Prescribing Opioids: Care amid Controversy

Recommendations from the California Medical Association’s Council on Scientific Affairs

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This paper summarizes the findings of the California Medical Association’s Council on Scientific Affairs, a panel of physician experts, which conducted a review of current literature, existing clinical guidelines and expert opinion in order to present an up-to-date, clinically relevant overview for its members and the wider population of prescribers. This report complements the 2013 CMA policy white paper entitled *Opioid Analgesics in California: Relieving Pain, Preventing Abuse, Finding Balance*. While the 2013 white paper focused on legislative and policy aspects of opioid prescribing, this paper is written by physicians to provide a balanced medical perspective. It summarizes updated guidance on this urgent and controversial topic. Key points of this paper include:

- All biologically active drugs pose risks if they are not used appropriately. Opioid analgesics share this characteristic with other types of medications.

- Opioid analgesics are widely accepted as appropriate and effective for alleviating moderate-to-severe acute pain, pain associated with cancer and persistent end-of-life pain.

- The use of opioids for chronic pain not associated with cancer is more controversial, and current research on the benefits and/or safety of opioids for this indication is either weak or inadequate.

- Opioids may be appropriate for certain patients with chronic pain, provided that opioids are prescribed cautiously and in a manner consistent with approved clinical practice guidelines.

- Opioids should be used for chronic pain only when safer options have been deemed ineffective and continued treatment should be based on maintenance of clinical and functional goals.

- Informed consent for opioid use for chronic pain includes patient knowledge of, and acceptance of, the following:
  - The potential benefits and/or safety of opioids are not proven by high-quality evidence, such as randomized controlled clinical trials;
  - Risks, including risk of abuse and overdose, tend to increase with dose;
  - Addiction, abuse, chemical coping and other problems associated with opioids are not uncommon;
  - Some patients have difficulty discontinuing opioid therapy;
  - Some pain doesn’t get better or can worsen with opioids;
  - Taking other substances/drugs with opioids (e.g., alcohol) or having certain conditions (e.g., sleep apnea, mental illness) can increase risk and cause serious adverse effects; and
  - Opioids should be used only as prescribed, should be stored securely and when a course of treatment is altered, discontinued or stopped, any unused opioids should be disposed of properly.

The overview and recommendations that follow are neither comprehensive nor should they be considered a standard of care. CMA believes that, in the treatment of any individual patient, the treating physician's professional obligation and ethical duty is to provide appropriate medical care and treatment for the patient based on the physician's training, experience and clinical judgment regardless of protocols meant to guide general practice.

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Introduction

In the 1990s, awareness of the high prevalence of un-treated or under-treated pain led to calls for a more liberal use of opioid analgesics, beyond the realms of moderate-to-severe acute pain or intractable end-of-life pain for which these medications were traditionally reserved. These efforts, along with legislative directives and pharmaceutical industry marketing initiatives, fueled a quadrupling of opioid analgesic sales between 1999 and 2010. The expanded use of opioids in the treatment of chronic pain that was not associated with cancer was supported by numerous professional practice guidelines, although most of these recommendations were acknowledged at the time to be based on experiential or low-quality evidence.

Concurrent with the rise in the prescription of opioid analgesics was a rise in abuse, addiction, and diversion of opioids for non-medical use. For example, between 1998 and 2008, the rate of opioid misuse increased 400%. Emergency-room visits related to non-medical use of opioids rose 111% between 2004 and 2008. In 2009 an estimated 7 million Americans were abusing prescription drugs (5.1 million of whom were abusing pain relievers) — more than the number abusing cocaine, heroin, hallucinogens and inhalants, combined.

In California, data from 2010 and 2011 suggests that the rate of past-year nonmedical use of prescription pain relievers among those aged 12 or older was 4.7%, which was slightly higher than the national rate of 4.6%. Drug overdose deaths (including illegal drugs) in California in 2008 were 10.4 deaths per 100,000 people, which is below the US average of 12.3 overdose deaths per 100,000 people. For comparison, the average death rate in California attributed to smoking was 235 per 100,000 people between the years 2000 and 2004.

In response to such statistics, there has been a shift in thinking among many pain specialists about the use of opioids for chronic pain, and legislative efforts to curtail the use of opioids are underway in many states, including California. Since professional opinions on this topic have shifted, the California Medical Association’s Council on Scientific Affairs has undertaken a review of current literature and existing clinical guidelines, and has sought expert opinion, in order to articulate an up-to-date set of consensus views for pain management with opioid analgesics. This paper summarizes those findings. It is intentionally brief, though extensively-referenced to facilitate access to more detailed information for those who seek it.

It is both possible and feasible in the practice of pain management to include opioids in one’s treatment armamentarium and to deploy these medications carefully and appropriately in ways that benefit selected patients while reducing the risk of harm. The characteristics of opioids that make them subject to abuse are not unique, nor are the diagnostic challenges associated with chronic pain. Despite the pressures on prescribers to simultaneously relieve pain while protecting patients and society from the hazards of diversion, misuse and abuse, there are general guideposts for action and agreed-upon steps that, when taken, can strengthen the overall quality of care while minimizing the aforementioned risks to patients and society at large.

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ii. For purposes of this document, misuse is defined as use of prescription drugs that were not prescribed for the person using them and the use of these drugs recreationally and not for medical necessity. Misuse also includes use by a patient who does not follow a physician’s order, such as taking drugs in amounts that exceed a physician’s orders.
Clarification of Key Concepts

**Pain:** The definition of pain proposed by the International Association for the Study of Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” It has also been said that “Pain is what the patient says it is.” Both definitions acknowledge the subjective nature of pain and are reminders that, with the rare exception of patients who intentionally deceive, a patient’s self-report and pain behavior are likely the most reliable indicators of pain and pain severity. As a guide for clinical decision-making, however, both of these definitions are inadequate. In addition, it is important to remember that the subjectivity of pain, particularly when the cause is not apparent, can lead to the stigmatization of those with pain.

**Acute and Chronic Pain:** Traditionally, pain has been classified by its duration. In this perspective, “acute” pain is relatively short-duration, arises from obvious tissue injury, and usually fades with healing. “Chronic” pain, in contrast, has been variously defined as lasting longer than would be anticipated for the usual course of a given condition, or pain that lasts longer than arbitrary cut-off times such as 3 or 6 months. Temporal pain labels, however, provide no information about the biological nature of the pain itself, which is often of critical importance.

**Nociceptive and Neuropathic Pain:** A more useful nomenclature classifies pain on the basis of its patho-physiological process. Nociceptive pain is caused by the activation of nociceptors, and is generally, though not always, short-lived and is associated with the presence of an underlying medical condition. It is a “normal” process; a physiological response to an injurious stimulus. Nociceptive pain is a symptom. Neuropathic pain, on the other hand, results either from an injury to the nervous system or from inadequately-treated nociceptive pain. It is an abnormal response to a stimulus; a pathological process. It is a neuro-biological disease. Neuropathic pain is caused by abnormal neuronal firing in the absence of active tissue damage. It may be continuous or episodic and varies widely in how it is perceived. Neuropathic pain is complex and can be difficult to diagnose and to manage because available treatment options are limited.

A key aspect of both nociceptive and neuropathic pain is the phenomenon of sensitization, which is a state of hyperexcitability in either peripheral nociceptors or neurons in the central nervous system. Sensitization may lead to either hyperalgesia or allodynia. Sensitization may arise from intense, repeated or prolonged stimulation of nociceptors, or from the influence of compounds released by the body in response to tissue damage or inflammation. Importantly, many patients—particularly those with persistent pain—present with “compound” pain that has both nociceptive and neuropathic components, a situation which complicates assessment and treatment.

Differentiating between nociceptive and neuropathic pain is critical because the two respond differently to pain treatments. Neuropathic pain, for example, typically responds poorly to both opioid analgesics and non-steroidal anti-inflammatory (NSAID) agents. Other classes of medications, such as anti-epileptics, antidepressants or local anesthetics, may provide more effective relief for neuropathic pain.

Cancer and Non-Cancer Pain: Pain associated with cancer is sometimes given a separate classification, although it is not distinct from a patho-physiological perspective. Cancer-related pain includes pain caused by the disease itself and/or painful diagnostic or therapeutic procedures. The treatment of cancer-related pain may be influenced by the life expectancy of the patient, by co-morbidities and by the fact that such pain may be of exceptional severity and duration.

A focus of recent attention by the public, regulators, legislators, and physicians has been chronic pain that is not associated with cancer. A key feature of such pain, which may be caused by conditions such as musculoskeletal injury, lower back trauma and dysfunctional wound healing, is that the severity of pain may not correspond well to identifiable levels of tissue damage.
Tolerance, Dependence and Addiction: Related to the nomenclature of pain itself is continuing confusion not only among the public, but also in the medical community, about terms used to describe the effects of drugs on the brain and on behavior. To help clarify and standardize understanding, the American Society of Addiction Medicine (ASAM), the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) have recommended the following definitions:\(^{21}\)

- **Tolerance.** A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.

- **Physical Dependence.** A state of adaptation that often includes tolerance and is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist.

- **Addiction.** A primary, chronic, neurobiological disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm and craving.

Pain as an Illness: Finally, it may be helpful to point out that pain can be regarded as an illness as well as a symptom or a disease. “Illness” defines the impact a disease has on an organism and is characterized by epiphenomena or co-morbidities with bio-psycho-social dimensions.\(^{22}\) Effective care of any illness, therefore, requires attention to all of these dimensions. Neuropathic pain, end-of-life pain and chronic pain should all be viewed as illnesses.
In treating pain, clinicians can avail themselves of five basic modalities of pain-management tools:

1. Cognitive-behavioral approaches
2. Rehabilitative approaches
3. Complementary and alternative therapies
4. Interventional approaches
5. Pharmacotherapy

Not all of these options are necessary or appropriate for every patient, but clinical guidelines suggest that all options should be considered every time a health care provider decides to treat a patient with chronic pain. These options can be used alone or in combinations to maximize pain control and functional gains. Only one of these options involves medications and opioids are only one of many types of medications with potential analgesic utility. Which options are used in a given patient depends on factors such as the type of pain, the duration and severity of pain, patient preferences, co-occurring disease states or illnesses, patient life expectancy, cost and the local availability of the treatment option. Each class of treatment option is briefly reviewed below, with a more extensive discussion of opioids.

**Cognitive-behavioral Approaches**

The brain plays a vitally important role in pain perception and in recovery from injury, illness or other conditions involving pain. Psychological therapies of all kinds, therefore, may be a key element in pain management. At the most basic level, such therapy involves patient education about disease states, treatment options or interventions, and methods of assessing and managing pain. Cognitive therapy techniques may help patients monitor and evaluate negative or inaccurate thoughts and beliefs about their pain. For example, some patients engage in an exaggeration of their condition called “catastrophizing” or they may have an overly passive attitude toward their recovery which leads them to inappropriately expect a physician to “fix” their pain with little or no work or responsibility on their part. Another way to frame this is to assess whether a patient has an internal or external “locus of control” relative to their pain. Someone with an external locus of control attributes the cause/relief of pain to external causes and they expect that the relief comes from someone else.23 Someone with an internal locus of control believes that they are responsible for their own well being; they own the experience of pain and recognize they have the ability and obligation to undertake remediation, with the help of others.

Some chronic pain patients have a strong external locus of control, and successful management of their pain hinges, in part, on the use of cognitive or other types of therapy to shift the locus from external to internal.24 Individual, group or family psychotherapy may be extremely helpful for addressing this and other psychological issues, depending on the specific needs of a patient.

In general, psychological interventions may be best suited for patients who express interest in such approaches, who feel anxious or fearful about their condition, or whose personal relationships are suffering as a result of chronic or recurrent pain. Unfortunately, the use of psychological approaches to pain management can be hampered by such barriers as provider time constraints, unsupportive provider reimbursement policies, lack of access to skilled and trained providers, or a lack of awareness on the part of patients and/or physicians about the utility of such approaches for improving pain relief and overall function.25

**Rehabilitative Approaches**

In addition to relieving pain, a range of rehabilitative therapies can improve physical function, alter physiological responses to pain and help reduce fear and anxiety. Treatments used in physical rehabilitation include exercises to improve strength, endurance, and flexibility; gait and posture training; stretching; and education about ergonomics and body mechanics.26 Exercise programs that incorporate Tai Chi, swimming, yoga or core-training may also be useful. Other noninvasive physical treatments for pain include thermotherapy (application of
heat), cryotherapy (application of cold), counter-irritation and electroanalgesia (e.g., transcutaneous electrical stimulation). Other types of rehabilitative therapies, such as occupational and social therapies, may be valuable for selected patients.

**Complementary and Alternative Therapies**

Complementary and alternative therapies (CAT) of various types are used by many patients in pain, both at home and in comprehensive pain clinics, hospitals or other facilities. These therapies seek to reduce pain, induce relaxation and enhance a sense of control over the pain or the underlying disease. Meditation, acupuncture, relaxation, imagery, biofeedback and hypnosis are some of the therapies shown to be potentially helpful to some patients. CAT therapies can be combined with other pain treatment modalities and generally have few, if any, risks or attendant adverse effects. Such therapies can be an important and effective component of an integrated program of pain management.

**Interventional Approaches**

Although beyond the scope of this paper, a wide range of surgical and other interventional approaches to pain management exist, including trigger point injections, epidural injections, facet blocks, spinal cord stimulators, laminectomy, spinal fusion, deep brain implants and neuro-augmentative or neuroablative surgeries. Many of these approaches involve some significant risks, which must be weighed carefully against the potential benefits of the therapy.

**Pharmacotherapy**

Many types of medications can be used to alleviate pain, some that act directly on pain signals or receptors, and others that contribute indirectly to either reduce pain or improve function. For patients with persistent pain, medications may be used concurrently in an effort to target various aspects of the pain experience.

**NSAIDs and Acetaminophen**

Non-steroidal anti-inflammatory drugs (NSAIDs), which include aspirin and other salicylic acid derivatives, and acetaminophen, are categorized as non-opioid pain relievers. They are used in the management of both acute and chronic pain such as that arising from injury, arthritis, dental procedures, swelling or surgical procedures. Although they are weaker analgesics than opioids, acetaminophen and NSAIDs do not produce tolerance, physical dependence or addiction. Acetaminophen and NSAIDs are also frequently added to an opioid regimen for their opioid-sparing effect. Since non-opioids and opioids relieve pain via different mechanisms, combination therapy can provide improved relief with fewer side effects.

These agents are not without risk, however. Adverse effects of NSAIDs as a class include gastrointestinal problems (e.g., stomach upset, ulcers, perforation, bleeding, liver dysfunction), bleeding (i.e., antiplatelet effects), kidney dysfunction, hypersensitivity reactions and cardiovascular concerns, particularly in the elderly. The threshold dose for acetaminophen liver toxicity has not been established, although the FDA recommends that the total adult daily dose should not exceed 4,000 mg in patients without liver disease (although the ceiling may be lower for older adults). In 2009, the FDA required manufacturers of products containing acetaminophen to revise their product labeling to include warnings of the risk of severe liver damage associated with its use. In 2014, new FDA rules went into effect that set a maximum limit of 325 mg of acetaminophen in prescription combination products (e.g., Vicodin and Percocet) in an attempt to limit liver damage and other ill effects from the use of these products. Of note, aspirin (> 325 mg/d), ibuprofen, ketoprofen, naproxen and other non-cyclooxygenase-selective NSAIDs, are listed as “potentially inappropriate medications” for use in older adults in the American Geriatrics Society 2012 Beers Criteria because of the range of adverse effects they can have at higher doses. Nonetheless, with careful monitoring, and in selected patients, NSAIDs and acetaminophen can be safe and effective for long-term management of persistent pain.
Opioids

Opioids can be effective pain relievers because, at a molecular level, they resemble compounds, such as endorphins, which are produced naturally in the human central nervous system. Opioid analgesics work by binding to one or more of the three major types of opioid receptors in the brain and body: mu, kappa and delta receptors. The most common opioid pain medications are called "mu agonists" because they bind to and activate mu opioid receptors. The binding of mu agonist opioids to receptors in various body regions results in both therapeutic effects (such as pain relief) and side effects (such as constipation).

Physical tolerance develops for some effects of opioids, but not others. For example, tolerance develops to respiratory suppressant effects within 5-7 days of continuous use, whereas tolerance to constipating effects is unlikely to occur. Tolerance to analgesia may develop early, requiring an escalation of dose, but tolerance may lessen once an effective dose is identified and administered regularly, as long as the associated pathology or condition remains stable.34

Opioids, as a class, comprise many specific agents available in a wide range of formulations and routes of administration. Short-acting, orally-administered opioids typically have rapid onset of action (10-60 minutes) and a relatively short duration of action (2-4 hours). They are typically used for acute or intermittent pain, or breakthrough pain that occurs against a background of persistent low-level pain. Extended-release/long-acting (ER/LA) opioids have a relatively slow onset of action (typically between 30 and 90 minutes) and a relatively long duration of action (4 to 72 hours). The FDA states that such drugs are "indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."35

### CONTROLLED SUBSTANCE SCHEDULES

Opioids are regulated by the U.S. Controlled Substances Act (21 U.S.C. §813). All controlled substances have some degree of abuse potential or are immediate precursors to substances with abuse potential. Controlled substances are placed in their respective schedules based on whether they are determined to have a currently accepted medical use in the United States and on their perceived abuse potential and/or likelihood of causing dependence.

- **Schedule I** substances are judged to have a high potential for abuse and no currently accepted medical use in the United States. Examples include heroin, LSD and peyote.

- **Schedule II** substances are viewed as having a high potential for abuse or which may lead to psychological or physical dependence, and yet which also have an accepted medical use in the United States. Most opioid pain medications are Schedule II drugs. Other Schedule II drugs include amphetamines, methamphetamines, methylphenidates and cocaine.

- **Schedule III** substances are considered to have a lower potential for abuse than substances in Schedules I or II. (Note that in 2013, some Schedule III opioid combination products containing hydrocodone [e.g., Vicodin] were recommended by the FDA to be rescheduled to Schedule II.)

- **Drugs in Schedules IV and V** are considered to have lower potentials for abuse than other schedules.

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iii An older term, “opiates,” referred specifically to preparations derived from opium itself. The word “opioids” is preferred today and refers to all drugs made either from opium directly or synthesized to have opium-like effects.
These agents achieve their extended activity in various ways. Some have intrinsic pharmacokinetic properties that make their effects more enduring than short-acting opioids, while others are modified to slow their absorption or to slow the release of the active ingredient. A given patient might be appropriate for ER/LA therapy only, short-acting only or a combination of an ER/LA opioid with a short-acting opioid. Note that patients may respond in very different ways to any given medication or combination of medications. One size does not fit all, and treatment is best optimized by titrating a given regimen on an individual basis. Combination products that join an opioid with a non-opioid analgesic entail the risk of increasing adverse effects from the non-opioid co-analgesic as doses are escalated, even if an increase of the opioid dose is appropriate.

In response to concerns about opioid misuse and abuse, abuse-deterrent and tamper-resistant opioid formulations have been developed. One class of deterrent formulation incorporates an opioid antagonist into a separate compartment within a capsule; crushing the capsule releases the antagonist and neutralizes the opioid effect. Another strategy is to modify the physical structure of tablets or incorporate compounds that make it difficult or impossible to liquefy, concentrate, or otherwise transform the tablets. Although abuse-deterrent opioid formulations do not prevent users from simply consuming too much of a medication, they may help reduce the public health burden of prescription opioid abuse.36

Patients who receive opioids on a long-term basis to treat pain are considered to be receiving chronic opioid analgesic therapy, which is differentiated from opioid use by patients who have an established opioid use disorder who use an opioid (e.g. methadone) as part of their treatment program.

Potential Adverse Effects of Opioids
Although opioid analgesics (of all formulations) may provide effective relief from moderate-to-severe pain, they also entail the following significant risks:3

- Overdose
- Misuse and diversion
- Addiction
- Physical dependence and tolerance
- Potentially grave interactions with other medications or substances
- Death

At the heart of much of the current controversy over the use of opioid analgesics for chronic pain are beliefs about the degree to which these pain medications are potentially addicting. Unfortunately, it is difficult to quantify the degree of addictive risk associated with opioid analgesics, either for an individual patient or the population of pain patients in general.

In this context, it is critical to differentiate addiction from tolerance and physical dependence (see discussion starting on page 4), which are common physiological responses to a wide range of medications and even to widely-consumed non-prescription drugs (e.g. caffeine). Physical dependence and tolerance alone are not synonymous with addiction. Addiction is a complex disease state that severely impairs health and overall functioning. Opioid analgesics may, indeed, be addicting, but they share this potential with a wide range of other drugs such as sedatives, alcohol, tobacco, stimulants and anti-anxiety medications.

Rigorous, long-term studies of both the potential effectiveness and potential addictive risks of opioid analgesics for patients who do not have co-existing substance-use disorders have not been conducted.5 The few surveys conducted in community practice settings estimate rates of prescription opioid abuse of between 4% to 26%.37, 38, 39, 40 A 2011 study of a random sample of 705 patients undergoing long-term opioid therapy for non-cancer pain found a lifetime prevalence rate of opioid-use disorder of 35%.41 The variability in results reflect differences in opioid treatment duration, the short-term nature of most studies and disparate study populations and measures used to assess abuse or addiction. Although precise quantification of the risks of abuse and addiction among patients prescribed opioids is not currently possible, the risks are large enough to underscore the importance of stratifying patients by risk and providing proper monitoring and screening when using opioid analgesic therapy.
Particular caution should be exercised when prescribing opioids to patients with conditions that may be complicated by adverse effects from opioids, including chronic obstructive pulmonary disease (COPD), congestive heart failure, sleep apnea, current or past alcohol or substance misuse, mental illness, advanced age or patients with a history of kidney or liver dysfunction.

In addition, opioids generally should not be combined with other respiratory depressants, such as alcohol or sedative-hypnotics (benzodiazepines or barbiturates) unless these agents have been demonstrated to provide important clinical benefits, since unexpected opioid fatalities can occur in these combination situations at relatively low opioid doses.

In addition to the potential risks just described, opioids may induce a wide range of side effects including respiratory depression, sedation, mental clouding or confusion, hypogonadism, nausea, vomiting, constipation, itching and urinary retention. With the exception of constipation and hypogonadism, many of these side effects tend to diminish with time. Constipation requires prophylaxis that is prescribed at the time of treatment initiation and modified as needed in response to frequent monitoring. With the exception of constipation, uncomfortable or unpleasant side effects may potentially be reduced by switching to another opioid or route of administration (such side effects may also be alleviated with adjunctive medications). Although constipation is rarely a limiting side effect, other side effects may be intolerable. Because it is impossible to predict which side effects a patient may experience, it is appropriate to inquire about them on a regular basis.

Patients should be fully informed about the risk of respiratory depression with opioids, signs of respiratory depression and about steps to take in an emergency. Patients and their caregivers should be counseled to immediately call 911 or an emergency service if they observe any of these warning signs.

As of January 2014, a California physician may issue standing orders for the distribution of an opioid antagonist to a person at risk of an opioid-related overdose or to a family member, friend, or other person in a position to assist a person at risk of an opioid-related overdose. A physician may also issue a standing order for the administration of an opioid antagonist to a person at risk of an opioid-related overdose to a family member, friend, or other person in a position to assist a person experiencing or reasonably suspected of experiencing an opioid overdose.

The potential of adverse effects and the lack of data about the addictive risks posed by opioids do not mean these medications should not be used. Common clinical experience and extensive literature document that some patients benefit from the use of opioids on a short or long term basis. Existing guidelines from many sources, including physician specialty societies (American Academy of Pain Medicine, The American Pain Society), various states (Washington, Colorado, Utah), other countries (Canada) and federal agencies (Department of Defense, Veterans Administration), reflect this potential clinical utility.

Recommendations from authoritative consensus documents have been summarized in concise, user-friendly formats such as: Responsible Opiate Prescribing: A Clinician’s Guide for the Federation of State Medical Boards; the 2013 Washington State Labor and Industries Guideline for Prescribing Opioids to Treat Pain in Injured Workers; and the Agency Medical Directors’ Group 2010 Opioid Dosing Guideline for Chronic Non-Cancer Pain.

Methadone

Particular care must be taken when prescribing methadone. Although known primarily as a drug used to help patients recovering from heroin addiction, methadone can be an effective opioid treatment for some pain conditions. Methadone is a focus of current debate because it is frequently involved in unintentional overdose deaths. These deaths have escalated as methadone has increasingly been used to treat chronic pain.

Methadone must be prescribed even more cautiously than other opioids and with full knowledge of its highly variable pharmacokinetics and pharmacodynamics. Of critical importance is the fact that methadone’s analgesic half-life is much shorter than its elimination half-life. This can lead to an accumulation of the drug in the body. In
addition, methadone is metabolized by a different group of liver enzymes than most other opioids, which can lead to unexpected drug interactions.

When rotating from another opioid to methadone, extreme caution must be used when referring to equianalgesic conversion tables. Consensus recommendations suggest a 75 to 90% decrement in the equianalgesic dose from conventional conversion tables when a switch is made from another opioid to methadone.47

Because the risk of overdose is particularly acute with methadone, patients should be educated about these risks and counseled to use methadone exactly as prescribed. They should also be warned about the dangers of mixing unauthorized substances, especially alcohol and other sedatives, with their medication. This should be explicitly stated in any controlled substance agreement that the patient receives, reads and signs before the initiation of treatment (such agreements are discussed in more depth on page 14).

Although uncommon, potentially lethal cardiac arrhythmias can be induced by methadone. The cardiac health of patients who are candidates for methadone should be assessed, with particular attention paid to a history of heart disease or arrhythmias.48 An initial ECG may be advisable prior to starting methadone, particularly if a patient has a specific cardiac disease or cardiac risk factors or is taking agents that may interact with methadone. In addition, it is important that an ECG be repeated periodically, because QT interval prolongation has been demonstrated to be a function of methadone blood levels and/or in response to a variety of other medications.

Adjuvant Pain Medications

Although opioid medications are powerful pain relievers, in the treatment of neuropathic pain and some other centralized pain disorders such as fibromyalgia, they are of limited effectiveness and are not preferred.49 Other classes of medications, however, may provide relief for pain types or conditions that do not respond well to opioids. Some of these adjuvant medications exert a direct analgesic effect mediated by non-opioid receptors centrally or peripherally. Others have no direct analgesic qualities but may provide pain relief indirectly via central or peripheral affects.

Commonly-used non-opioid adjuvant analgesics include antiepileptic drugs (AEDs), tricyclic antidepressants (TCAs) and local anesthetics (LAs). AEDs, such as gabapentin and pregabalin, are used to treat neuropathic pain, especially shooting, stabbing or knife-like pain from peripheral nerve syndromes.50 TCAs and some newer types of antidepressants may be valuable in treating a variety of types of chronic and neuropathic pain, including post-herpetic neuralgia and diabetic neuropathy.51 LAs are used to manage both acute and chronic pain. Topical application provides localized analgesia for painful procedures or conditions with minimal systemic absorption or side effects.52 Topical LAs are also used to treat neuropathic pain. Epidural blocks with LAs, with or without opioids, play an important role in managing postoperative and obstetrical pain.

iv: A QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias and a risk factor for sudden death.
Given the potential risks of opioid analgesics, careful and thorough patient assessment is essential. Obtaining a complete patient history, physical examination, review of past medical records, psycho-social evaluation and assessment of potential for substance abuse are all considered to be part of a complete evaluation.

A patient’s self-report is likely the most reliable indicator of the presence and nature of pain, though there are times when self-report is not possible, for example, in some palliative care scenarios. Talking to patients and asking them about their pain (i.e., obtaining a “pain history”) is integral to pain assessment. The pain history is usually part of the overall patient history, which includes the patient’s past medical history, medications, habits (e.g., smoking, alcohol intake), family history and psychosocial history. Ideally, patients are given the opportunity to tell their stories in their own words, without being rushed. Asking open-ended questions may elicit more information than asking yes/no types of questions.

A physical examination with special attention to the musculoskeletal and neurological systems and site(s) of pain may help identify underlying causes of the pain and assure the patient that his or her complaints are being taken seriously. Patients with neuromuscular pain may require more extensive neurological and musculoskeletal assessment and/or referral to a specialist.

Because persistent pain can affect every major sphere of a person’s life, a psychosocial evaluation is important and helpful. It is important for clinicians to be alert for signs of depression or anxiety, which are common in patients with persistent pain, as well as for suicidal thoughts, since the risk of suicide is roughly double for patients with chronic pain. Referral to a mental-health professional may be advisable if a patient has active, untreated psychological issues. Clinicians should also inquire about ways that pain may be affecting a patient’s relationships, job, recreation and sexual or social activities. Addressing dysfunctions in any of these areas should be part of the pain management plan.

A variety of tools may facilitate pain assessment. Unidimensional rating scales (numeric, verbal or visual descriptors) assess a patient’s self-reported pain intensity, which may be useful in cases of acute pain of clear etiology (e.g., postoperative pain) and longitudinal assessment of pain intensity, although such scales may oversimplify other types of pain. Multidimensional tools may provide important information about the characteristics of pain and its effects on the patient’s daily life. Examples of validated multidimensional tools include the Initial Pain Assessment Tool, the Brief Pain Inventory (BPI) and the McGill Pain Questionnaire (MPQ).

Several validated screening tools have been developed for distinguishing neuropathic pain from nociceptive pain. The Neuropathic Pain Scale (NPS) allows for the evaluation of 8 common qualities of neuropathic pain (i.e., sharp, dull, hot, cold, sensitive, itchy, and deep versus surface pain). The NPS was validated for assessing multiple components of neuropathic pain and for detecting changes in neuropathic pain with opioid analgesic therapy.

The need for, and type of, diagnostic studies are determined by characteristics of the pain and the suspected underlying condition. Appropriately selected tests can lead to more accurate diagnosis and improved outcomes. Diagnostic studies are confirmatory, however — they supplement, but do not replace, a comprehensive patient history and physical examination. Diagnostic studies of potential utility include imaging studies (x-ray, CT, MRI, myelography), diagnostic nerve blocks and nerve conduction studies.

Clinicians considering treatment with an opioid medication should be alert to the risk that a patient may not use the medication as prescribed. This reality was quantified by Fleming et al., who conducted in-depth interviews with 801 patients receiving long-term opioid therapy. They found patients engaging in purposeful over-sedation (26%), increasing dose without prescription (39%), obtaining extra opioids from other doctors (8%), using for purposes other than pain (18%), drinking alcohol...
### Table 1: Characteristics of Chronic Pain Patients Versus Addicted Patients

<table>
<thead>
<tr>
<th>Chronic Pain Patient</th>
<th>Addicted Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication use is not out of control</td>
<td>Medication use is out of control</td>
</tr>
<tr>
<td>Medication use improves quality of life</td>
<td>Medication use impairs quality of life</td>
</tr>
<tr>
<td>Wants to decrease medication if adverse effects develop</td>
<td>Medication use continues or increases despite adverse effects</td>
</tr>
<tr>
<td>Is concerned about the physical problem being treated with the drug</td>
<td>Unaware of or in denial about any problems that develop as a result of drug treatment</td>
</tr>
<tr>
<td>Follows the practitioner-patient agreement for use of the opioid</td>
<td>Does not follow opioid agreement</td>
</tr>
<tr>
<td>May have left over medication</td>
<td>Does not have leftover medication</td>
</tr>
<tr>
<td>Loses prescriptions</td>
<td>Always has a story about why more drug is needed</td>
</tr>
</tbody>
</table>

Adapted from: Webster LR, Dove B. Avoiding Opioid Abuse While Managing Pain. Sunrise River Press, North Branch, MN. 2007.

To relieve pain (20%) and hoarding pain medications (12%). A recent article in Medscape compiles research that further reinforces the fact that patient noncompliance with respect to all medical management is not unusual.

No consensus exists on exactly who to suspect and when to be proactive in investigating risk factors for abuse of opioid analgesics. This means prescribers should be vigilant with all patients — an analog of the “universal precautions” approach used in other realms of medicine. Any patient in pain could have a drug misuse or abuse problem, in the same way that any patient requiring a blood draw could have HIV or other blood borne communicable disease.

Some patient characteristics, however, may suggest drug abuse, misuse or other aberrant behaviors (Table 1). The factor that appears to be most strongly predictive in this regard is a personal or family history of alcohol or drug abuse. Some studies have also shown that younger age, male gender and the presence of psychiatric conditions are also associated with aberrant drug-related behaviors.

A more formal assessment of a patient’s risk of substance misuse can be made with the following brief tools: Current Opioid Misuse Measure; Diagnosis, Intractability, Risk, Efficacy; Opioid Risk Tool; and the Screener and Opioid Assessment for Patients with Pain (Version 1 and Revised).

An important part of initial and ongoing assessment of a patient being considered for opioid therapy is using a Prescription Drug Monitoring Program (PDMP), if one is available. Most PDMPs offer point-of-care access via a secure website to records of controlled substances from other prescribers and dispensing pharmacies. From these, clinicians can quickly glean patterns of prescription drug use that may help confirm or refute suspicions of aberrant behaviors. Information from a PDMP may also be clinically relevant because it can reveal that a patient is being prescribed medications whose combinations may be contraindicated. Unfortunately, despite their potential to improve care delivery, PDMP programs across the country tend to be underutilized, underfunded and poorly connected with other state PDMPs or health care information systems.

California’s PDMP is called the Controlled Substance Utilization Review and Evaluation System (CURES). Under the oversight of the Attorney General, the California Department of Justice (DOJ) manages CURES. While funding cuts at the DOJ have created significant system and staffing limitations, legislation was passed in 2013 that included funding to modernize CURES by 2016 and increased funding for ongoing operational costs. CMA has undertaken a major effort to educate physicians and others about the public health importance of CURES and continues to facilitate physician registration and use of the system.
Finally, clinicians should assess a patient’s need to drive or use machinery. Patients initially prescribed opioid medications, or those who have their dose increased, should be cautioned about operating dangerous machinery, including motor vehicles. No consensus exists about how long patients on opioid medications should abstain from driving, although some patients on long-term, stable opioid therapy may be able to safely operate motor vehicles. Clinicians should be aware that certain professions (e.g., school bus drivers, truck drivers, pilots) may be restricted in their use of opioid medications. State medical boards and public health agencies may be able to provide up-to-date information about professional restrictions related to the use of opioid medications.
A written treatment plan should be considered in the management of chronic non-cancer pain with opioid analgesics. Such plans can improve patient/provider communication, clarify patient expectations and responsibilities, establish a transparent and enduring record of a clinician’s treatment rationale, and set clear guidelines for treatment monitoring. Such plans can also be an effective part of the informed consent process.

Treatment plans—and therapy in general—should be framed in terms of quality of life and functional goals. Although the relief of pain is important, such relief cannot be objectively confirmed and, hence, it should not be the sole indicator of treatment success. By setting functional treatment goals, clinicians create an objective foundation on which to base prescribing decisions. This is particularly important when prescribing opioid pain medications, because functioning usually decreases with opioid addiction, while it typically improves with effective pain relief.

Treatment goals should be developed jointly between patient and clinician. A patient’s pain score is just one of many variables to be considered in framing goals, which should be realistic, meaningful to the patient and verifiable. Since persistent pain often results in slow physical and psychological deconditioning, it may take months or years to restore patients to their previous level of functional activity.

When setting functional goals, aiming slightly too low rather than slightly too high may prove to be most effective. Raising goals after a patient has succeeded in achieving them is more motivational and encouraging than lowering goals after a patient has “failed.” Table 2 illustrates some simple functional goals and ways they might be verified.

Patients provide the evidence used to measure progress, and this should be made explicit in the treatment plan. If a patient cannot document progress, or, at least, maintenance of their functional status, treatment may need to be reassessed. Failure to reach a functional goal may result from a range of problems, including inadequate pain relief, non-adherence to a regimen, function-limiting side effects, untreated co-morbid disorders, or misuse or addiction.

### Table 2: Examples of Evidence Used to Assess Functional Goals

<table>
<thead>
<tr>
<th>Functional Goal</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begin physical therapy</td>
<td>Letter from physical therapist</td>
</tr>
<tr>
<td>Sleeping in bed as opposed to lounge chair</td>
<td>Report by family member or friend (either in-person or in writing)*</td>
</tr>
<tr>
<td>Participation in pain support group</td>
<td>Letter from group leader</td>
</tr>
<tr>
<td>Increased activities of daily living</td>
<td>Report by family member or friend</td>
</tr>
<tr>
<td>Walk around the block</td>
<td>Pedometer recordings or written log of activity</td>
</tr>
<tr>
<td>Increased social activities</td>
<td>Report by family member or friend</td>
</tr>
<tr>
<td>Resumed sexual relations</td>
<td>Report by partner</td>
</tr>
<tr>
<td>Returned to work</td>
<td>Pay stubs from employer or letter confirming the patient is off of disability leave</td>
</tr>
<tr>
<td>Daily exercise</td>
<td>Gym attendance records or report from family member or friend</td>
</tr>
</tbody>
</table>

* Involving other persons requires explicit permission from the patient and this permission should be documented, preferably in writing.
A critical component of any treatment plan is informed consent. This is particularly important in the context of long-term opioid therapy because of the potential risks involved. Key questions related to informed consent include:

1. Does the patient understand his or her treatment options? This may require the provision of agreements in multiple languages. Agreements written at the sixth- to seventh-grade level or even lower helps ensure patient comprehension.

2. Has the patient been informed of the potential benefits and risks associated with each treatment option? With opioids, these include anticipated side effects, the realities of tolerance and physical dependence, and the potential need to taper the medication slowly to avoid withdrawal if treatment is discontinued. Patient education includes the possibility that tapering opioids may be difficult, that opioids may be either ineffective or have intolerable adverse effects, and that physical or psychological dependence may lead to misuse or addiction. Other aspects of opioid risks and benefits might need to be addressed with the patient.

3. Is the patient free to choose among treatment options and free from coercion by the prescriber, the patient’s family or others?

4. Does the patient have the capacity to communicate his or her preferences verbally or in other ways?

Because stopping opioid therapy is often more difficult than starting it, this is an important issue to discuss in a treatment plan. Termination may be required for many reasons:

- Healing or resolution of the painful condition;
- Intolerable side effects (provided all options for mitigation have been explored);
- Failure to achieve anticipated pain relief or functional improvement (although ensure that this failure is not the result of inadequate treatment);
- Evidence of non-medical or inappropriate use;
- Failure to comply with monitoring, such as urine drug screening; and/or
- Failure to comply with a recommended treatment plan.

Patient education about the safe use, storage, and disposal of opioid medications can be integrated into treatment plans or patient/provider agreements and is an important component of opioid prescribing. Safe use means that patients carefully follow all medication instructions, that they not share medications or take them with alcohol or other sedatives, and that they take ER/LA opioid medications in the form and by the route prescribed. Patients need to be reminded that even children or close relatives can be tempted to use pain medications they have not been prescribed. Opioids are often obtained by teens, for example, from un-secured medicine cabinets of family and friends. A 2011 survey by the federal Substance Abuse and Mental Health Services Administration (SAMHSA) found that 70.8% of those who reported using pain relievers non-medically obtained the drugs from a friend or relative. Patients should thus be strongly encouraged to store opioid pain medications as securely as possible.

Patients should be aware of guidance for disposal of unused medications. If a controlled substances take-back option is not immediately available, the FDA currently recommends that some drugs, including unused opioid pain medications, be flushed down a toilet. Another option is to mix the medications with an undesirable substance, such as used coffee grounds or kitty litter, and put the mixture into the trash in an unrecognizable container, as recommended by the Medical Board of California. Patients should also be encouraged to use any drug take-back programs available in the local community. At the time of writing, the U.S. Drug Enforcement Agency is expected to release new rules on the disposal of controlled substances in March 2014, which may impact the options available to patients and physicians. Their pharmacist may be able to help identify opportunities for proper disposal.
Before initiating chronic opioid therapy the following four points should be considered:

1. Other potentially effective treatments have been considered or tried;
2. A complete evaluation has been performed and documented;
3. The patient's level of opioid tolerance has been determined via self report and/or the medical record; and
4. Informed consent and agreement to treat have been obtained.

Both the clinician and the patient should view a new opioid prescription as a short-term trial of therapy that will generate data to guide decisions about continuation or dosing. Such a trial might be as brief as a few days or as long as several months. Realistic expectations of outcome need to be discussed prior to initiation of treatment, during the trial and periodically during long term treatment.

Continuation of opioid therapy after an appropriate trial should be based on outcomes such as: making progress toward functional goals; presence and nature of side effects; pain status; and a lack of evidence of medication misuse, abuse, or diversion.

Patients with no, or modest, previous opioid exposure should be started at the lowest appropriate initial dosage of a short-acting opioid and titrated upward to decrease the risk of adverse effects. The selection of a starting dose and manner of titration are clinical decisions made on a case-by-case basis because of the many variables involved. Some patients, such as frail older persons or those with comorbidities, may require an even more cautious therapy initiation. Short-acting opioids are usually safer for initial therapy since they have a shorter half-life and may be associated with a lower risk of overdose from drug accumulation. The general approach is to “start low and go slow.”

Oral administration, especially for the treatment of chronic pain, is generally preferred because it is convenient, flexible and associated with stable drug levels. Intravenous administration provides rapid pain relief and, along with rectal, sublingual and subcutaneous administration, may be useful in patients who cannot take medications by mouth. Continuous infusions produce consistent drug blood levels but are expensive, require frequent professional monitoring and may limit patient mobility.

Transdermal administration is a convenient alternate means of continuous drug delivery that does not involve needles or pumps. Patient-controlled analgesia (PCA) allows patients to self-administer pain medications and may be useful if analgesia is required for 12 hours or more and mobility is not required. Intrathecal delivery of opioids is a viable option for patients with chronic pain who have not responded to other treatment options, or for whom the required doses result in unacceptable side-effects. Patients with intrathecal delivery systems typically require ongoing ambulatory monitoring and supportive care.

Patients on a steady dose of an opioid medication may experience pain that breaks through the analgesic effects of the steady-state drug. Paper or electronic pain diaries may help patients track these breakthrough episodes and spot correlations between the episodes and variables in their lives. A short-acting opioid is typically prescribed for treatment by patients with breakthrough pain.

Since opioids are known in some circumstances to worsen pain (hyperalgesia), instances of ongoing pain may suggest opioid insensitivity (or an inadequate dose). Careful assessment must be undertaken. If hyperalgesia is suspected, a dose reduction, opioid rotation or tapering to cessation could be considered.

Family physicians and other primary care practitioners should know their own limits when treating patients with complex, inter-related physical and psycho-social dysfunctions or patients with known or suspected substance use disorder or addiction. Primary care physicians should take advantage of additional resources when needed, such as referrals to appropriate pain specialists, and they should not start prescribing opioids for a patient if they are not willing or able to stop the treatment if needed.
If a trial of an opioid medication is deemed successful and opioid therapy is continued, periodic review and monitoring should be performed for the duration of treatment. The tests performed, questions asked and evaluations made should be tailored to the patient and guided by the physician’s clinical judgment with an awareness of the appropriate risk/benefit ratio always clearly in mind. Progress is evaluated against the agreed-upon functional treatment goals based on evidence the patient provides, as well as by reported levels of pain relief, quality of life and the presence of adverse effects. The nature, intensity and frequency of monitoring is governed, in part, by the patient’s risk for abuse, diversion or addiction. The tools and techniques used during an initial assessment of a patient’s risk can be used to re-assess or monitor this risk.

Relatively infrequent monitoring may be appropriate for low-risk patients on a stable dose of opioids. More frequent or intense monitoring may be warranted for patients during the initiation of therapy or if the dose, formulation or opioid medication is changed. Those with a prior history of an addictive disorder or past substance abuse, older adults, patients with an unstable or dysfunctional social environment, or patients with comorbid psychiatric or medical conditions may also need more frequent monitoring.

Drug testing of a patient on chronic opioid therapy may be a part of regular monitoring, although this is left to a physician’s clinical assessment. In family practice settings, unobserved urine collection is usually an acceptable procedure for drug testing, although urine specimens can be adulterated in many ways and prescribers should be alert to this possibility. If possible, urine temperature and pH should be measured immediately after collection. Clinicians should also familiarize themselves with the metabolites associated with each opioid that may be detected in urine, since the appearance of a metabolite can be misleading. A patient prescribed codeine, for example, may test positive for morphine because morphine is a codeine metabolite. Similar misunderstandings may occur for patients prescribed hydrocodone or oxycodone. These same issues must be thoroughly understood by coroners, of course, because a lack of such understanding could lead to erroneous coroners reports.

“Opioid rotation,” the switching from one opioid to another in order to better balance analgesia and side effects, may be used if pain relief is inadequate, if side effects are bothersome or unacceptable, or if an alternative route of administration is suggested. Opioid rotation must be done with great care, particularly when converting from an immediate-release formulation to an ER/LA product. Equianalgesic charts, conversion tables and calculators must be used cautiously with titration and appropriate monitoring. Patients may exhibit incomplete cross-tolerance to different types of opioids because of differences in the receptors or receptor sub-types to which different opioids bind, hence clinicians may want to use initially lower-than-normal doses of the switched-to opioid.

Although there is no widely-agreed-upon dose of opioids that constitute an absolute “red flag” for prescriber concern that opioid therapy may not be working, doses above 100 mg daily of morphine or morphine equivalence have been suggested as worthy of clinician concern because the risk of overdose or adverse effects often rises with doses above this level. This suggestion is controversial, however. The FDA, in responding to a petition by Physicians for Responsible Opioid Prescribing, in 2012, rejected a request for a 100 mg morphine equivalent dose (MED) daily limit on opioids, citing weaknesses in the various studies offered in support of the proposal.

Referral to an appropriate specialist should be considered when higher doses are considered. There is no absolutely safe ceiling dose of opioids, however, and
caution and monitoring are appropriate for applications of these medications. Opioid therapy must be re-evaluated whenever the risk of therapy is deemed to outweigh the benefits being provided.

If a patient is suspected of abuse or diversion, a careful re-assessment of the treatment plan is called for.\textsuperscript{vi}
Non-adherence to a regimen, by itself, is not proof of abuse or diversion. Non-adherence may result from inadequate pain relief, a misunderstanding about the prescription, misunderstandings due to language differences, patient fears of addiction, attempts to "stretch" a medication to save money or other valid reasons. A face-to-face, non-accusatory conversation may clear up a situation or, alternatively, may support suspicions of misuse. If abuse is confirmed, consultation with an addiction medicine specialist or psychiatrist may be desirable, and/or referral to a substance use disorder treatment program.\textsuperscript{vii}

Treatment termination may be necessary for many reasons including: the healing of, or recovery from, an injury, medical procedure or condition; intolerable side effects; lack of response; or discovery of misuse of medications. Regardless of the reason, the termination process should minimize unpleasant or dangerous withdrawal symptoms by tapering the opioid medication, or by carefully changing to a new formulation. Approaches to weaning range from a slow 10% reduction per week to a more aggressive 25 to 50% reduction every few days.\textsuperscript{v} In general, a slower taper will produce fewer unpleasant symptoms of withdrawal.

If complete termination of care is necessary (as opposed to termination of a specific treatment modality), clinicians should treat the patient until the patient has had a reasonable time to find an alternative source of care, and ensure that the patient has adequate medications, if appropriate, to avoid unnecessary risk from withdrawal symptoms. Practitioners can be held accountable for patient abandonment if medical care is discontinued without justification or adequate provision for subsequent care.\textsuperscript{vii} If a patient is known to be abusing a medication, initiating a detoxification protocol may be appropriate. Consultation with an attorney and/or one’s malpractice insurance carrier may be prudent in such cases.\textsuperscript{viii}

Physicians may want to also consult health plan contracts to ensure compliance.

\textsuperscript{vi} For additional information on this topic, see the FDA-approved Collaborative for REMS Education (CO*RE) website at: www.core-rem.org.

\textsuperscript{vii} One source for finding such treatment programs in any geographic region is the SAMSHA facility locator, available at: http://findtreatment.samhsa.gov.

\textsuperscript{viii} CMA provides additional California-specific information on this topic in CMA On-Call #3503: Termination of the Physician-Patient Relationship, January 2013.
**Emergency Departments**

Pain is a frequent complaint of emergency room (ER) patients, and ER physicians are among the higher prescribers of opioids to patients ages 10-40. ER physicians, however, face considerable challenges in determining a patient’s appropriateness for opioid therapy. A medical history is often lacking and the physician seldom knows the patient personally. Time constraints, as well, can preclude the kinds of careful assessment and evaluation recommended for responsible opioid prescribing. Because of this, current guidelines from the American College of Emergency Physicians include the following recommendations:2

- ER/LA opioid medications should not be prescribed for acute pain conditions;
- PDMPs should be used where available to help identify patients at high risk for opioid abuse or diversion;
- Opioids should be reserved for more severe pain or pain that doesn’t respond to other analgesics; and
- If opioids are indicated, the prescription should be for the lowest effective dose and for a limited duration (e.g. < 1 week);

**Cancer Pain**

Pain is one of the most common symptoms of cancer, as well as being one of the most-feared cancer symptoms. Pain is experienced by about 30% of patients newly diagnosed with cancer, 30% - 50% of patients undergoing treatment and 70% - 90% of patients with advanced disease. Unrelieved pain adversely impacts motivation, mood, interactions with family and friends, and overall quality of life. Survival itself may be positively associated with adequate pain control. Opioid pain medications are the mainstay of cancer pain management and a trial of opioid therapy should be administered to all cancer patients with moderate or severe pain, regardless of the known or suspected pain mechanism.

ER/LA opioid formulations may lessen the inconvenience associated with the use of short-acting opioids.

Patient-controlled analgesia with subcutaneous administration using an ambulatory infusion device may provide optimal patient control and effective analgesia. The full range of adjuvant medications covered earlier should be considered for patients with cancer pain, with the caveat that such patients are often on already complicated pharmacological regimens, which raises the risk of adverse reactions associated with polypharmacy. If cancer pain occurs in the context of a patient nearing the end of life, other treatment and care considerations may be appropriate. In these cases, treating the patient in conjunction with a specialist in palliative medicine may be advisable.

**Pain at the End of Life**

Pain management at the end of life seeks to improve or maintain a patient’s overall quality of life. This focus is important because sometimes a patient may have priorities that compete with, or supersede, the relief of pain. For some patients, mental alertness sufficient to allow lucid interactions with loved ones may be more important than physical comfort. Optimal pain management, in such cases, may mean lower doses of an analgesic and the experience, by the patient, of higher levels of pain.

Since dying patients may be unconscious or only partially conscious, assessing their level of pain can be difficult. Nonverbal signs or cues must sometimes be used to determine if the patient is experiencing pain and to what degree an analgesic approach is effective. In general, even ambiguous signs of discomfort should usually be treated, although caution must be exercised in interpreting such signs. Reports by family members or other people close to a patient should not be overlooked. In the Study to Understand Prognosis and Preference for Outcomes and Risks of Treatment (SUPPORT), surrogates for patients who could not communicate verbally had a 73.5% accuracy rate in estimating presence or absence of the patient’s pain.

Opioids are critical to providing effective analgesia at the end of life, and they are available in such a range...
of strengths, routes of administration and duration of action that an effective pain regimen can be tailored to nearly each patient.\textsuperscript{84} No specific opioid is superior to another as first-line therapy. Rectal and transdermal routes of administration can be valuable at the end of life when the oral route is precluded because of reduced or absent consciousness, difficulty swallowing or to reduce the chances of nausea and vomiting.\textsuperscript{85} When selecting an opioid, clinicians should also consider cost, since expensive agents can place undue burden on patients and families.

Fear of inducing severe or even fatal respiratory depression may lead to clinician under-prescribing and reluctance by patients to take an opioid medication.\textsuperscript{28} Despite this fear, studies have revealed no correlation between opioid dose, timing of opioid administration and time of death in patients using opioids in the context of terminal illness.\textsuperscript{86} A consult with a specialist in palliative medicine in these situations may be advisable.

**Older Adults**

The prevalence of pain among older adults has been estimated between 25% and 50%.\textsuperscript{87} The prevalence of pain in nursing homes is even higher. Unfortunately, managing pain in older adults is challenging due to: underreporting of symptoms; presence of multiple medical conditions; polypharmacy; declines in liver and kidney function; problems with communication, mobility and safety; and cognitive and functional decline in general.\textsuperscript{88}

Acetaminophen is considered the drug of choice for mild-to-moderate pain in older adults because it lacks the gastrointestinal, bleeding, renal toxicities, and cognitive side-effects that have been observed with NSAIDs in older adults (although acetaminophen may pose a risk of liver damage). Opioids must be used with particular caution and clinicians should “start low, go slow” with initial doses and subsequent titration. Clinicians should consult the American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults for further information on the many medications that may not be recommended.\textsuperscript{31}

The various challenges of pain management in older adults, only sketched here, suggest that early referral and/or consultation with geriatric specialists or pain specialists may be advisable.

**Pediatric Patients**

Children of all ages deserve compassionate and effective pain treatment. In fact, due to their more robust inflammatory response and immature central inhibitory influences, infants and young children actually may experience greater pain sensations and pain-related distress than adults.\textsuperscript{89} Effective pain management in the pediatric population is critical since children and adolescents experience a variety of acute and chronic pain conditions associated with common childhood illnesses and injuries, as well as some painful chronic diseases that typically emerge in childhood such as sickle cell anemia and cystic fibrosis.

The same basic principles of appropriate pain management for adults apply to children and teens, which means that opioids have a place in the treatment armamentarium. Developmental differences, however, can make opioid dosing challenging, especially in the first several months of life. In the first week of a newborn’s life, for example, the elimination half-life of morphine is more than twice as long as that in older children and adults, as a result of delayed clearance.\textsuperscript{90} For older children, dosing must be adjusted for body weight.

Although a thorough discussion of this topic is not possible in this document, the following are summary recommendations for pain management in children and teens from the American Pain Society and the American Academy of Pediatrics:\textsuperscript{91}

- Provide a calm environment for procedures that reduce distress-producing stimulation;
- Use age-appropriate pain assessment tools and techniques;
- Anticipate predictable painful experiences, intervene and monitor accordingly;
- Use a multimodal approach (pharmacologic, cognitive, behavioral and physical) to pain management and use a multidisciplinary approach when possible;
- Involve families and tailor interventions to the individual child; and
• Advocate for the effective use of pain medication for children to ensure compassionate and competent management of their pain.

**Pregnant Women**

Current American Pain Society-American Academy of Pain Medicine (APS-AAPM) guidelines suggest that clinicians should encourage minimal or no use of opioids during pregnancy unless the potential benefits clearly outweigh risks. Some data suggests an association between the use of long-term opioid therapy during pregnancy and adverse outcomes in newborns, including low birth weight and premature birth, though co-related maternal factors may play a role in these associations and causality is not certain. If a mother is receiving long-term opioid therapy at or near the time of delivery, a professional experienced in the management of neonatal withdrawal should be sought. Helpful guidance about the appropriate use of opioids during pregnancy can be found in the report *Opioid Abuse, Dependence, and Addiction in Pregnancy* by a joint committee of the American Congress of Obstetricians and Gynecologists and the American Society of Addiction Medicine. The guidelines include the following recommendations:

- Early identification of opioid-dependent pregnant women improves maternal and infant outcomes.
- Pregnancy in the opioid-dependent woman should be co-managed by the obstetrician–gynecologist and addiction medicine specialist.
- When opioid maintenance treatment is available, medically supervised withdrawal should be discouraged during pregnancy.
- Hospitalized pregnant women who initiate opioid-assisted therapy need to make a next-day appointment with a treatment program before discharge.
- Infants born to women who used opioids during pregnancy should be closely monitored for neonatal abstinence syndrome and other effects of opioid use by a pediatric health care provider.

**Patients Covered by Workers’ Compensation**

This population of patients presents its own unique circumstances. Injured workers are generally sent to an occupational medicine facility for treatment. Ideally, the injured worker recovers and returns to work in full capacity. If recovery or healing does not occur as expected, early triage and appropriate, timely treatment is essential to restore function and facilitate a return to work.

The use of opioids in this population of patients can be problematic. Some evidence suggests that early treatment with opioids may actually delay recovery and a return to work. Conflicts of motivation may also exist in patients on workers’ compensation, such as when a person may not want to return to an unsatisfying, difficult or hazardous job. Clinicians are advised to apply the same careful methods of assessment, creation of treatment plans and monitoring used for other pain patients but with the added consideration of the psycho-social dynamics inherent in the workers’ compensation system. Injured workers should be afforded the full range of treatment options that are appropriate for the given condition causing the disability and impairment.

**Patients with History of Substance Use Disorder**

Use of opioids for patients with a history of substance use disorder is challenging because such patients are more vulnerable to drug misuse, abuse and addiction. In patients who are actively using illicit drugs, the potential benefits of opioid therapy are likely to be outweighed by potential risks, and such therapy should not be prescribed outside of highly controlled settings (such as an opioid treatment program with directly observed therapy). In other patients, the potential benefits of opioid therapy may outweigh potential risks. Although evidence is lacking on best methods for managing such patients, potential risks may be minimized by more frequent and intense monitoring compared with lower risk patients, authorization of limited prescription quantities and consultation or co-management with a specialist in addiction medicine. Clinicians should use PDMPs, if available, to help identify patients who obtain drugs from multiple sources.
If either the patient’s medical history, self-report or scores on screening assessment tools such as the Opioid Risk Tool suggest an above-average risk of substance abuse, clinicians should consider the following steps in proceeding with a pain management strategy5, 64:

- Exhaust all non-opioid pain management methodologies prior to considering opioid therapy;
- Consult with a specialist in addiction medicine;
- Create a written treatment plan and patient agreement and review carefully with the patient, obtaining their signed informed consent;
- Closely monitor and assess pain, functioning and aberrant behaviors;
- Regularly check with a PDMP for compliance with prescribed amounts of opioids (using cross-state PDMP systems whenever they are available);
- While the patient is on chronic opioid therapy, implement urine drug testing, if possible;
- If misuse or abuse of opioid analgesics is suspected or confirmed, initiate a non-confrontational in-person meeting, use a non-judgmental approach to asking questions, present options for referral, opioid taper/discontinuation or switching to non-opioid treatments, and avoid “abandoning” the patient or abruptly stopping opioid prescriptions.
Conclusions

In recent years, attention has focused on the demonstrated risks that opioid analgesics can pose to both patients and society, while evidence for the benefits of these medications for managing chronic pain has remained weak. This paper outlines an up-to-date review of pain management with opioids, focusing on patients with chronic pain. It is intended neither as an exhaustive review nor a standard of care. Rather, it summarizes established methods for appropriately prescribing opioid analgesics.

Opioids are not a panacea. They seldom, by themselves, adequately address the usually complex physical and psycho/social dimensions of patients with chronic pain. In addition, the wide range of potential adverse effects associated with opioid use can expose a patient to serious morbidity and mortality. Opioids remain, however, essential clinical tools and, in well-selected and well-monitored cases, are uniquely capable of relieving pain and suffering, restoring and preserving quality of life, and facilitating a return to full functioning.

Appropriate prescribing of opioids can be challenging, but it is not inherently different from the challenges physicians face when using any other treatment option that carries significant risks of harm. It is both feasible and necessary for clinicians to treat pain effectively while minimizing risk.
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92 Opioid Abuse, Dependence, and Addiction in Pregnancy (Joint Committee Opinion #624 with the American Society of Addiction Medicine)