an increased dose to get the same effect. Tolerance quickly develops (within days) to the sedative and nauseating effects of opioids, but typically not to the constipating effect of the drugs. It is a myth that tolerance to the pain-relieving effect of opioids is to be expected.¹¹ A need for increasing the dose early on in treatment is far more likely to result from increased activity and is a highly desired outcome of treating pain. It is not true that patients on high doses of opioids necessarily require ever-increasing doses, as clinicians who treat noncancer pain with opioids have learned. Many patients who require over 1000mg of morphine equiv-

alents a day reach a plateau dosage after titration and may remain in a relatively constant dosage range, albeit high, for many years.¹² Increased pain after months or years is more likely to be due to disease progression rather than a late development of tolerance.

Who Should Treat Ultra-High Opioid Patients?

Since these patients require very close monitoring and family involvement, the authors don't recommend that they be treated in settings or practices that intermingle other types of patients. Ultra-high dose opioid treatment must be closely monitored. The authors are aware of physicians who block off time periods (i.e. one day a week) to attend to such patients.

Complications of Treatment

The major complication of ultra-high dose opioid therapy is testosterone suppression in males and some females. Patients may require testosterone replacement. Suppression of serum cortisol, pregnenolone, and estrogen, however, seldom occur. Sudden suppression of adrenal corticoids in an opioid-maintained patient is usually accompanied by nausea, weakness, and drop in blood pressure. In these cases, hormone replacement may be necessary if opioids are still required to suppress pain.

Summary

Although not common among the general population of chronic pain patients, there are a subset of patients who require ultra-high dosages of opioids which the authors define as at least 1,000mg morphine equivalents per day. These patients are usually quite ill and impaired when they first present as they have usually been bed- or house-bound and withdrawn from socialization for a considerable period of time. The goal of ultra-high dosage therapy is to relieve pain and improve function in patients who require it—without producing sedation. Treatment must be closely monitored and family involvement is highly desired. It is incumbent on the treating physician to set some treatment goals and evaluate the patient's function over time to determine and document the merits of the treatment. Medical records must be kept to document the need and success of ultra high dose opioid therapy. ■

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