



Opioid “mythstakes”: Opioid analgesics—current clinical and regulatory perspectives

WILLIAM VILENSKY, DO, RPH

Barriers to appropriate prescribing of opioids include the deficit in educating medical students in core curricula. Other barriers include physicians' lack of knowledge of pain management, failure to educate their patients or include them in treatment options, and failure to take adequate medical histories and obtain records of their patients' previous treatment. In addition, physicians often lack the ability to distinguish the patient who is suffering pain from the addict. Patients, too, may fear that opioid therapy may cause addiction. This article provides an overview of guidelines and federal regulations for prescribing opioids, along with some caveats, in the hope that physicians and patients alike will appreciate that pain management is an integral part of treatment. And, that treatment is aimed at decreasing or eradicating pain and maintaining patients' function to the greatest possible degree while monitoring and treating side effects.

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Pain management in the United States has labored under “myths” regarding use of morphine, a natural alkaloid of the opium plant, and synthetic analgesics (opioids) that have similar characteristics. During the past 15 years, physicians in both pain and addiction medicine have recognized and heralded the need for change in attitudes in treating patients in pain as well as those who suffer from the neurobiologic disease of addiction. Those myths have raised the prescribing stakes that in the past escalated physicians' fears and governmental restrictive regulations.

Old concepts

Myths have made their way into medical practice, causing both physicians and patients to become wary and weary of using opioids for pain management. The term *pain management* should now be used instead of *pain treatment*. Treatment implies that the pain exists and the physician has to fight the battle to quell the pain; management refers to addressing the pathologic process causing the pain and preventing its appearance.

In a 1954 *JAMA* report, Rayport¹ stated that 27% of patients who were given morphine for pain had become addicted. In 1980, changes in attitude were seen in a study by Porter and Jeck² that concluded that only 4 of 11,882 patients given opioids in the hospital had difficulty in discontinuing such use. In 1982, Perry and Heidrich³ found that none of approximately 10,000 burn patients became addicted to opioids used in their management of pain. In lecturing and questioning physicians and nurses

Dr Vilensky is a clinical associate professor of psychiatry at the University of Medicine and Dentistry of New Jersey—New Jersey Medical School, in Newark, NJ.

Correspondence to William Vilensky, DO, RPH, Executive Medical Director, Forensic & Educational Consultants, 110 S Nassau Ave, Margate, NJ 08402-2520.

E-mail: wvilensky@hotmail.com

during the past 30 years, not one could recall any patient dying of respiratory failure as the result of opioid therapy in the hospital. Clinical experience has shown that death from the use of opioids in the patient in real pain is a rarity when titrating doses upwards until the most pain-free state is reached. In fact, we now know that there is no upper limit on dosing of the pure opioids, that is, without aspirin (ASA) or acetaminophen (APAP).

*Myth*stakes of inadequate pain management is the obvious suffering, but other parameters involve loss of society with family and friends, functionality, and employability in addition to significant financial burden. Sleep deprivation from pain compromises the homeostatic balance of many physiologic functions and delays healing. Loss of appetite and ensuing nutritional deficits hinder biosyntheses of neurochemical transmitters. As a result, many patients in pain are plagued with anxiety and depression. Patients should never have to wish for death as the answer to persistent pain. "Pain should never be a suicide-dogen," according to Goldstein.⁴

A major hindrance to pain management is the deficit in educating medical students in core curricula. Other barriers to appropriate opioid prescribing include physicians who:

- lack knowledge of pain management;
- fear causing respiratory depression and addiction;
- fail to understand that pain management is an integral part of treatment;
- neither educate their patients nor include them in treatment options;
- take poor histories and do not obtain prior treatment records; and
- fear their inability to tease apart the pain patient from the addict. Contributing to this problem is the patient who also fears becoming an addict when placed on opioid therapy.

In speaking with a patient, the physician should eliminate the word "narcotic," which conjures up images of the craving addict. It is better to use "opioid analgesic," which has the same meaning but without the stigma. The media have unfortunately confused and hypersensationalized use of extended-release opioids for chronic pain and abuse of these useful medications by

addicts. In a recent trial against an unlicensed physician who criminally prescribed to addicts the only extended-release opioid, oxycodone hydrochloride, the headline described this excellent analgesic as a "heroin-like anti-cancer drug."⁵ This product does not resemble heroin (diacetylmorphine), nor is it used just for malignancies. This negative and ignorant terminology fails to inform that the same drug is used for nonmalignant maladies such as headaches, arthritis, osteoporosis, and severe neck and back pain.

Goals of pain management

The goals of pain management are to decrease or eradicate pain, keep the patient as functional as possible, monitor and treat side effects such as respiratory depression, sedation, dizziness, and gastrointestinal side effects and pruritic rash from morphine-induced histamine release. Do not confuse such side effects with allergies, and document what you do and think!

New concepts

In 1992, the then-US Department of Health and Human Services Agency for Health Care Policy and Reform,⁶ now the Agency for Healthcare Research and Quality (AHRQ), recognized "the ethical obligation to manage pain and relieve the patient's suffering is at the core of a healthcare professional's commitment."

In 1997, the Federation of State Medical Boards (FSMB) of the United States recognized the imbalance in use of opioids in management of pain; in 1998, the *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain*⁷ was developed and published, emphasizing:

■ **Evaluation of the patient**—complete history and physical examination documenting the presence of a pathologic process to substantiate prescribing of opioids.

■ **Treatment plan**—Written statements of objectives to determine success.

■ **Informed consent and agreement for treatment**—explanation of risks and benefits; use a written contract outlining patient's responsibilities if there is a history of substance abuse, and include drug testing; receive prescriptions from one physician and one pharmacy where possible.

■ **Periodic review**—check for progress or retrogress, evaluate tests and medications. Any new or complicating conditions?

■ **Consultations**—functional, occupational, psychosocial, psychiatric, and addiction comorbidities need addressing.

■ **Medical records**—documentation of all the foregoing parameters, especially prior medical records of treatments, hospitalizations, and analgesic use.

■ **Compliance with controlled substances laws and regulations**—as of January 1, 2001, the Joint Commission for the Accreditation of Healthcare Organizations (JCAHO) mandated pain management education and practice, and included patients' education and rights in treatment decision making. Similarly, the American Osteopathic Association's Healthcare Facilities Accreditation Program has issued standards for a multidisciplinary approach to pain management and patients' rights to effective treatment (see *Table 1* on page S2).

The Controlled Substances Act of 1970

The Code of Federal Regulations (21CFR 1306.04 and 1306.05)⁸ set the standards:

A prescription for a controlled substance to be effective must be issued for:

1. a legitimate medical purpose by an individual practitioner,
2. acting in the usual course of his professional practice, and
3. in the scope of a Doctor/Patient relationship,
4. a corresponding responsibility rests with the pharmacist filling the Rx,
5. an order purporting to be a prescription issued *not* in the course of professional treatment, is *not* a prescription within the meaning and intent of the Act and shall be subject to penalties for violating the law.
6. all prescriptions for controlled substances shall be *dated* as of, and *signed* on the *date when issued* and shall bear the *full name, address of the patient, the drug name, the strength, the dosage, form, quantity prescribed, directions for use and the name, address, and the registration number of the practitioner*. [Italics added for emphasis.]

The FSMB guidelines, although not

law, create the force and impact of the “standard of care” that is assessed by state licensing boards and malpractice attorneys in judging the physicians’ competency.

The pendulum of pain management has now swung the opposite way so that physicians are now being held responsible in malpractice litigation for inappropriate underprescribing of opioids, allowing patients to suffer needlessly in pain. The Pain Relief and Promotion Act,⁹ The Conquering Pain Act,¹⁰ and the Compassionate Care Act¹¹ are all positive efforts on the part of government liberalizing and encouraging physicians to manage pain appropriately and effectively. In October 2001, the Drug Enforcement Agency and 21 national health, pain, and addiction organizations issued a joint statement, in an unprecedented collaboration, emphasizing the need for a “balanced” approach to opioid diversion and pain management. This came after media attacks on an extended-release oxycodone product that was being abused—not by patients in true pain, but by addicts.

Prescribing opioids in the clinical setting—2002

Acute pain

Acute pain is short lasting, usually after surgery or trauma. Short-acting opioids should be given around the clock on a time-contingency—not on an as-needed—basis, titrated upwards to analgesic effect, and reduced as the body heals and pain dissipates. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used first and supplemented with opioids. *Avoid* using meperidine hydrochloride because of its rapid and long-lasting metabolite, normeperidine, which can cause central nervous system stimulation and tremors that can escalate to seizures with or without prior renal embarrassment; meperidine should never be used for management of chronic pain.

Chronic pain

Opioids are appropriate for chronic intractable pain, defined as pain lasting longer than a few months from the same or multiple etiologies and unrelieved by other therapeutic modalities. The *Figure* lists types of opioids.

Aspirin can cause serious gastroin-

Checklist

- **Pure opioids**
 - Short acting (2 to 4 hours)
 - morphine sulfate (MSIR, (Roxanol)
 - oxycodone (OxyIR, Roxicodone, and generic products)
 - hydromorphone (Dilaudid)
 - hydrocodone
 - codeine
 - propoxyphene (plain Darvon)
 - Intermediate acting (6 to 8 hours)
 - methadone (Dolophine and generic products)
 - levorphanol (LevoDromoran)
 - Extended release (12 to 24 hours)
 - oxycodone (OxyContin)
 - morphine (MS Contin, Oramorph SR, Kadian [24 hours])
- **Opioid compounds**
 - Mixed with aspirin or acetaminophen (2 to 4 hours)
 - propoxyphene (Darvon Comp, Darvocet, and generic products)
 - codeine (Tylenol with codeine, aspirin with codeine, and generic products)
 - hydrocodone bitartrate (Vicodin, Lorcet, Lortabs, Anexsia, and generic products)
 - oxycodone (Percodan, Percocet, Tylox, and generic products)

Figure. Types of opioids.

testinal causticity and reduce coagulation; APAP in doses greater than 4000 mg daily can cause hepatotoxicity and is the limiting factor in dosing, not the opioid. It must be recognized that some combinations have large amounts of APAP, such as 5 mg, 7.5 mg, or 10 mg of hydrocodone contain 325 mg, 500 mg, 650 mg, or 750 mg of APAP per tablet (only five tablets of the latter will reach the upper limit). Oxycodone preparations newly approved by the US Food and Drug Administration have increased opioid levels while maintaining the 325 mg of APAP, reducing APAP hepatotoxicity; for example, Percocet, in 2.5-mg, 5.0-mg, 7.5-mg, and 10-mg strengths of oxycodone, contains APAP in a fixed dose of 325 mg.

Three drugs are not appropriate for

management of chronic pain: meperidine, methadone, and propoxyphene. Methadone has a cumulative metabolite, but unlike meperidine, it is *not* neurotoxic. Also, methadone has a variable absorption, distribution, and metabolic breakdown, causing marked sedation in some patients when used several times a day for analgesia. “Care must be taken when escalating the dosage, because of the prolonged half-life of the drug, its tendency to accumulate over a period of several days with repeated dosing.”^{12(p597)} The strength may have to be reduced or the frequency prolonged—a problem when trying to manage a patient’s chronic pain at home.¹² Because the analgesic action is shorter than the respiratory-depressant effect, death has occurred when patients overmedicated themselves in an attempt to gain better pain relief. This problem is not seen in a one-time daily dose for blocking the craving of opioid-dependent addicts. Methadone is a cheap drug, but the complex pharmacokinetic profile renders this opioid not the best choice unless a patient can fully understand the need to avoid increasing the dose until conferring with his or her physician; following this plan will allow appropriate assistance in managing the escalating pain. In addition, the use of short-acting opioids and/or adjuncts may allow the patient to remain on methadone. (See “Adjuncts to opioids,” beginning on page S15.)

Propoxyphene is structurally related to methadone. In large doses, or relatively large doses in the elderly, propoxyphene can deepen depression and may cause convulsive seizures. Like methadone, it has great variability between subjects in the rate of clearance and the plasma concentrations that are achieved.^{12(p598)} All morphine-like opioids can depress respiration.

How to dose

Start low and titrate upwards as often as every 24 hours. With single-opioid therapy, one can titrate up with no upper limit, restricted only by intolerable side effects. If side effects appear at the beginning of treatment, treat the side effects—do not stop the use of the analgesic. Frequent side effects are nausea, vomiting, and pruritic rash from histamine release.

These are not allergic reactions and tolerance usually develops. Clinically significant respiratory depression rarely occurs with standard morphine doses in absence of underlying pulmonary dysfunction. Combinations of opioids with general anesthetics, tranquilizers, alcohol, or sedatives/hypnotics may present a greater risk of respiratory depression.^{12(p584)} Remember, severe pain is its own respiratory stimulant. When using combinations, the strength of one or both should be reduced.

Give laxatives at the start of treatment because patients do not usually become tolerant to constipation; milder agents such as stool softeners should be given first while restricting harsher laxatives for more resistant cases.

■ **Chronic pain: continuous- or extended-release opioids (morphine or oxycodone)**—Freedom from pain and living in dignity is the main goal of management. *Start with a low dose every 12 hours in the opioid-naïve-patient.* If the patient has been on significant opioid therapy recently, there may be some opioid tolerance requiring a higher starting dose. *Review of documented medical records from prior physicians, hospitals, and pain clinics is necessary, including at least phone communication with previous physician.* The patient with chronic pain has a long medical record trail; check it out before starting a physician/patient relationship. Follow the FSMB guidelines, and *document!*

Extended-release opioid analgesics may also allow patients to become more active and improve their activities of daily living; as a result of occasional breakthrough pain, a rescue dose of a

short-acting opioid may be required. The best plan is to use the same opioid as in the extended-release form until the next every-12-hour dose. A patient's need for more than two or three rescue doses per day indicates that the every-12-hour dose is too low. Escalate the every-12-hour dose, and caution the patient to hold off taking the rescue dose if possible until stabilization occurs (usually within 24 hours). Keep in mind that when the patient is taking a higher every-12-hour dose, the strength of the "rescue" dose may also have to be elevated.

Warn the patient that extended-release tablets last for 12 hours and should only be swallowed whole and never broken, chewed, crushed, inhaled, injected, or placed in a body cavity other than the oral cavity.

Withdrawal

If pain is lessened as the result of recovery or the addition of other modalities, the analgesic dose can be lowered by 25% to 50% per day (lower percent if pain is chronic, higher percent reduction if use is for acute pain). If signs of physical withdrawal occur, level off and reduce the dose more gradually.

Comment

Physicians have a moral, ethical, legal, and medical obligation to treat pain. Examine the patient and document fully. Use opioids when other modalities fail. Obtain laboratory/x-ray studies and consultations. Educate and inform the patient of treatment options, risks, and benefits. Obtain drug screens if patient has a past or present history of substance

abuse. Do not convert the *war on drug abuse* to the *war on patients in pain*. Stop the *myths*—the stakes are too high!

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