A MULTIDISCIPLINARY CONTINUING EDUCATION PROGRAM

USE OF OPIOIDS IN CHRONIC NONCANCER PAIN

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PURDUE

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The content of this activity was planned to be balanced, objective, and scientifically rigorous. Occasionally, authors may express opinions that represent their own viewpoints. Conclusions drawn by participants should be derived from objective analysis of scientific data.

TARGET AUDIENCE

This accredited program is oriented to physicians, nurses, pharmacists, case managers, and other allied health personnel who deal with opioid use in chronic noncancer pain.

Program Release Date: April 1, 2000
Program Expiration Date: April 1, 2002

Program Time Requirements: The estimated time to complete this program is 120 minutes.

GOAL

To provide evidence-based clinical and scientific information upon which health professionals can base pharmaceutical care using opioid analgesics.

OBJECTIVES

After completing this program, participants should be able to:

1. Define pain and differentiate among acute, chronic nonmalignant, and chronic malignant pain by physiological, psychological, neurological, and therapeutic parameters.
2. List the major classes of opioid receptors that impact on analgesic effects and differentiate the clinical effects of stimulating each.
3. Explain why long-acting opioids are usually preferred to short-acting opioids in chronic pain management.
4. Describe and contrast immediate-release and controlled-release opioids in patient care.
5. Define pseudo-addiction and pseudo-tolerance and describe how they can be differentiated from inappropriate drug seeking behavior.
6. Describe and refute common misconceptions about opioid addiction, dependence, tolerance, respiratory depression, and cognitive impairment.

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USE OF OPIOIDS IN CHRONIC NONCANCER PAIN

INTRODUCTION

The use of opioids in the management of chronic, nonmalignant pain (CNMP) remains the most debated controversy in pharmacotherapy of pain today.[1] Powerful arguments have been made both for and against the use of these drugs for this purpose. Fordyce, recognized by many as the father of behavioral medicine in pain management, indicated in 1976 that behavioral elements should be given priority over nociceptive elements in the management of CNMP.[2] He argues that continued use of powerful analgesics perpetuates pain behavior and that effective cognitive-behavioral approaches to CNMP should emphasize reduction in medication use. Indeed, in this decade, an editorial stated that "there is no place for opiates in the treatment of chronic benign pain."[3]

In 1992, the American Pain Society surveyed physician members on this issue.[4] The majority of respondents had little concern about tolerance, dependence, and addiction with the use of these drugs while maintaining that opioids are probably underutilized in CNMP.[4]

Opioids and Chronic Pain

Reports of health professionals losing their licenses for "inappropriate" use of opioids are often cited as reasons for excessive conservatism in opioid utilization.[5] While clearly there are cases of overly aggressive regulation of controlled substance prescribing and use, the majority of punitive actions taken in such cases can be traced to lack of adequate documentation in patients' records. It is becoming clear that opioids do have a place in the management of CNMP in many patients. It is equally evident that these drugs should be used selectively and are not helpful in all CNMP patients.

The literature and clinical experience provide some guidance in determining which CNMP patients are reasonable candidates for opioids, how these drugs might best be dosed, and warning signs for patients who may be using the medications inappropriately. In 1997, the American Academy of Pain Medicine and the American Pain Society published a joint consensus statement entitled, "The Use of Opioids for the Treatment of Chronic Pain."[6] A year later, the Federation of State Medical Boards of the United States published "Model Guidelines for the Use of Controlled Substances in the Treatment of Pain."[7] These two authoritative publications clearly document that opioids have a place in the management of many patients' chronic nonmalignant pain.

DIFFERENTIATING PAIN

Pain is not a single entity. Health professional education and training commonly teach the acute pain model. The implication is that chronic pain is similar to acute pain, but simply lasts longer. That profoundly false assumption leads to mismanagement of chronic pain and can greatly impair communication between clinicians and chronic pain patients. The 1986 NIH Consensus Development Conference report entitled "The Integrated Approach to the Management of Pain" wisely suggested differentiating among acute pain, chronic pain associated with malignant disease, and chronic pain not associated with malignant disease.[8] These three categories of pain differ physiologically, pathologically, neurologically, psychologically, and therapeutically as described in Table 1.[9]

The careful review and analysis of the pain literature that became the basis for the federal clinical practice guidelines on the management of acute pain[10] and cancer pain[11] clearly document that opioids are greatly underused in the management of both of these types of pain. These clinical practice guidelines are based upon meta-analyses and best-evidence synthesis. They reflect the science on the topics, not simply the opinions of expert committees.

Acute pain includes post-operative, procedural, and trauma pain. Cancer pain is actually an incomplete name for the second federal clinical practice guidelines. The principles

TABLE 1. CATEGORIES OF PAIN*

	Acute Pain	Chronic Pain of Nonmalignant Origin	Chronic Pain of Malignant Origin
DURATION	hours to days	months to years	unpredictable
ASSOCIATED PATHOLOGY	present	often none	usually present
PROGNOSIS	predictable	unpredictable	increasing pain with possibility of disfigurement and fear of dying
ASSOCIATED PROBLEMS	uncommon	depression, anxiety, secondary pain issues	many, especially fear of loss of control
NERVE CONDUCTION	rapid	slow	slow
AUTONOMIC NERVOUS SYSTEM INVOLVEMENT	present	generally absent	present or absent
BIOLOGICAL VALUE	high	low or absent	low
SOCIAL EFFECTS	minimal	profound	variable, usually marked
TREATMENT	primarily analgesic drug	multimodal; primarily behavioral and physical therapy; drugs may be primarily adjunctive	multimodal; analgesics usually play a major role

* Adapted from Reference 9

that are clearly described and documented apply to pain due to cancer. AIDS, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), sickle cell disease, and end-stage organ system failure. Most chronic, unremitting, progressive diseases and disorders that produce severe chronic pain fit into this model.

Risks of Undertreating Pain

Many clinicians hesitate to use opioids in the management of even severe pain due to inadequate assessment and management skills, and negative attitudes about drug use for pain relief.[12] Adverse physiological, psychological, and immunological effects of pain are well documented[9,13] and are listed in Table 2. These effects of pain can be more deleterious than any potential negative outcomes of the drugs used to manage them. Good clinical care should be based upon optimal risk/benefit considerations. Such considerations should lead thoughtful clinicians to recognize that more aggressive use of opioids often is in the interest of better patient outcomes.

OPIOID MECHANISM OF ACTION

Opioid receptors are found in the central nervous system (CNS) and gastrointestinal (GI) tract. Opioid receptors can also be found to a lesser extent in peripheral tissues. Opioid drugs exert their analgesic effects mainly by activating these receptors in the CNS. Interaction between exogenous opioids, e.g., morphine and opioid receptors, mimics the interaction seen when endogenous opioid peptides, i.e., dynorphins, endorphins, or enkephalins, bind with these same receptors.[14]

The three generally recognized classes of opioid receptors are the mu, delta, and kappa receptors. Sigma and epsilon receptors are not currently considered to be opioid receptors since activation does not necessarily result in analgesia and these receptors are not opioid specific.[14]

Opioids are classified as full agonists, partial agonists, or mixed agonist-antagonists. Full agonists are also referred to as pure mu agonists. Partial agonists occupy only part of a mu opioid receptor producing a lesser degree of analgesia than a full agonist. Mixed agonist-antagonists are agonists at kappa receptors and either antagonistic or neutral at mu receptors. Antagonists displace agonists from receptors and prevent opioids from occupying antagonized receptors. Any agonist or antagonist with a higher affinity for a receptor than one already at the receptor may displace the drug with a lower affinity. If the agent with higher affinity provides less activity, withdrawal may occur.[9]

DEFINING CHRONIC NONMALIGNANT PAIN

One of the major confounds in appropriate management of CNMP is that it is not a homogeneous disorder or set of syndromes. Most CNMP shares several characteristics, but different pain clinicians and clinics can see very different case mixes. Common types of CNMP include myofascial pain syndromes, neuropathic pain syndromes, complex regional pain syndromes (formerly called sympathetically maintained pain or SMP), radiculopathies, failed back syndrome, headaches, fibromyalgia, rheumatoid arthritis, and osteoarthritis. When addressing CNMP, it is essential to define the types and etiologies of pain being considered. Whenever safe and effective specific treatments for the underlying cause of the pain might obviate the need for chronic opioids, those specific therapies should be considered first.

Chronic pain patients' subjective complaints often outweigh their objective findings. This does not mean that the pain is not real. It may indicate a degree of somatization and exaggeration of the pain complaints. That, in itself, is not a contraindication to opioids. Patients with more persistent and dramatic pain complaints are not necessarily better candidates for opioids than patients who describe their pain

less emphatically.

Management of CNMP often includes multiple medications, often from multiple prescribers. Opioids and other CNS depressants are prominent on these patients' drug lists. While this may indicate drug-seeking behavior, in many cases it more commonly reflects patients feeling a need to "take something for their pain." Many patients report that they prefer not to take medications, but lack alternative pain management strategies.

Complications from other therapies often confound the management of CNMP. Multiple surgeries, interacting drugs, and excessive use of pharmacologically active nutritional and herbal supplements are common. Careful medical and drug histories often reveal ineffective concurrent or prior therapies. Experience often makes CNMP patients mistrusting of new clinicians. Psychiatric issues, most notably anxiety, depression, and somatization are common among CNMP patients. Clinicians must remain aware of the risks of polypharmacy from attempts to institute drug therapy for too many symptoms at the same time. Secondary gain issues and adverse environmental factors also are prominent.

Minimal physical activity and postural changes characterize the lifestyle of many CNMP patients. While there is a risk of opioids demotivating patients and making them less active, the risk of chronic pain causing those undesired effects is usually far greater. Attempts to treat CNMP patients with only medical and pharmacological modalities often lead to failure. Integration of behavioral and physical therapy into the patient's care plan is often more effective than using stronger drugs alone. It usually is essential to integrate appropriate physical activity as well as behavior changes to achieve optimal outcomes. A common cause of treatment failures is "over-medication" of CNMP with too little attention to well integrated and coordinated behavioral and physical therapy.

Management of CNMP is often best effected using an interdisciplinary team approach (Table 3).

TABLE 2. ADVERSE EFFECTS OF UNDERTREATED PAIN*

Adverse Physiological Sequelae of Pain

Increased catabolic demands
- Muscle breakdown
- Poor healing
- Weakness

Impaired respiratory effort
- Risk of atelectasis, pneumonia

Impaired limb movement
- Risk of thromboembolic events

Water retention

Inhibited GI motility

Hypertension, tachycardia, and tachypnea (acute)

Adverse Psychological Sequelae of Pain

Negative emotions
- Anxiety
- Depression

Sleep deprivation

Existential suffering

Adverse Immunological Sequelae of Pain

Impaired immune response
- Decreased natural killer (NK) cells

* Adapted from References 10, 11.

Are Opioids Routinely Indicated in CNMP?

There is no single, definitive answer to this important question. Available evidence suggests that many CNMP patients whose quality of life is poor due to pain can improve markedly with regularly scheduled opioids. But some patients' functionality decreases when they start receiving opioids. Individualization of therapy is essential with attention to the single most important set of outcome measures, i.e., functional improvement measures (FIMs). Unfortunately, few physicians other than those trained in physiatry (physical medicine and rehabilitation) are familiar with the use of FIMs. Most clinicians evaluate improvements in the activities of daily living. These activities can be as mundane as climbing stairs or may be more encompassing as returning to normal work patterns or recreational activities. Improvement or restoration of the performance of these tasks indicates improved function over a period of time. Videotaping of patients carrying out standardized physical activities at baseline and periodically as they progress in a treatment program provides visual, objective documentation of progress. Progress or lack of progress may be an indication for drug dosage adjustments. Fortunately, many physical and occupational therapists use FIMs as well to provide objective, quantifiable data on a patient's ability to function.

While reports of pain relief are important, pain reports and medication use are not sufficient to document meaningful outcomes. Determining the place for opioids in managing CNMP patients requires consistent documentation of functional improvement.

There is a belief among some clinicians that neuropathic pain is less responsive to opioid therapy than other types of CNMP. Some older reports support this contention,[15] but there is increasing evidence to refute it.[16] There is no specific type of CNMP for which opioids are consistently ineffective.

Numerous uncontrolled surveys and commentaries on opioids in CNMP have been published. The majority suggest that the drugs have a definite place in this type of therapy. Portenoy reviewed published controlled trials of opioid efficacy in CNMP and identified critical issues in this type of drug therapy.[17] Papers on opioids in CNMP pain published

in the 1980s and 1990s reported good analgesic efficacy in about half to nearly all patients studied.[17] The authors reported aggregate misuse of the drugs by about 16% of the patients.[17] Improved functional outcome measures were reported consistently when patients' pain was reduced by opioids.[17] In some cases, improvement in functional outcome measures was reported when patients were weaned off of opioid analgesics.[17]

In 1992, Zenz et al published their experience with opioids in 100 patients who had been treated for CNMP for 2 weeks to 14 years; 23 had pain for more than a year.[18] This report is one of the most useful in a very limited literature because it has a reasonable sample size, good documentation, and appropriate outcome measures. The patients received morphine, dihydrocodeine, or buprenorphine for 14 to 1472 days with a mean duration of therapy of 224 days.[18] The daily morphine-equivalent opioid dose ranged from 20 to 2000 mg. Outcomes were described in terms of performance measures that correlated with analgesia. Fifty-one patients reported good pain relief and another 28 patients reported partial pain relief. However, 21 patients did not respond to opioid therapy and 10 patients were noncompliant with the prescribed opioids.

It appears reasonable to conclude that opioids are not always indicated in the management of CNMP. But neither are they routinely contraindicated. Selection criteria for CNMP patients who are good candidates for opioid therapy are needed.

Which CNMP Patients are Appropriate Candidates for Opioids?

In 1990, Portenoy proposed 11 guidelines for chronic opioid therapy for nonmalignant pain.[19] Each of these is discussed below in the context of clinical experience that has evolved since the guidelines were proposed.

1. Opioid maintenance therapy should be considered only after all other reasonable attempts at analgesia have failed.

Conservative use of any dependence-inducing drug is wise. When specific therapies are available which may correct the underlying cause of the pain, they should be given a full trial before committing to maintenance opioid therapy. But short-term opioids may be an important–even essential–adjunct to the more definitive therapy in some cases. For example, a patient who is incapacitated by chronic myofascial pain may experience resolution of the problem with appropriate behavioral and physical therapy to lessen stressors, lessen learned pain behaviors, release the trigger points, and strengthen affected muscles. But patients who are in a lot of pain often cannot or will not participate in either behavioral or physical therapy. Myofascial trigger point injections may help to facilitate these therapies. But many patients may require opioid analgesics as well, for a period of time, until they gain confidence in the more definitive therapies, so those can become effective. Only then can the need for maintenance opioid therapy be determined.

2. A history of substance abuse should be viewed as a relative contraindication.

Current or recent substance abuse may be a contraindication to maintenance opioid therapy for many patients. Careful personal and family medication and substance use histories are essential to identify that small segment of the population who may be genetically predisposed to addiction.

It is important to differentiate between primary and secondary substance abuse. Primary abuse antedates the onset of the pain complaint and is continuing. Secondary substance abuse results from unsuccessful attempts to manage the pain with the substances now being abused. Primary substance abusers are usually better managed by referral to a substance abuse program than in a pain management setting. Many secondary substance abusers report that they do not want to continue taking drugs, but have experienced withdrawal symptoms when they tried to stop abruptly. Secondary abusers often can be well managed in a pain management clinic.

A history of remote substance abuse usually is not problematic. Many persons experimented with recreational drugs when young and have not used them much or at all in recent years. Those types of experiences need not be considered contraindica-

TABLE 3. INTERDISCIPLINARY PAIN MANAGEMENT TEAM MEMBERS AND ROLES

Physicians
(Preferably board certified by the American Board of Pain Medicine or Anesthesiologists having earned the American Board of Anesthesiology additional qualification in pain)
- Medical management
- Most commonly
  - Anesthesiologists
  - Neurologists
  - Physiatrists
  - Psychiatrists

Mental Health Professionals
- Cognitive-behavioral therapy
- Address learned pain behaviors
- Management of psychological disorders and somatization
- Most commonly psychologists, usually with advanced training in behavioral medicine; sometimes social workers

Nurses
- Patient educators
- Case managers

Rehabilitation Professionals
- Physical therapists
- Occupational therapists
- Vocational counselors
- Recreational therapists

Pharmacists
- Obtain detailed medication histories
- Monitor and manage drug therapy (pharmaceutical care plans)
- Manage detoxification of inefficacious drugs
- Provide patient education
- Provide drug information to staff

tions to maintenance opioid therapy.

3. A single practitioner should take primary responsibility for treatment.

A very clever patient who is abusing or diverting controlled substances may occasionally fool even the most experienced clinician. A very useful strategy to minimize this risk is insisting, a priori, that the patient receives prescriptions from only one prescriber and obtains the medications at only one pharmacy. These requirements should be clearly communicated, verbally and in writing, including the fact that violation of this guideline will result in discontinuation of care. Some clinicians permit patients one or two violations ("three strikes you're out") before dismissal.

4. Patients should provide informed consent before initiation of therapy.

Written informed consent provides protection for both the clinician and the patient. This is most easily achieved through use of a written medication management agreement. The term "contract" has connotations that might best be avoided. Both the patient and each clinician who participates in the patient's care should sign the document. These may include a physician, psychologist, and pharmacist. Experience with such formal treatment agreements has been published.[9]

5. Medications should be administered on an around-the-clock basis with the goal of maintaining an acceptable level of comfort.

Long-acting opioids are preferred to short-acting drugs for both limited term and maintenance therapy. Animal and clinical studies of addictive behavior strongly suggest that patients who are potential abusers are at greater risk with short-acting medications that produce serum level "peaks and valleys." Medications that maintain relatively flat dose-response curves produce effective levels of analgesia without the high peaks that sometimes cause euphoria.

6. Failure to achieve at least partial analgesia (improved comfort level with improved function) raises questions as to the propriety of continued opioid treatment.

Most patients require only a small fraction of their previous opioid dose for maintenance therapy. This most often is determined by tapering the drug. Patients who are initially anxious about discontinuing opioids often successfully taper off of their medications when this is done in a coordinated manner. Procedures for such tapers have been published elsewhere.[9] Patients who do well initially, but who become far less able to function during the latter part of their tapers, may be candidates for maintenance opioid therapy. It is wise to attempt the taper twice before reaching this conclusion.

7. Emphasis should be given to attempts to capitalize on improved analgesia by gains in physical and social function.

Physicians or any other clinicians who attempt to provide comprehensive care to complex CNMP patients as solo practitioners often fail. Psychologists and physical therapists are essential in monitoring and maintaining CNMP patients' progress. It has been documented for over a quarter of a century that pharmacists are the most effective professionals to obtain medication histories and to monitor for drug therapy.[22]

8. Patients should be allowed to escalate drug doses transiently when needed.

Breakthrough pain is a well-described and recognized phenomenon in chronic malignant pain patients.[11] Based on the assumption that opioids are used to lower nociceptive input and pain perception in CNMP patients, it is logical to expect some intermittent or breakthrough pain among many CNMP patients. For that reason, limited intermittent "rescue" doses for breakthrough pain may be needed by some patients. Escalating use of such doses may indicate that the regularly scheduled doses are too low. Excessive use of breakthrough doses may also indicate substance abuse.

9. Most patients should be seen and drugs prescribed at least monthly. Efficacy, adverse effects, and signs of drug misuse should be monitored. Results of careful assessments of drug use should be documented in the medical record.

All clinicians must remain aware of the potential for patients to misuse controlled substances and recognize that an occasional patient may abuse or divert drugs. It is therefore essential to monitor carefully for both desired and untoward outcomes. It is also essential to be careful and thorough when documenting this monitoring. Failure to document why and how controlled substances are being used is the most common reason for regulatory and legal action to be taken against health professionals who are maintaining patients on controlled substances. Likewise, thorough medical records are the best defense if any action against the practitioner is ever initiated.

10. Pain exacerbations not managed by transient, small increases in dose are best managed in the hospital where dose escalation can be observed closely, and return to baseline dose can be achieved in a controlled environment.

This advice appeared sound when it was provided in 1990. Today, extensive CNMP management experience supports care being provided on an outpatient basis. Additionally, managed care limitations on hospitalization may make inpatient admission for pain medication titration difficult. Before considering admission for monitoring, clinicians should assure that a thorough psychosocial and physical evaluation are completed to identify stressors or injuries that may explain the dose escalation and suggest alternative treatment strategies.

11. Tapering and discontinuation of opioid maintenance therapy should follow evidence of drug hoarding, acquisition of drugs from other prescribers, uncontrolled dose escalation, or other aberrant behaviors.

Unfortunately, some well-intentioned clinicians freely prescribe opioids for patients in pain without attention to these issues. Serious adverse outcomes have resulted. Clinicians must believe their patients' reports of pain; they must also be aware of the small number of patients whose incorrect use of drugs can impact the prescribers and the ability of all health care practitioners to provide needed opioids to CNMP patients in the future. Restrictive laws, regulations, and regulatory practices are often responses to a few abusers without

consideration of the real needs of many patients in pain. Pain clinicians should be proactive through professional societies and informal networks to minimize inappropriate prescribing by colleagues who may be lax in assuring that opioids are indicated and not include meticulous monitoring and documentation of the use of opioids in their patients' care.

Adverse Effects of Chronic Opioid Therapy

Opioids are remarkably well tolerated in chronic use. Adverse effects are seen primarily when "opioid-naive" patients first start the drugs. Tolerance to the cognitive and other nonspecific CNS depressing effects of the drugs commonly occurs within a few days of initiating therapy or escalating the dose.[23] Tolerance to respiratory depression also occurs within a week of starting regularly scheduled, around-the-clock opioid therapy.[24] Patients do not become tolerant to the constipating effects of opioids. Therefore, most patients taking regularly scheduled opioids need scheduled, stimulating laxatives.[25] Osmotic and saline laxatives often are ineffective due to marked reduction in peristalsis from activation of opioid receptors in the patient's intestinal tract. Stool softeners alone are of no value in fostering evacuation of a narcotized gut. Bulk-producing laxatives can cause pressure that does not produce peristalsis in a narcotized gut. The result can be colicky pain.

Several emerging neuropsychiatric toxicities of opioids have been identified in patients receiving high doses for chronic malignant pain. These include cognitive failure, hallucinations, delirium, severe sedation, generalized myoclonus, hyperalgesia, allodynia, and seizures.[25] These effects have been seen primarily with morphine, most probably due to the accumulation of the neurotoxic metabolite morphine-3-glucuronide.[25]

Opioids do not produce the end-organ toxicity commonly seen with nonsteroidal anti-inflammatory drugs (NSAIDs) on the gastrointestinal tract and kidneys, nor the hepatotoxicity that can occur with high doses of acetaminophen. Opioids are remarkably safe drugs when used chronically in appropriate doses and when monitored effectively.

BARRIERS TO USE OF OPIOIDS

Many clinicians recognize the place for opioids in the management of CNMP. However, several important barriers to more broad acceptance and use of these efficacious analgesics continue to impede their use in the care of patients who could benefit greatly from these drugs. These barriers are not limited to any one group nor are they due simply to a lack of knowledge. Failure to use indicated opioids results from faulty knowledge, attitudes, and practices. These problems exist among clinicians, patients and their support groups, and throughout the health care system.

TABLE 4. SOME WARNING SIGNS OF INAPPROPRIATE OPIOID USE

- Preoccupation with drugs
- Refusal to participate in a medication taper
- Reports that nothing but a specific opioid works
- Strong preference for short-acting over long-acting opioids
- Use of multiple prescribers and pharmacies
- Use of street drugs or other patients' drugs
- Not taking medications as prescribed
- Loss of medications more than once
- Decreased function

The most common misconceptions among clinicians and the public relate to dependence, addiction, and tolerance.

Dependence

Dependence is a physical or pharmacological phenomenon characterized by an abstinence syndrome upon abrupt drug discontinuation, substantial dose reduction, or administration of an antagonist.[26] Dependence is nearly universal among patients receiving continual opioid therapy for a week or more. Dependence occurs with many common medications such as glucocorticoids and some common antihypertensives. Just as with the latter drugs, opioids can be discontinued in dependent patients without withdrawal difficulties by simply tapering them over about a week.

CNMP patients often are dependent on their medications, but this is not a clinical problem. By definition, abrupt withdrawal of medications upon which patients are dependent produces abstinence syndromes. More often than not, patients can be tapered off of drugs used randomly or when only a few tablets are taken per day in 3 to 5 days.[21]

Addiction

Addiction is a very different psychological phenomenon that is characterized by loss of control over drug use and compulsive use of the drug despite harm from that use.[27] It is unfortunate that several definitions of addiction incorrectly imply that dependence and addiction are similar states. Many of the published conclusions about risk of addiction to opioids are based on studies of addicts. Clearly, the addicts were addicted. Their response to drugs is not relevant to patients in pain who are apt to be dependent, not addicted. Iatrogenic addiction from opioid analgesia in patients experiencing pain is exquisitely rare. The Boston Collaborative Drug Surveillance Program study revealed only four cases of iatrogenic addiction among 11882 patients without a prior history of substance abuse who received opioids for a broad range of indications.[27] A national survey of over 10000 burn patients without prior histories of drug abuse who received opioids revealed no cases of addiction.[28] Only three of 2369 chronic headache patients, most of whom had access to opioids, abused the analgesics.[29]

Addicts normally exhibit profound drug-seeking behavior. But drug-seeking behavior is not necessarily indicative of abuse. Such behavior may be appropriate if the patient is a candidate for an opioid and the drug is not available in sufficient dose to allow the patient to function and maintain a reasonable lifestyle. Such patients have been described in the oncology setting as "pseudoaddicts."[30] Pseudoaddiction

is appropriate drug seeking behavior for the purpose of comfort, not abuse. Such patients may demand more drugs and display anger and hostility toward the health care system. Pseudoaddiction can be differentiated from drug misuse by increasing the dose by an appropriate amount and determining if the complaints abate. In 1997, the American Society of Addiction Medicine published a public policy statement recognizing the phenomenon of pseudoaddiction.[31] An occasional patient will abuse opioids that are prescribed for the management of CNMP. Clinicians should be aware of several warning signs of inappropriate drug use. These are listed in Table 4.

Tolerance

Fear of tolerance to opioids often presents a barrier to effective use of these medications. Three distinct types of tolerance occur with opioids. Tolerance to centrally mediated effects, i.e., respiratory and CNS depression, normally occurs within 5 to 7 days of continuous administration of regularly scheduled opioids.[24,25] These patients are commonly referred to as opioid-tolerant. Tolerance to the constipating effects of opioids does not occur.[25] Activated mu opioid receptors in the colon inhibit peristalsis. Therefore, constipation with opioid therapy is common and should be anticipated with relatively high-dose therapy. Stimulant laxatives, e.g., senna or bisacodyl, should be used to induce peristalsis. Stool softeners alone are ineffective. The risk of severe constipation, or even fecal impaction, is an indication for prophylaxis with stimulant laxatives when opioid therapy is initiated.[25]

Increases in opioid doses may be required over the first few days or weeks of therapy while finding an effective dose. This is not tolerance; it is titration to response. Tolerance to opioid analgesia typically does not occur once an effective dose of opioid is identified and administered regularly. When stable opioid doses cease to be effective, pseudotolerance may be a factor.[32] Pseudotolerance can result from increasing or new pathology, excessive physical activity after the pain decreases, drug interactions, noncompliance, and other nonpharmacologic factors. Opioid receptor regulation, i.e., up or down regulation, does not occur with regularly scheduled dosing.

Opioids can impair both judgement and psychomotor function when therapy is started. Moreover, these side effects may recur when doses are escalated. However, once a patient has been receiving opioids on a consistent and regular schedule for approximately 7 days, these adverse effects usually diminish markedly. In Finland, no significant difference was found in the number of motor vehicle crashes involving 24 drivers taking opioids on a regular schedule for chronic pain management than among the general population.[33] Patients experiencing no observable opioid-induced impairment after taking a stable opioid dose for a week or more can usually drive and carry out other normal functions safely. When opioid doses are increased, patients should refrain from these activities for at least a week and until any impairment due to the increased dose resolves.

Many patients believe that parenterally administered opioids are more effective than analgesics administered by the oral or other noninvasive routes. This, of course, is not true. Once an opioid occupies a receptor, activity will occur regardless of how the medication was administered. For many patients, the use of the parenteral route can signal advancing disease and may be a psychological disadvantage.

Potency is commonly misunderstood. Potency indicates the amount of drug needed for effect. For example, 1.5 to 2 mg of parenteral hydromorphone is equivalent to 10 mg of parenteral morphine. Hydromorphone is more potent than morphine, but no more effective. Typically when patients ask for more potent drugs, they mean more effective drugs.

Many clinicians use very conservative dose increments when escalating opioid therapy. This unfortunately can lead to treatment failure. Doses should be increased to response. Appropriate dose increments are normally 50% of the dose and can be increased every five half-lives (twice a day for morphine). This percent increase applies no matter what the prior dose. When patients know that opioid doses have increased, but do not experience adequate analgesia, anxiety often ensues. This can lead to increased pain perception, which in turn may increase the opioid requirement further. Often, it is better to err slightly in the direction of too much opioid rather than too little. Initially, sedation may be advantageous for anxious patients or those with sleep deficits.

As more studies and clinical experience are documented, knowledge about appropriate use of opioids should improve. Supplementing deficient knowledge alone is not sufficient to correct the problem, however. Attitudes such as "No one ever died from pain" and "Since I can't find the cause, the pain must be psychosomatic" also must be changed through peer support and pressure. Instituting good pain management must become a priority for each practice, clinic, institution, and healthcare system if patients are to receive optimal care. Fortunately, this is occurring more frequently in acute and cancer pain management.[34] Far more work is needed in the area of CNMP.

Resistance to using needed opioids has been documented among physicians,[35] nurses,[36] and pharmacists[37] in the management of cancer pain which is far less controversial than in the management of CNMP. Patients, family members, and other members of the patient's support group sometimes resist opioids or discontinue them due to misplaced fears of addiction and adverse effects. Education, reinforcement, and follow-up are needed to support appropriate use of the analgesics.

Surveys of prescribers consistently demonstrate that concern about overly aggressive regulators sometimes impedes the prescribing of controlled substances that might have been considered. Open and proactive communication with state regulators about opioid use with carefully documented monitoring and follow-up often avoids regulatory problems. Many concerns about excessive regulatory oversight are more perception than reality.

TABLE 5. DOSING COMPARISON FOR SOME COMMON OPIOIDS[50]

Drug	Approximate Equianalgesic Oral Dose (mg)	Approximate Equianalgesic Parenteral Dose (mg)	Approximate Onset (minutes)	Approximate Duration (hours)
Codeine	200*	120	10 - 30	4 - 6
Fentanyl	25 mcg/hr (transdermal)	0.1 - 0.2 IM	7 - 8	1 - 2
Hydrocodone	5 - 10	No data	No data	4 - 6
Hydromorphone	7.5	1.5	15 - 30	4 - 5
Levorphanol	No data	No data	30 - 90	6 - 8
Meperidine	300**	75	10 - 45	2 - 4
Methadone	10 - 20	10	30 - 60	4 - 6
Morphine	30 - 60	10	15 - 60	3 - 7
Oxycodone	30	10 - 15***	15 - 30	4 - 6
Oxymorphone	Rectal 5, 10	1	5 - 10	3 - 6
Propoxyphene	130	No data	30 - 60	4 - 6
Sufentanil	No data	0.01 - 0.04 IM	1.3 - 3	No data

*Codeine doses above 65 mg are usually not appropriate due to diminishing incremental analgesia with increasing doses but continually increasing constipation side effect.

**Meperidine and agonist-antagonist analgesics are not recommended for cancer pain management due to potential adverse effects.

***Parenteral form is not available in the United States.

Published tables vary in their suggested equianalgesic doses. Clinical response is the criterion that must be applied for each patient. Because there is not complete cross tolerance among these drugs, in patients whose pain is well controlled, it is usually necessary to use 10% to 20% lower than equianalgesic doses when changing opioid drugs and then retitrate to response. If pain is not well controlled, use equianalgesic or 10% to 20% higher than equianalgesic doses of the new opioid drug and retitrate to response.

OPIOID DOSING

Opioids can be administered by a number of routes, including oral, parenteral, rectal, sublingual, transdermal, and transmucosal. Morphine remains the standard opioid for comparisons. The majority of equianalgesic dose tables use parenteral morphine 10 mg every 4 hours as the standard. Equianalgesic doses of commonly used opioids are listed in Table 5. However, no one table can apply to all patients due to interpatient variability in opioid response. Tables can provide approximate equally effective doses, but patients must be titrated to response when opioids are changed.

Dose-ceiling Effect

The dose-ceiling effect limits the usefulness of mixed agonist-antagonists and partial agonists. Two types of dose ceilings occur. A true dose ceiling results from lack of additional efficacy after the dose exceeds a predetermined level while incurring additional toxicity. Mixed agonist-antagonist opioids (butorphanol, nalbuphine, pentazocine, and dezocine) and the partial agonist (buprenorphine) have true dose ceilings. These drugs should not be administered at doses that exceed those listed in the FDA-approved labeling. These drugs can displace pure mu agonists from mu receptor sites resulting in withdrawal.

The second type of dose ceiling is a functional dose ceiling that is commonly seen with codeine. Oral doses of codeine administered every 4 hours should normally not exceed 65 to 100 mg. A dose-response relationship for analgesia does not exist for oral codeine doses greater than 60 mg.[58]

Pure mu opioid agonists do not exhibit a true dose ceiling effect, however they can present a functional ceiling that varies broadly among patients. Fortunately, the functional ceiling is usually higher than doses needed clinically. Since the dose or serum concentration at which this functional ceiling occurs cannot be predicted in advance, doses of these drugs should be titrated upward until either analgesia is achieved or unacceptable adverse effects occur.

Absorption

Opioids are readily absorbed from the gastrointestinal tract following oral or rectal administration. Oral administration is preferred due to its convenience, simplicity, and cost. Oral administration does not reinforce the sick role, nor does it signal advancing disease as does parenteral administration. Opioids given orally are subject to hepatic first-pass metabolism, i.e., they must pass through the liver before reaching the systemic circulation. As a consequence, larger doses of oral opioids are required to produce the same effects as parenterally administered opioids. In most patients, immediate-release oral opioid formulations have an onset of analgesia of about 20 to 40 minutes. Peak analgesia occurs about 45 to 60 minutes after oral administration. Oral morphine is reported to require 30 to 45 minutes to reach peak plasma levels, while oxycodone may take 60 to 90 minutes to peak after oral administration.[59] Delayed peak concentrations seem to make oral opioids less than ideal for managing breakthrough pain.[59] However, the author's experience has shown this not to be the case. Oral opioids can usually manage breakthrough pain effectively.

Some opioids can be administered rectally if the oral route is not feasible. This is usually applicable in the management of CNMP only for short periods of time. Rectal administration avoids the hepatic first-pass effect when administered correctly. There are three sets of veins responsible for rectal blood return: the superior, middle, and inferior rectal veins. The superior vein is responsible for the uppermost region of the rectum (approximately 15 to 20 cm high) and returns blood to the portal vein. This leads to immediate hepatic metabolism, i.e., the first-pass effect. In contrast, the middle and inferior rectal veins return blood to the inferior vena cava. Opioid administration into the lower rectal vault allows for more of the parent drug to reach the systemic circulation, bypassing the first-pass effect.[40,41] Hydromorphone, morphine, and oxymorphone are currently available as commercially prepared rectal suppositories.

Intravenous (IV) opioids, by definition, provide 100% bioavailability. Subcutaneous (SC) opioid infusions provide for a similar drug level to those achieved with IV infusion at 24 and 48 hours.[42] Peak effects may be more pronounced after IV administration, but duration is shorter than the oral route.[50] Time to peak effect is delayed for IM and SC administration because of absorption. However, these latter two routes provide similar levels at similar times.

Metabolism

Opioids not readily eliminated by the kidneys in the parent form must be metabolized in the liver to more water-soluble metabolites, i.e., dealkylation, glucuronidation, hydrolysis, and oxidation. Opioids can also be metabolized to a minor extent in various other body compartments, e.g., central nervous system, kidneys, lungs, and placenta.

Selection of a particular opioid, in part, hinges on the metabolic fate of the agent. Metabolites may cause untoward neurotoxicity,[25] and may displace the parent compound from opioid receptor sites. Patients with impaired renal function (which includes most elderly) and those receiving high-dose or long-term opioid therapy are at risk from the toxicities of metabolite accumulation. Accumulation of normeperidine, a metabolite of meperidine, causes neurotoxicity especially in elderly patients and in those with poor renal function. Use of meperidine should be limited to 1 to 2 days for acute pain and should be avoided in the management of chronic pain.

Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) are the two major morphine metabolites.[44] As much as 50% of the parent drug may be renally excreted as M3G, while M6G accounts for about 5%.[45] Both compounds are water-soluble glucuronides that require renal elimination for clearance. M3G appears to be antinociceptive and has been associated with hyperalgesia and neurotoxicities.[25,46] M6G possesses analgesic properties and may be significantly more potent than morphine. Accumulation of both metabolites, as a function of poor renal status, predisposes patients to toxicity as well as poor pain control.

Why Long-Acting Opioids Should be Used

Long-acting opioids, which provide consistent levels over extended time periods, favor compliance and minimize serum level fluctuations. Effective opioid levels should be maintained in chronic pain as long as the noxious stimulus is present. This avoids repeated stimulation of the afferent nociceptive neurons which can sensitize both those neurons producing the phenomenon known as physiological windup and cells in the dorsal horn of the spinal cord resulting in neuronal plasticity.[47] Such sensitization induces neurological changes that last long after the initial insult has healed. Neuronal plasticity, or changes in the CNS, may lead to hyperalgesia. Windup is the progressive increase in the frequency of elicited action potentials seen in neurons as a result of slowly repeated stimulation of C fibers.[48] Thus it may take less drug to prevent the recurrence of pain than would be required to treat recurring pain.

Maintenance of effective analgesia is most effectively accomplished with long-acting medications used on a regular schedule or time-contingent basis. Two oral opioids, methadone and levorphanol, are inherently long acting. Methadone has a biphasic elimination which provides up to 12 hours of analgesia per dose from the alpha elimination phase once steady-state serum levels have been reached. Until then, i.e., for the first 2 to 3 days of therapy, only 4 to 6 hours of analgesia may result from each dose. The beta elimination phase provides low levels of methadone for up to 60 hours. Those levels are usually not sufficient for analgesia but do protect against opioid withdrawal. That is why methadone is useful in opioid detoxification and maintenance programs. However, the low levels resulting from the beta elimination phase accumulate over time and may cause obtundation from accumulation after 1 to 3 weeks of therapy. The pharmacokinetics of levorphanol have not been well defined but appear similar.

CONCLUSION

There is consensus from controlled trials and consistent clinical experience that opioids should be used more readily and aggressively in the management of acute pain and chronic malignant pain. There is a growing consensus and increasing documentation that they also have a place in the management of CNMP. There is also markedly increased acceptance among knowledgeable pain clinicians that opioids do have a place in CNMP. These drugs are commonly used appropriately for patients with mechanically-induced pain such as failed back syndrome. They can also be important therapy in other chronic pain syndromes for which more specific

therapies have not been effective. Opioids can be key adjuncts in facilitating physical or behavioral therapy for patients in severe pain that is responsive to opioids. Frequently, the analgesics can be tapered or discontinued once the desired outcomes are achieved.

Chronic opioid therapy can dramatically improve the quality of many CNMP patients' lives. But opioids may decrease another patient's ability to function and carry out activities of daily living. Any drug that is not effective or that produces more adverse than beneficial effects should be discontinued. Opioid analgesics frequently permit CNMP patients to maintain relatively normal function and lifestyle. It would be as unwise to assume that opioids are always indicated in the management of severe CNMP as it would be to conclude that they have no place in the care of these patients. Individualization according to patient outcomes is the key to determining appropriate drug therapy.

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SELF ASSESSMENT QUESTIONS

1. In clinical practice, pain is most effectively differentiated as being:
a. acute or chronic
b. acute or malignant
c. acute, chronic malignant, or chronic nonmalignant
d. somatic or visceral
e. mild, moderate, or severe

2. The route of choice for analgesic therapy, whenever possible, is:
a. oral b. IV c. IM d. epidural e. rectal

3. Inadequately managed pain can produce adverse effects that are:
a. physiologic b. psychologic
c. immunologic d. a and b
e. a, b, and c

4. Mu agonist opioids and agonist-antagonists should not be given together due to risk of:
a. additive effects b. increased costs
c. opioid withdrawal d. diminished effects
e. all of the above

5. Which of the following is a clinical problem with opioids that commonly precludes therapy:
a. addiction b. cognitive depression
c. tolerance d. dependence
e. none of the above

6. Chronic pain patients with a history of substance abuse:
a. should never receive opioids
b. should take analgesics only PRN
c. seldom require analgesics
d. can receive opioids just as any other patient
e. usually can receive opioids if they have not abused substances for several years.

7. Chronic nonmalignant pain is:
a. a homogeneous set of syndromes
b. always treated the same way
c. amenable to cure with drugs alone in most cases
d. a heterogeneous set of disorders
e. easily managed

8. Long-acting opioids have the advantage of:
a. favoring medication compliance
b. maintaining serum levels longer
c. lessening the risk of neuronal plasticity due to intermittent drug level fluctuations
d. lessening the risk of physiological windup due to intermittent drug level fluctuations
e. all of the above

9. Which of the following drugs is not recommended to be used for more than 2 days due to risk of accumulating a neurotoxic metabolite?
a. morphine b. methadone c. oxycodone
d. meperidine e. hydromorphone

10. Which of the following morphine metabolites has been associated with CNS adverse events?
a. morphine-6-glucuronide
b. normorphine
c. morphine-3-glucuronide
d. morphine itself
e. all of the above

11. Pharmaceutically formulated controlled-release dosage forms of morphine and oxycodone are most effective when dosed on a regular schedule.
a. true b. false

12. A person with renal disease may experience poor pain control and increased toxicity due to the accumulation of morphine metabolites.
a. true b. false

13. Drug-seeking behavior is nearly always indicative of addiction.
a. true b. false

14. Which subtype of opioid receptors provides the most useful target for opioid analgesic therapy?
a. delta b. kappa c. epsilon
d. mu e. sigma

15. Which of the following is a common cause of increased opioid dose requests from patients whose pain was previously well-controlled on a consistent dose?
a. tolerance b. increased or new pathology
c. drug interactions d. all of the above
e. b and c

16. Opioids cause more end-organ toxicity than NSAIDs.
a. true b. false

17. The risk of addiction in chronic pain patients taking opioids for pain relief is:
a. very high (>>50%) b. high (30%-40%)
c. moderate (10%-20%) d. low (1%-10 %)
e. extremely low (<<1%)

18. To which of the following effects do most patients become tolerant within a week of regularly scheduled opioid therapy?
a. analgesia b. respiratory depression
c. cognitive impairment d. b and c
e. all of the above

19. Opioids have been reported in the literature to provide effective analgesia in what percent of CNMP patients?

a. <10% b. 10% to 20% c. 21% to 40%
d. 4% to 50% e. 50% to 90%

20. The most important indicator of continued opioid therapy for CNMP is:

a. improved function b. lower pain report
c. improved mood d. less demand for drug
e. all of the above

PROGRAM EVALUATION

21. How would you rate this educational program overall?

a. excellent b. very good
c. good d. fair
e. poor

22. How well did this program achieve its educational objectives?

a. very well b. well
c. somewhat d. not at all

23. How well did this program improve your knowledge of the subject matter?

a. very well b. well
c. somewhat d. not at all

24. Will this be useful and relevant in your practice?

a. very useful/relevant
b. useful and relevant
c. somewhat useful/relevant
d. not at all useful/relevant

25. How much time did it take you to complete the lesson and exam?

a. less than 1 hour b. 1-2 hours
c. 2-3 hours d. 3-4 hours
e. over 4 hours

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P-27020 _ 00016