KADIAN®

Learning Systems

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SECTION ONE

Pain Management

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CHAPTER ONE

Overview of Pain Management

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe how a pain signal travels through the nervous system to the brain.
- Differentiate acute, chronic benign, and cancer pain.
- Discuss the goals of pain treatment for each type of pain.
- State the types of clinicians who practice pain management.
- Understand the concept of interdisciplinary pain management.
- Understand current practice patterns for chronic benign pain and cancer pain.
- Describe the objectives of palliative care and hospice programs.
- Identify patients who are eligible for hospice care.
- Describe the common reasons for undertreatment of pain with opioids.
- Define substance abuse, addiction, and pseudoaddiction.
- Describe opioid phobia.

Terminology

Acute pain:	Short-term pain experienced after surgery or a traumatic injury.
Chronic benign pain:	Pain from problems that are neither fatal nor curable.
Central pain:	Pain that results from injury or disease in the spinal cord or brain.
Dependence:	A withdrawal syndrome develops if a medication is stopped suddenly.
Descending pathways:	Nerve fibers that travel down the spinal cord from the brain and inhibit pain signals.
Diversion:	Utilization of selling or abusing medication prescribed for a medical condition.
Fellowship trained:	Having 1 year or more of additional medical training specifically in pain management in an accredited pain management program.
Neuralgic pain:	Localized pain resulting from damage to a single nerve.
Neuron:	A nerve cell, including its body and its dendrites (very short branch-like extensions of the cell body) and axon.
Neuropathic pain:	Pain resulting from damage to the nerves.
Nerve:	A bundle of nerve axons (outside the brain or spinal cord) that run together within a connective tissue sheath.
Nerve fiber:	A long, typically singular branch of the nerve cell that relays messages to and from the area it serves. These branches can be several feet long in the extremities. A fiber is also called an axon.
Nerve tract:	A bundle of nerve axons that run together within the spinal cord or brain, functioning in a manner similar to a nerve.
Nociception:	The sensation of pain.
Opioid phobia:	An irrational fear of using strong opioid analgesics.
Peripheral neuropathy:	Pain in areas such as the feet and/or hands resulting from damage to the long nerve fibers that supply the limbs.
PRN:	An acronym made from the Latin 'pro re nata', which means as needed. It is typically used in medical orders and prescriptions.
Pseudoaddiction:	Behaviors (that mimic addictive behaviors) exhibited by patients with inadequately treated pain.
Sensory nerve:	This is a nerve that carries sensation signals, including pain.
Somatic pain:	Sharp, localized pain originating from the skin, muscles, tendons, ligaments, and bones.
Synapse:	This is a communication point between nerves. The synapse consists of a gap between the cells; chemical messengers cross the gap to relay a signal from one nerve to the next. Tolerance: The need for increased doses of medication over time to achieve the same level of pain control.
Visceral pain:	Poorly localized pain originating from internal organs.
Visual analog:	A pain severity rating scale.

Introduction

The first goal of medicine is to cure disease. In many cases, however, the disease cannot be cured. In these cases, the goal becomes management of the symptoms of the disease so that the patient can live a normal life. For patients suffering from a variety of different diseases, pain is the symptom that causes the most severe disruption of day-to-day activities. Between 10% and 15% of the population suffers from chronic pain severe enough to require medical treatment.

This chapter will review the various causes of pain and briefly describe the common treatments used to control pain. In addition, it will discuss the types of medical practices involved in pain treatment and the barriers that prevent some patients from receiving effective pain control.

Pain Signal Transmission

What is pain? The most commonly used definition of pain is "any sensation the patient perceives to be uncomfortable." By this definition, things like anxiety, depression, insomnia, and hunger would all be considered painful, and in some ways they are. What we normally consider pain, however, is any of several different unpleasant sensations that (in theory) serve to warn us that some part of our body is being damaged.

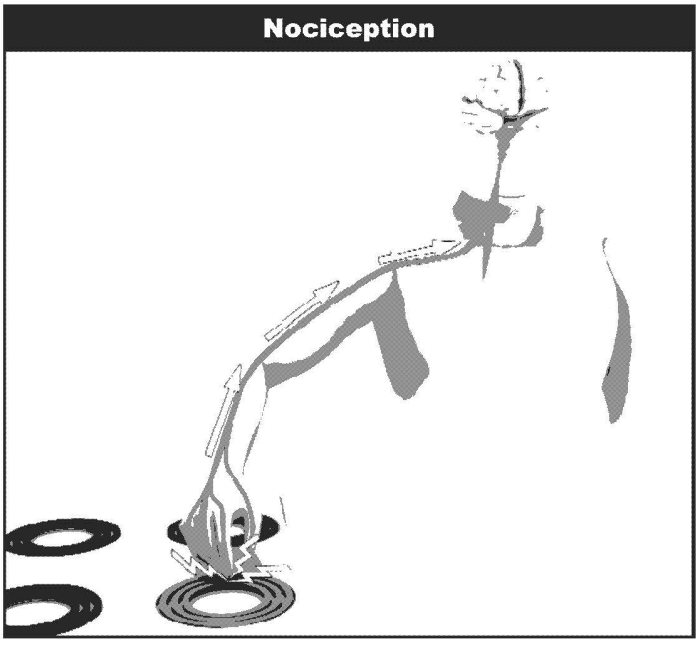
This section describes the origin, transmission, and modification of pain signals, including:

- Nociception
- Transmitting the Pain Sensation to the Spinal Cord
- Connections in the Spinal Cord and Brain
- The Descending Pathways

Nociception

Medically, the pain sensation itself is referred to as nociception (pronounced 'noe-sis-sep-tion'; 'noci' refers to pain). The sensation may lead to some secondary symptoms such as anxiety, nausea, or sweating that add to the discomfort.

Figure 1-1



Nociception begins when a sensory nerve ending in some part of the body is strongly stimulated and sends an electrical signal. These nerve endings normally do not send any signals, but if they are disturbed by a mechanical, thermal or chemical force that might damage the body, they begin actively sending repetitive electrical signals to the spinal cord. The pain sensing nerves function much like a smoke detector in a house: most of the time they are quiet and don't create any "noise", but when activated, they fire off a strong electrical signal to warn the brain of a possible problem.

Transmitting the Pain Sensation to the Spinal Cord

The pain signal travels from the nerve cell (neuron) ending to the spinal cord along a single fiber that is a long branch (also called an axon) off the cell body. Although each individual fiber is microscopically small in diameter, it is long enough to reach from the spinal cord to whatever part of the body that nerve monitors. Every part of the body sends pain signals along thousands of different nerve fibers, which differ in size and structure. The two most important types of pain-transmitting fibers are called C-fibers and A-delta fibers. A-delta fibers transmit the pain signal very rapidly, because their fiber (axon) is covered with a special insulation called myelin that speeds up conduction. C-fibers lack this covering and transmit their signals more slowly. The slow C-fibers transmit at about 1.5 to 6 feet per second, whereas the A-delta signal can travel 40 to 90 feet per second.

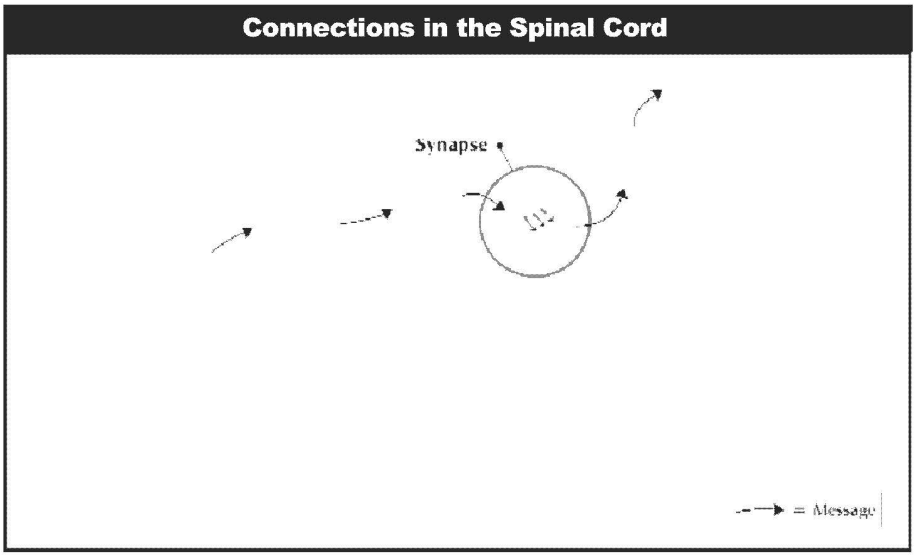
This speed difference is significant enough so that most people can clearly sense the separate pain sensations carried by A-delta versus C-fibers. The fast-conducting A-delta messages arrive first after an injury. This pain typically feels sharper and

"brighter". The C-fibers' message comes a second or so later, and tends to feel more dull, throbbing, and aching. For example, if you've ever hit your thumb with a hammer, you may remember an immediate, sharp pain that in a second or two gave way to a deeper, throbbing pain.

Connections in the Spinal Cord and Brain

An individual pain nerve fiber does not transmit its signal all the way to the brain, but instead connects to a group of second neurons just outside the spinal cord. At the connection between the neurons (which is actually a small gap between the two neurons called a synapse; pronounced "sin-aps"), the sensory neuron releases a small burst of chemical messengers (neurotransmitters) that drift across the gap and bind to special receptors located on the second neuron.

Figure 1-2

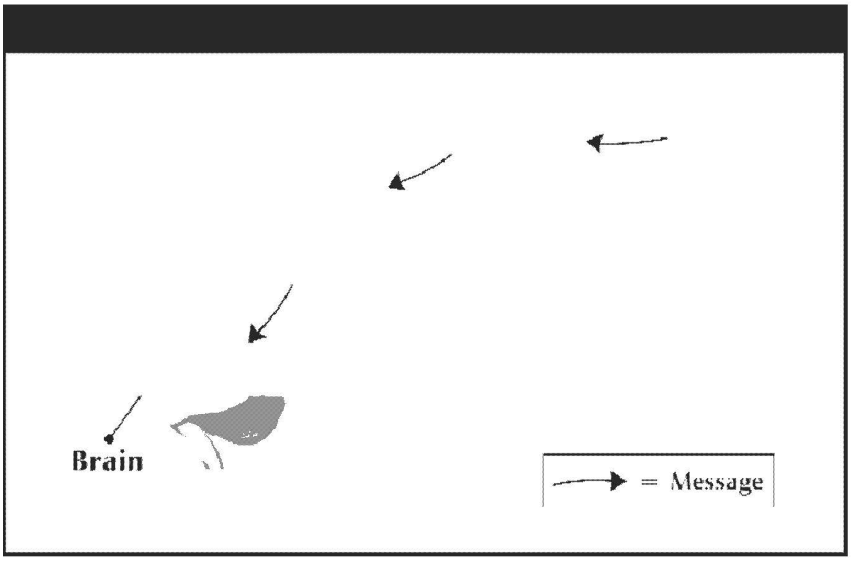


The chemical messenger does not necessarily cause the second neuron to send a signal. Some connections (which are called excitatory synapses) make the second neuron more likely to send a signal, whereas others (called inhibitory synapses) make the second neuron less likely to send a signal. The second neuron is simultaneously receiving signals from dozens or hundreds of peripheral nerves, and the overall sum of the stimulating and inhibiting input determines whether the second neuron will send a signal up the spinal cord.

These secondary neurons send fibers up the spinal cord in large bundles called tracts. The nerve fibers eventually connect to a third set of neurons located in the brainstem. From there the pain message is transmitted to the conscious brain (where we actually

perceive it), to the midbrain (where it activates motivation and the emotional response center), and to parts of the unconscious brain that control bodily functions like blood pressure and sweating. Still other branches carry the pain message to parts of the brain that can modify the pain response.

Figure 1-3



The Descending Pathways

This last set of neurons, the ones that modify the pain response, are of particular interest to us. These neurons send fibers (known as the "descending pathways") back down the spinal cord, giving off branches to the same neurons that originally received the pain input from the sensory nerves. Chemical messengers from these descending fibers inhibit the transmission of ongoing incoming pain signals, reducing these pain signals before they enter the spinal cord to be transmitted to the brain.

The neurotransmitters (chemical messengers) from these pain-inhibiting neurons (descending fibers) chemically resemble opioids such as morphine. The pain-relieving effects of opioids, such as morphine, occur largely because the opioids bind to the receptors of the excitatory neurons (the neurons that first transmit the pain signal), making it less likely that they will send a pain message.

Types of Pain

There are many different types of pain, each of which is a slightly different sensation. For example, stomach cramps and a toothache are both causes of pain, but those two types of pain feel very different. Doctors classify pain into several broad categories to better understand what is causing it and more importantly how to treat it.

One way to separate the types of pain is by location. From a medical standpoint, however, it is more helpful to separate pain according to the kind of organ or tissue that the pain originates from and the type of nerves involved in carrying the pain message. This classification also provides a useful way to think about response to opioids and other pain medications. Such a classification divides pain into the following types:

- Somatic Pain
- Visceral Pain
- Neuropathic Pain
- Central Pain

Somatic (soe-mat-ick) Pain

Somatic pain originates from the skin, muscles, tendons, ligaments, and bones. These parts of the body are well monitored by the brain because they are so important to how we function every minute. One can easily pinpoint the exact location of somatic pain: when you cut your finger with a knife, you do not have to look for the blood to know exactly which finger has been cut. Somatic pain is often sharp, stabbing, throbbing, or aching in nature. Although somatic pain can be severe, it tends to respond well to treatment with opioids.

Visceral (vis-sur-ull) Pain

The body's internal organs, such as the liver, intestines, and stomach, generate visceral pain. In many diseases, somatic pain and visceral pain exist together, as when a tumor begins in an internal organ and then metastasizes to a bone. In contrast with somatic pain, visceral pain tends to be poorly localized and more likely to generate referred pain that is felt some distance away from the actual problem. For example, the pain of angina, which originates in the heart, often radiates to the arm or jaw. This can make the diagnosis of the cause of visceral pain difficult and frustrating

for both clinicians and patients. Opioids are not as effective for visceral pain as they are for somatic pain, although they do provide some relief.

Neuropathic (new-roe-path-ick) pain

Neuropathic pain results when the nerves themselves are damaged. This may happen when a tumor invades a nerve, when a ruptured spinal disk presses on a nerve, or when a nerve is injured. Neuropathic pain is typically burning in nature, although it may also be aching or cause an electric shock sensation. The area involved in neuropathic pain often has allodynia (pronounced "al-oh-din-ee-ah", meaning hypersensitivity) to even light touch.

There are two broad categories of neuropathic pain involving the peripheral nerves. The first type, which involves injury to a single nerve, is termed "neuralgic". The second type is caused by certain diseases, such as diabetes, that damage nerves throughout the body. The longest nerves are the most severely affected, so the pain is most severe in the hands and feet. This type of neuropathic pain is called "peripheral neuropathy". For unknown reasons, opioid medications are often rather ineffective for treating neuropathic pain.

Central pain

Central pain is pain that results from injury, stroke, malignancy, or other lesion in the spinal cord or brain. It is often quite severe, yet unique in that the patient is often unable to describe it and often cannot even describe where the pain is. This leads to frustration for the patient and can be confusing to the health care provider. The pain can affect a large area or may be localized. An increased sensitivity to touch or pain may be present (hyperalgesia or allodynia). The key to the diagnosis of this type of pain is the history of a stroke, injury, or other lesion of the spinal cord or brain in a patient with vague and unusual descriptions of intense discomfort. Treatment of this type of pain is difficult. Lidocaine is often effective, but has to be given intravenously, limiting its usefulness. Tricyclic antidepressant drugs may be useful, but opioids are often not helpful in relieving the pain.

Goals of Pain Management

Pain management is simply reducing a person's pain to a tolerable level that allows the person to function as normally as possible. It is the primary treatment available when curing the underlying disease or condition is not possible. All clinicians practice pain management, at least occasionally. However, a growing number of clinicians either specialize in pain management or dedicate a significant portion of their practice time to pain management.

Obviously, reducing the patient's level of pain is the primary goal of pain management. It should be kept in mind that complete pain relief is often not possible or can only be obtained temporarily. However, a dramatic reduction in pain is almost always obtainable. The pain management clinician or team will have slightly different goals depending on the patient's specific type of condition. Pain management can be divided into 3 types based on the type of pain:

- Acute Pain Management
- Cancer Pain Management
- Chronic Benign Pain Management

Acute Pain Management

The goals in acute pain management are to provide the patient with effective pain relief that allows them to rest comfortably and to rehabilitate after their surgery or injury. Because this type of pain often waxes and wanes over time, short-acting PRN (as-needed) medications may be appropriate.

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Cancer Pain Management

The World Health Organization recommendations for pain management, referred to as the pain ladder, suggests starting with nonsteroidal anti-inflammatory drugs then to weaker and finally, stronger opioids as needed to control pain. The recommendation included as-needed medications to manage break-through pain. Over the years, the efficacy of this approach has been questioned, and some experts have suggested that it is more appropriate to start with opioids (specifically morphine) in patients with more severe pain. (Ventafridda 1987, Zech 1995, Maltoni 2005)

The goal of cancer pain treatment is to provide long-term, effective control of the patient's symptoms. Treatment should be adjusted so that the patient remains alert and largely free of side effects, able to enjoy life.

During the course of their disease, cancer patients may develop depression, insomnia, and anxiety. All of these symptoms can be worsened by uncontrolled pain, which adds to the importance of pain control. It is important, however, to realize that depression, insomnia and anxiety can also worsen the patient's perception of their physical pain. Treatment with specific medications (usually referred to as "adjunctive medications") to address these problems may help reduce the patient's pain significantly. Unfortunately, many patients do not volunteer that they have these symptoms, leading the clinician to incorrectly conclude that the opioid medication is not working effectively, when actually the patient needs an adjunctive medication, a change of dosage, or a change in therapy.

Because cancer pain may require long-term treatment with opioid medications, many patients will eventually develop tolerance to and dependence on opioids. Tolerance refers to the need for increased doses of the medication to achieve the desired pain relief. Physical dependence is a condition that takes place when the body gets so used to having a drug in the system that it experiences symptoms of withdrawal if the person abruptly stops taking the drug or suddenly takes a lower dose. Many clinicians fear the development of tolerance and dependence so much that they do not provide sufficient doses of opioids during the early stages of treatment, hoping that this will prevent the patient from developing tolerance too quickly. In reality, although tolerance and dependence do often occur late in the treatment of cancer pain, they rarely prevent effective pain relief. Undertreatment of pain results in patients with a very poor quality of life and may lead to feelings of hopelessness and despondency.

Whereas undertreatment is the most common problem in cancer pain control, a few patients are overtreated with opioids. This may result in excessive side effects, such as somnolence, that can leave the patient unable to enjoy their life. The primary goal of cancer pain management is to relieve the patient's pain without such disabling side effects.

In summary, the goal of cancer pain treatment is to provide long-term, effective control of the patient's symptoms. Treatment should be adjusted so that the patient remains alert and largely free of side effects and able to enjoy life as much as possible. Unfortunately, these goals are not achieved for a substantial proportion of patients with cancer pain. Despite widespread educational efforts by the National

Cancer Institute, the World Health Organization, and other groups, many clinicians are still not entirely familiar with the correct principles of cancer pain management. Undertreatment of cancer pain and failure to treat associated symptoms with adjunctive medications remain a widespread problem.

Chronic Benign Pain Management

Chronic benign pain refers to pain caused by diseases or conditions that are neither fatal nor completely curable. There are thousands of causes of chronic benign pain; some common examples include

The goal of chronic benign pain treatment is to restore the patient to the highest degree of

- Rheumatoid arthritis
- Traumatic nerve injury
- Migraine headaches
- Chronic back pain
- Endometriosis
- Diabetic neuropathy
- Lupus erythematosus
- Sickle cell anemia

The goals of treating chronic benign pain vary depending on several factors including the temporal (over time) course of the patient's pain, the general type of pain (as discussed in the preceding section) associated with the condition, the patient's functional status, and the presence of associated factors. Some conditions, such as migraine headaches, cause only intermittent episodes of pain and can therefore be treated with short-acting opioids. Most chronic conditions cause some degree of constant pain, however, and are best treated with long-acting or sustained release opioids. Other conditions, such as those involving neuropathic pain, may be treated entirely without opioids.

Many patients with chronic benign pain are candidates for long-acting or sustained release opioid therapy. These patients are very likely to suffer depression, anxiety, and insomnia. However, significant differences exist between the treatment of chronic benign pain and that of cancer pain; therefore, these symptoms may be reated differently.

Patients with chronic benign pain are expected to have a near normal life expectancy; therefore, they will take medications for a longer period of time than some cancer patients. Their condition is not considered terminal, so the primary emphasis of management is on restoring the patient's ability to function. Controlling subjective symptoms is a secondary goal. For example, it may be acceptable for a cancer patient to sleep for 16 hours a day if he or she gets excellent pain relief. The same situation

would not be acceptable for a patient with chronic benign pain who needs to maintain gainful employment.

In addition, the diagnosis of most benign conditions depends on the patient's description of symptoms. A clinician can usually order tests to actually "see" a tumor, but there is no test to "see" a headache. The clinician depends on the patient's description of symptoms to make the diagnosis. Because of this, clinicians are always aware that some patients who want treatment for a chronic benign pain condition may not actually have that condition. Some of these patients may be actively seeking drugs for abuse or resale. Others may have significant psychological problems that lead them to seek medical care inappropriately.

Finally, many chronic benign pain conditions can be treated with a number of therapies, such as nerve blocks or physical therapy, either in addition to, or instead of, treatment with opioids. Some conditions respond very well to such therapies; others respond poorly.

These factors lead to a wide variation in how different clinicians and pain management practices treat patients with chronic benign pain. Some practices rely largely, or even entirely, on nonopioid therapies to treat chronic benign pain. In other practices, most patients receive long-acting opioid medications. This variation depends upon geographic location (some areas of the country still do not readily accept chronic opioid therapy for chronic benign pain), the individual clinician's training or background, and the type of patients seen in that practice.

In general, however, the goal of chronic benign pain treatment is to restore the patient to the highest degree of function possible. Because of the lifelong nature of the condition, high priority is given to avoiding side effects when possible and managing unavoidable side effects, such as constipation.

Pain Management Practitioners

You can communicate with a clinician about pain management much more effectively if you are aware of the perspectives the individual practitioner has before you call on him or her. Each specialist involved in treating pain has different training, perspectives, and techniques to offer. Perhaps the most obvious difference is the techniques each specialist is most likely to use. Most anesthesiologists, for example,

use nerve blocks in their practice quite frequently, whereas fewer non-anesthesiologist clinicians are trained to do those procedures.

The type of therapy the clinician normally uses will also differ depending on the type of condition he/she is treating. Cancer patients are usually treated primarily with opioids, and often with additional medications. Patients with chronic benign pain may be treated through several different therapies including psychotherapy, physical rehabilitation, nerve blocks, acupuncture, and medications.

A few psychiatrists, neurosurgeons, and orthopedic surgeons also specialize in pain management. The practice of oncologists and rheumatologists usually involves some pain management as part of their treatment of cancer and rheumatology patients, respectively. A newer specialty, known as palliative care, focuses on the treatment of patients near the end of life and in hospice settings. Palliative care clinicians come from several disciplines, including family practice and internal medicine.

Currently, subspecialty board certification for pain management is available for anesthesiologists, physical medicine, rehabilitation clinicians, and neurologists. Such clinicians often state that they are "fellowship trained", meaning that they completed a year or more of training specifically in pain management after completing a residency in their specialty.

Credentialing is available through the American Academy of Pain Management (AAPM) as well as the American Academy of Pain Medicine offering designations as a Diplomate, Fellow, or Clinical Associate. The credentialing for all levels requires at least two years of experience working with people in pain and a passing score on the AAPM credentialing test. The level of credentialing is based on education in a healthcare field, but not fellowship training. If these requirements are met, the credential of Diplomate is awarded to those who have a doctorate degree, a designation of Fellow is awarded if the individual has a master's degree, and a Clinical Associate designation is awarded to individuals with a bachelor's degree (or equivalent).

Clinician specialties involved in pain management

Anesthesiologists are commonly consulted to assist in the management of chronic benign pain patients. Many anesthesiologists limit their pain practice almost entirely to performing nerve blocks. Some only perform nerve blocks ordered by other practitioners and after the nerve block is complete, the patients return to the original

practitioner for follow-up care and medical management. Most anesthesiologists who specialize in pain management, however, offer a more complete therapy and follow-up care, including opioid and nonopioid medications.

Physical Medicine and Rehabilitation Clinicians are the fastest growing group of pain management clinicians. In addition to supervising physical therapy, these clinicians may also perform nerve blocks and most offer long-term medication therapy.

Medical Oncologists specialize in the diagnosis, assessment, and treatment of cancer. Some, but not all, oncologists have extensive experience in treating cancer pain. Most are comfortable with prescribing long-term opioid medications but may refer the patient to other clinicians when additional pain management techniques are needed. For most cancer patients with advanced disease, the medical oncologist functions as a primary care clinician and coordinates care until the patient dies.

Neurosurgeons provide surgical treatment of neurologic conditions that cause pain. They may also perform pain-relieving surgical procedures (such as spinal cord stimulation or implantation of medication pumps) in patients who have not had adequate relief of pain with other interventions

Psychiatrists can assist in the management of patients who are also suffering from psychoses, depression, anxiety, or confusion. They also provide supportive psychotherapy to help patients cope emotionally with pain. Psychiatrists involved in pain management have the option of obtaining subspecialty certification in pain management through the American Board of Psychiatry.

Palliative Care Clinicians generally provide end-of-life care to patients who are in hospice or who have terminal conditions. They generally prescribe opioid analgesics and other medication therapy and follow patients through a home health agency or hospice.

Radiation Therapists may be eventually involved in the treatment of cancer patients with advanced disease. The radiation therapist administers radiation treatment that can lead to invaluable relief of the pain due to bone metastasis or tumor growth. A few radiation therapists are also actively involved in cancer pain management and palliative care, but most limit their practice to administering radiation therapy.

General Surgeons and Orthopedic Surgeons provide treatment of medical and orthopedic diseases that can be corrected surgically. They generally provide acute

pain management in the immediate pre- and post-operative period. Orthopedic surgeons may be involved in the management of chronic arthritis pain or back pain, but often refer such patients to their primary care physician or a pain specialist.

Primary Care Physicians are increasingly more willing to provide pain management and prescribe opioids. Although some family physicians have at least basic training in pain management techniques, many do not. In direct contrast with pain specialists, family physicians usually only care for a small number of chronic pain patients at any time. It should not be surprising, therefore, that family physicians may report difficulties with managing both chronic benign and cancer pain patients.

Rheumatologists specialize in treating arthritis, rhematologic, and musculoskeletal disease. These diseases are often associated with chronic benign pain and part of patient disease management is management of the pain symptoms.

Internal Medicine Physicians provide primary care services to a wide range of adult patients. They treat many common illnesses and ailments, including problems such as chronic back pain. Internal medicine physicians may also opt for additional certification in subspecialty fields, such as palliative medicine or rehabilitation medicine.

Nonphysician specialties involved in pain management

Most licensed **nurses**, including nurse practitioners, have daily contact with patients in pain and play a valuable role in the administration of medications for pain relief. In many states, nurse practitioners are allowed to prescribe all schedule II medications. Nurses spend more time with patients than do any other health professionals, thus nurses' assessments of the adequacy of pain control measures and the incidence of drug side effects are extremely important. Other members of nursing staff, such as medical assistants, also provide valuable services in caring for pain patients and communicating information on response to pain medication and adverse effects of medication.

Home care or community nurses play a key role in managing pain patients at home or in hospice. They are sources of advice and information for patients and their treating clinicians and also provide general nursing care, psychosocial support, and symptom management to the patient.

Similarly, office nurses assume an important role in terms of assessment of a medication's effects on the patient's symptoms and quality of life. The physician's

opinion of a medication's effectiveness often is greatly influenced by the reports he or she receives from the office nurse.

Pharmacists, of course, dispense medications for pain patients. They also provide information about drugs to the clinician and the patient. The pharmacist may be the first person to recognize that a patient is over- or under-using his or her medication on the basis of the frequency of prescription refills. Most multidisciplinary pain centers include a pharmacist as a member of the treatment team.

Physician Assistants

Therapists provide an important adjunct in pain management, particularly in situations where movement provokes pain. They can be particularly helpful in the management of patients with back or muscle problems that are causing pain.

Chaplains and Clergy provide support for the patient and the family as they face difficult spiritual and psychological issues and may also help patients resolve guilt, fears, anger, and doubts. These members of the health care team are predominantly used in hospice and palliative care settings.

Psychologists provide counseling and teach relaxation techniques and stress management skills that help patients cope with their pain more effectively. They also work with family members, who often have trouble coping with their loved one's pain.

Alternative Medicine

Biofeedback monitors measure galvanic skin response, hemodynamic changes, and body temperature to increase patient awareness of and control over physiologic processes (such as muscle tension) that may contribute to pain.

Acupuncturists and Massage Therapists may also be useful in select patients. These therapies offer temporary relief of pain to many patients with somatic pain.

Interdisciplinary Team Approach

The interdisciplinary (often called multidisciplinary) team approach to pain management has been a widely accepted standard of pain treatment for decades. As previously mentioned , each type of medical specialist has expertise in certain pain treatment techniques and experience with certain types of patients. It has been recognized since the 1950s that the complex nature of pain management demands the efforts of a team of specialists if the best results are to be obtained.

A multidisciplinary team (Table 1-1) brings many diverse diagnostic and therapeutic skills to the management of a patient's pain. The composition of the team, which will vary from one pain treatment center to another, reflects a growing appreciation of the importance of treating the "whole patient" rather than just the primary symptom. The ultimate aim of the pain management team is to provide rational, integrated, and consistently effective care for every patient.

Table 1-1

The Interdisciplinary Pain Management Team

Patient and family members

Physicians:

- Anesthesiologist
- Physical Medicine and Rehabilitation Specialist
- Medical Oncologist
- Neurosurgeon, Neurologist
- Psychiatrist
- Palliative Care Specialist
- Radiation Therapist
- General Surgeon, Orthopedic Surgeon
- Primary Care Physician

Nonphysicians:

- Nurses (office, hospital, hospice, home care)
- Pharmacist
- Physical, Occupational Therapist
- Chaplain and Clergy
- Psychologist, Counselor, Social Worker
- Massage Therapist
- Acupuncturist

The physical location and makeup of the multidisciplinary team can vary considerably. Medical universities and large hospitals may have very large pain clinics or pain centers with dozens of clinicians and other health care professionals. Smaller pain clinics may have only 3 or 4 clinicians and a dozen or so employees.

Not every patient with pain requires the services of a multidisciplinary team. In some cases, a solo practitioner may be comfortable managing a pain patient. For example,

many oncologists manage pain quite effectively for most of their patients without needing the input of an entire team of specialists. Only those patients who do not get relief through a routine pain treatment protocol are referred to a specialist or multidisciplinary center. As a simple guide, a patient may be considered suitable for referral to a pain clinic or pain center when:

- Pain has persisted for more than six weeks despite attempts to manage the pain with oral medications.
- All appropriate diagnostic investigations have been conducted.
- The recommended treatment of the underlying condition has been shown to be ineffective in that patient.

Pain clinics work with patients who have pain problems that cannot be cured or managed adequately by individual health care professionals offering routine pain management. The pain clinic provides the patient access to clinicians and staff with experience and a variety of approaches to pain management that other medical providers cannot offer. A patient who is referred to a pain center will be adequately assessed and appropriately counseled about the potential benefits and limitations of the available treatment options. After the initial assessment, if the team feels the patient may benefit, the patient can be treated by the specific members of the pain management team who are most likely to be able to provide effective treatment.

The patient will at least be adequately assessed, appropriately counseled and treated. Pain clinics also facilitate the referral of patients to the specific members of the pain management team who are most likely to provide effective therapy.

Current Practice Patterns

Even though a multidisciplinary team is the ideal way to manage a patient with a difficult pain problem, actually organizing and maintaining such a practice can be difficult. Many managed care plans will not reimburse more than one clinician for treating the same patient. In other cases, the patient's insurance may allow certain specialties to bill for pain management, whereas others cannot. For these and other reasons, many pain treatment clinicians remain in solo or small group practice, despite the theoretic advantages of the multidisciplinary team. In such cases, the clinicians often maintain a multidisciplinary approach by referring the patient within a small group of individual consultants from different specialties, all of whom are involved in pain management.

Chronic Benign Pain

Several factors have influenced practice patterns in pain management over the last several years. Reimbursement changes made in 2000 and 2002 have had a dramatic effect on physicians who treat chronic benign pain. These changes have led many physicians, particularly anesthesiologists, to no longer accept patients for chronic medication maintenance. Some pain centers only accept patients for a 90- or 120-day "diagnosis and treatment evaluation", after which the patient must find a primary care provider willing to write prescriptions for his or her medications. Almost half of all pain centers no longer accept any Medicare or Medicaid. Further reimbursement cuts instituted in 2007 are likely to lead to further cutbacks in care available for these patients.

Many pain treatment physicians who perform procedures such as surgery or nerve blocks now focus on those procedures because they are reimbursed at much higher rates than are office visits. In some cases, this has resulted in fragmenting of pain centers with the "invasive" physicians practicing separately from the "medication" physicians. For the same reasons, some primary care and palliative care physicians now provide medical management and chronic opioid prescriptions to chronic benign pain patients, simply because pain specialists are not willing to do so.

Beginning in 1999, the diversion and abuse of opioids, particularly OxyContin®, led to a widespread focus of attention on prescription drugs. Federal and local drug enforcement agencies arrested many physicians who had participated in drug diversion and some who simply overprescribed opioids or kept poor records of the prescriptions and pain patient's diagnosis and response to therapy. In reaction, many physicians have become reluctant to prescribe opioids for medical problems other than acute and cancer pain. Most, however, continue to prescribe opioids when they are indicated, although they exercise greater caution to prevent diversion.

Cancer Pain

Cancer pain can be the result of the disease process itself or from the treatment for the disease. About two-thirds of patients with bone metastases have severe, debilitating pain. Of these, about a fourth continue to have pain despite analgesic therapy. Pain from the effects of the disease on the viscera as well as pain from the treatment of the disease (scarring, neuropathic pain, radiation injury) is also common.

As many as 60% of cancer patients have inadequately controlled pain, yet opioid therapy, given in conjunction with dose titration and frequent assessment, offers pain control in up to 90% of patients. (Cleeland 2005, Koizumi 2004) Despite the availability of effective pain medications and pain management guidelines, a number of studies have demonstrated that cancer pain remains undertreated. Barriers to adequate treatment include physician under-estimation of patient's pain, inadequate assessment, and a reluctance on the part of patients to report pain. (Gralow J 2007, Shaiova 2006)

Palliative Care and Hospice Care

Cancer pain management can be divided into 1) management during active anticancer therapy, which is usually handled by the treating oncologist, and 2) end-of-life pain management. End-of-life care has increasingly become managed by palliative care clinicians who work through hospice agencies. Although some hospices are actual buildings, most are home health agencies that provide terminal care to the patient at home.

According to the National Association for Home Care and Hospice, there were 3078 active hospice programs in the United States. More than 894,000 Medicare beneficiaries receive hospice care each year, 43% of whom have cancer. However, it is not necessary to have cancer to receive hospice care; anyone with a terminal illness is eligible.

There are three generic criteria for admission of terminally ill patients to hospice:

- Completion of all active curative treatment.
- Patient's awareness of the terminal nature of his or her condition.
- Patient and family's clear understanding of the goals of hospice care.

Medicare also requires that the person have a life expectancy of approximately six months or less. However, 15% of hospice patients live longer than six months.

Hospice agencies provide complete symptom management, but do not provide any curative treatments. Cost-effective treatment is extremely important to hospice providers, because Medicare pays the hospice organization a per diem of approximately $118 for every day the patient spends in home-based hospice care. The hospice organization is responsible for paying all of the patient's expenses from that amount, including hospital bills, lab tests, clinician's visits, and medications. For

this reason, hospice providers and palliative care clinicians attempt to use long-acting or sustained release oral opioids whenever possible and avoid more expensive intravenous medication.

Barriers to Effective Pain Control

Despite the improvements in pain management that have occurred over the past decade, several barriers to effective pain control remain:

- Fear of addiction
- Lack of education about pain and pain control
- Opioid phobia
- Fear of legal or regulatory action

Fear of Addiction

Fear of addiction to opioids remains a major obstacle to effective treatment for pain. Unfortunately, few clinicians and even fewer patients understand exactly what addiction (which is more properly termed "substance abuse") is. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders defines substance abuse as "a maladaptive pattern of use of a chemical substance that significantly interferes with the person's life". It is important to recognize that tolerance and dependence (discussed above) do not indicate addiction. Rather, they are an expected consequence of taking opioids in

Table 1-2

Signs Associated with Substance Abuse

- Repeated requests for short-acting medications (e.g. a short-acting opioid in tablet-form that is chewed or broken).
- Repeated requests for early refills, especially when the patient has "typical" excuses such as "the pills fell in the toilet", "the dog ate them*", "someone stole my medicine".
- Frequent telephone calls, particularly after hours or on weekends.
- Frequent requests to change medication because of side effects or lack of efficacy.
- More than a single incidence of other physicians prescribing opioids.
- Past history or family history of substance or alcohol abuse.
- History of preexisting psychiatric illness, especially bipolar disorder, schizophrenia, or personality disorder.
- Social history of dysfunctional or high-risk behaviors including multiple arrests, multiple marriages, abusive relationships, etc.

* unless the dog is very large, eating a bottle of prescription opioids should result in the pet's untimely demise.

moderate to high doses for a significant length of time.

Proper use of opioids is not "maladaptive" nor does it "interfere with the person's life"; instead, it allows the patient to return to a functional life. However, some chronic pain patients do have a substance abuse problem (Table 1-2).

The problem is even more complex because some patients who are undertreated for their physical pain show the symptoms of "pseudoaddiction". Pseudoaddiction is a set of behaviors (Table 1-3) that are exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors are not signs of substance abuse, but rather should be considered symptoms of inadequate treatment.

Lack of Education about Pain and Pain Control

In their medical training, doctors typically receive only a few lectures on the subject of pain management. Many practitioners are therefore not comfortable with assessing pain complaints and prescribing the proper treatment. Some of the areas in which misunderstandings about the evaluation and management of chronic pain commonly occur are pain assessment and underuse and underdosing of opioids.

Pain Assessment

Pain is a subjective experience that may or may not correlate with the observer's perception of underlying pathology. It is not unusual for clinicians to minimize a patient's pain complaints and therefore prescribe inadequate amounts of opioids. Pain assessment instruments such as the visual analog or verbal rating scales may help patients to communicate the presence and severity of pain. Information about the characteristics of pain (i.e., pain location and quality, temporal pattern of the pain, and response to any previous treatment) may also help to refine treatment. (Berry 2000) The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has issued pain assessment recommendations that include performing an initial pain screening assessment, a more comprehensive pain assessment if pain is identified, and collection of data to monitor the appropriateness and effectiveness of pain management. A visual analog scale is often used to accomplish this task.

Underuse and Underdosing of Opioids

Oral administration of opioids often fails because the patient is not given a high enough dose of medication. This is quite likely to occur when the patient is switched from intramuscular or intravenous routes to the oral route or when a different opioid is substituted. Clinicians should refer to equianalgesic charts and titrate the dose to

the individual patient. Clinicians can also consult pharmacists for advice regarding changing opioids and determining equianalgesic dosing.

Opioid Phobia

An irrational fear of using opioid analgesics is a fairly common cause of undertreatment of pain. Opioid phobia can be exhibited by patients, their families, health care professionals, legislative and regulatory agencies, governments, healthcare insurers, and societies as a whole. Its end result is unavailability and underutilization of opioids, and its victim is the inadequately treated patient with pain.

Fear of Legal or Regulatory Action

Since 1999, government agencies and state medical boards have arrested and disciplined doctors with increasing frequency for improper prescribing. The vast majority of these actions have involved criminal selling of prescriptions by doctors or overprescribing of massive amounts of controlled substances without proper documentation. Unfortunately, many ethical clinicians have become fearful of prescribing opioids after learning of these incidents.

In reality, regulatory agencies have focused on those drugs with the highest diversion potential and street value. In the 2005 Drug Abuse Warning Network (DAWN) report, hydrocodone, oxycodone, and methadone were the most frequently abused prescription opioids. (US Depart. of Health and Human Services 2005)

NOTE: Any opioid can be abused in an individual case, and you should never state that one opioid is "safer" or "less abusable" than others. It is more appropriate to quote current data on the frequency of abuse or the street value of the different opioids, which corresponds with the demand for diversion of that product. For example, at the time that this manual was prepared, oxycodone and hydromorphone had very high street values, whereas time-release morphine preparations had very low street values. Current statistics are maintained on the web pages of the National Institute on Drug Abuse (www.nida.nih.gov), the Drug Enforcement Agency (www.dea.gov), and the National Criminal Justice Reference Service (www.ncjrs.gov).

Summary

Pain is a primary symptom of many different diseases. The treatment of pain can be simple and straightforward or extremely complex. Some patients may be well managed by their primary care clinician, whereas others require the efforts of a team of specialists representing a variety of disciplines. Clinicians that are often involved in pain care include primary care clinicians, palliative care clinicians, oncologists, physical medicine specialists, anesthesiologists, neurologists, nurse practitioners, physician assistants, and surgeons. Additionally, invaluable assistance in the care of these patients may be provided by nurses, physical therapists, psychologists, pharmacists, clergy, acupuncturists, massage therapists, and others.

The type of care the patient receives differs depending on the type of pain (chronic benign or cancer), the cause of pain, and other factors, such as the presence of depression, whether the pain is visceral, somatic, or central and whether the pain is acute or chronic. Other factors include: home life, social/economic status, etc.

Although some progress has been made in providing good pain control to every patient, many factors still interfere with pain management. These include inadequate education of health care providers, fear of regulatory action by clinicians, and inappropriate fear of addiction.

Resources

American Academy of Pain Management
http://www.aapainmanage.org/

American Academy of Pain Medicine
http://www.painmed.org/

The American Chronic Pain Association
http://www.theacpa.org/

American Pain Foundation
http://www.painfoundation.org/

American Pain Society
http://www.ampainsoc.org/

Pain Balance (Alpharma)
www.painbalance.org

National Institute of Neurological Disorders and Stroke
http://www.ninds.nih.gov/disorders/chronic_pain/chronic_pain.htm

National Institute on Drug Abuse
http://www.drugabuse.gov/

American Society for Pain Management Nursing
http://www.aspmn.org/

The American Society of Anesthesiologists
http://www.asahq.org/

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Self-Assessment Test

Circle the best response

1). The medical term for painful sensation is
   a. Neuropathic
   b. Nociception
   c. Viscerosation
   d. Anesthesiologist

2). The nerve fibers that travel from the brain and modify the pain response by secreting neurotransmitters that chemically resemble opioids make up the
   a. Descending pathway
   b. C-fibers
   c. Synapse
   d. Drug Enforcement Circuit

3). There is a consensus among experts that cancer pain can be well controlled in what percent of patients through the use of noninvasive, low-technology approaches?
   a. 8%
   b. 18%
   c. 50%
   d. 80%

4). The primary goal of pain management for chronic benign pain is to restore the patient's
   a. Ability to function
   b. Pain-free state
   c. Home life to normal
   d. Finances

5). Opioid_____is an irrational fear of using opioid analgesics.
   a. Overprescribing
   b. Addiction
   c. Tolerance
   d. Phobia

6). Hospice services are primarily provided at
   a. Major hospitals
   b. Small community based hospitals
   c. Clinician's offices
   d. The patient's home

7).Which of the following statements are TRUE?
   a. Substance abuse may be characterized by "a maladaptive pattern of use of a chemical substance that significantly interferes with the person's life"
   b. Opioid tolerance refers to the need for increased doses of the medication to achieve the desired pain relief.
   c. Opioid dependence means that the patient develops physical dependence and a withdrawal syndrome will develop if the opioid medications are stopped suddenly
   d. All of the above?

8). Which of the following are NOT barriers to effective pain control?
   a. Fear of addiction
   b. Lack of clinician education
   c. Development of tolerance
   d. Fear of regulatory action

9). True or False – Visceral pain arises from muscles, joints, and tendons.
   a. True b. False

10). Neuropathic pain arises from damaged nerves.
   a. True b. False

11). Somatic pain is usually sharp, stabbing, or aching in nature
   a. True b. False

12). Somatic pain responds to opioids better than neuropathic pain does.
   a. True b. False

13). Anesthesiologists make up the majority of pain specialists.
   a. True b. False

14). Most cancer patients receive their pain medication from family practice clinicians.
   a. True b. False

Answers to Self-Assessment Test

1) b	8) c
2) a	9) b
3) d	10) a
4) a	11) a
5) d	12) a
6) d	13) a
7) d	14) b

CHAPTER TWO

Clinical Evaluation of Pain

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the frequency of both chronic benign and cancer pain.
- List at least 6 adverse effects of chronic benign pain.
- Describe the basic steps in the initial assessment of a patient in chronic benign pain.
- Understand the difference between intensity and characteristics of pain.
- Understand the benefits of psychological assessment of patients with chronic benign pain.
- Know the common types of psychological factors that may influence chronic benign pain.
- Understand the indication for performing diagnostic tests in patients with chronic benign pain.
- Understand that ongoing evaluation of treatment is necessary.

Terminology

Inflammation:	Pain, redness and possible swelling due injury or infection.
Pain behaviors:	Exaggeration or magnification of the effects of pain.
Psychological:	Originating from the conscious or subconscious mind.
Physiologic:	Originating from the physical processes of the body.
Neurological:	Originating from the nerves or nervous system.
Socio-environmental:	Originating from, or strongly influenced by, social or environmental pressures.
Somatoform disorders:	Psychological conditions that produce medically unexplainable physical complaints even though there is nothing physically wrong with the patient.
Temporal:	The course of a situation or circumstance over time.

Introduction

Chronic benign pain results not only from the patient's physical problems, but also as a result of the complex emotional factors that the patient and family experience. The key to effectively managing chronic benign pain is a thorough assessment and proper diagnosis. Only when all of the factors contributing to the patient's pain are known can effective treatment be given. This module focuses on the key parts of the chronic benign pain assessment.

- Initial assessment of the pain with a focus on identifying the cause
- Assessing the pain intensity
- Assessing the characteristics of the pain
- Psychosocial assessment
- Past medical history
- Physical examination
- Diagnostic tests
- Evaluation of treatment

The Scope of Chronic Benign Pain

Chronic pain (including both chronic benign pain and cancer pain) is a common, and largely unrecognized problem in American society. Even 20 years ago, chronic benign pain was found to be the country's most costly health problem. The problem has increased since then as the average age of the population has increased. Currently, about 75 million persons suffer from some form of chronic benign pain, and the total costs of chronic benign pain are estimated at 90 billion dollars a year.

About 50% of all hospital patients and 40% of all patients seen in general practice clinics suffer from at least one type of chronic benign pain. Between one-third and one-half of these chronic benign pain sufferers have pain severe enough to require daily medication. Low back pain is the most common cause of disability in persons under 45 years of age and affects more than 8 million Americans.

About 50% of all hospital patients and 40% of all patients seen in general practice clinics suffer from at least one type of chronic pain.

Although the number of persons who suffer from cancer pain is far smaller than the number suffering from chronic benign pain, it still is a big problem. Cancer is diagnosed in about 1 million Americans per year. With the increased length of survival due to modern cancer treatment, almost 10 million persons have a diagnosis of cancer at any one time, and most of them experience some degree of chronic pain.

Unfortunately, the treatment these patients receive is largely using the acute pain model, which is often inadequate for treating chronic benign pain. Chronic pain not only affects bodily functions it also causes anxiety and depression, results in numerous unsuccessful medical interventions, disrupts family lives, and causes financial and social problems for the sufferer. Unlike acute pain, the severity of chronic benign and cancer pain cannot be accurately predicted by observing obvious tissue damage. An individual's perception of pain is a complex phenomenon that involves psychological and emotional processes. Pain perception is a far more complex process than the simple activation of nociceptive (pain-sensing) pathways in the nervous system (see Chapter 1).

For most chronic benign pain patients, the proper treatment of their condition, while rarely curative, can markedly reduce suffering and improve ability to function. However, it must always be remembered that there is no single approach that

effectively treats all types of chronic benign pain. Instead, an individualized pain management plan must take into account the type of disease, characteristics of the pain, concurrent medical problems, and the psychological and cultural characteristics of the patient.

To individualize the patient's therapy, a thorough and complete evaluation of the condition must be made. Failure to properly evaluate the condition results in repetitive, unnecessary tests and procedures, which carry risks for complications and increased medical care costs.

Initial Pain Assessment

The initial assessment should focus on identifying the cause of the pain, which in turn leads to the development of a pain management plan. The initial evaluation of pain should include a detailed history and an assessment of the pain's intensity and characteristics. A physical examination, emphasizing the neurological examination, should be performed. At least a brief psychosocial assessment should be obtained in every patient, with a more in-depth evaluation performed on those with obvious emotional or psychological symptoms. Depending on the information found by the evaluation, further diagnostic tests may be required to determine the cause of the pain.

Attention to detail is important as a delayed or incorrect diagnosis results in increased morbidity and needless pain and suffering. The evaluation should begin by obtaining a complete description of the patient's pain. The following information is needed:

- *Intensity* – How much does it hurt right now? How much does it hurt at its worst? How much does it hurt at its best?
- *Location*- What part of the body hurts?
- *Onset and temporal pattern* – When did the pain start? How often does it occur? Does its intensity change over time?
- *Description* – What words accurately describe the pain?? Does the pain start in one area and travel to another?
- *Aggravating and relieving factors* – What makes the pain better or worse? What other symptoms occur with the pain?
- *Previous treatment* – What types of treatments have you or your health care provider tried in relieving the pain? Have you used any nonprescription methods or medications to relieve the pain? Were any of these

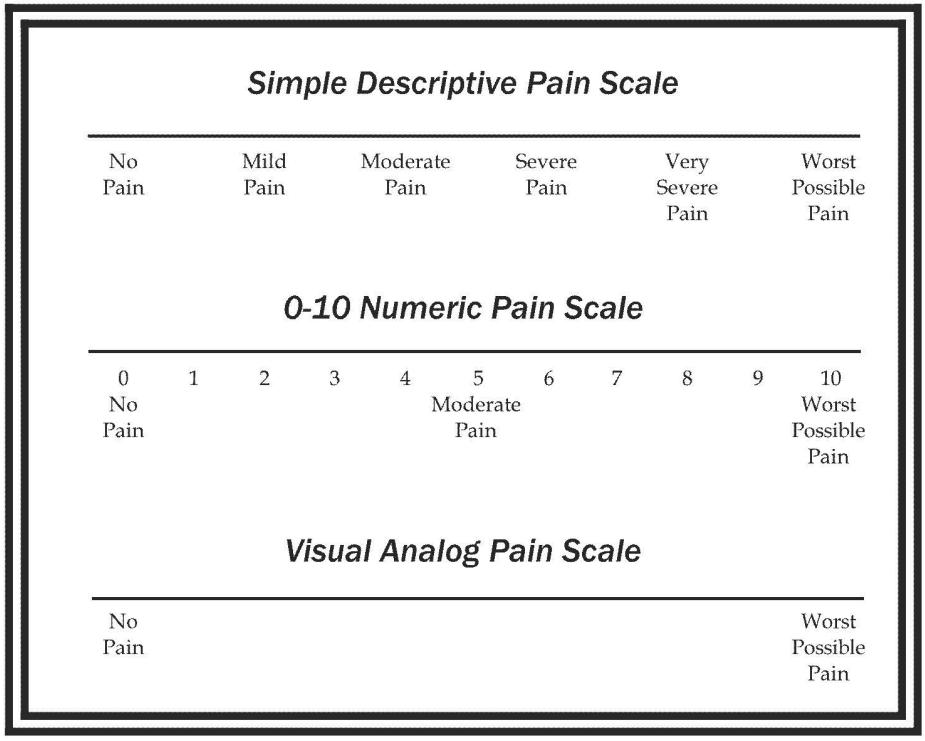
treatments effective?

- *Effects* – How does the pain affect mood, physical function, and social function?

Assessing Pain Intensity

One effective method of assessing pain intensity is to provide the patient with a visual scale, examples of which are shown in Figure 2-1. The patient is asked to grade the intensity of pain on the basis of the scale. Although all of the scales shown in Figure 2-1 are still in use, the Visual Analog Scale (VAS) has been validated and is considered to be the most reliable.

Figure 2-1.



Assessing the Characteristics of the Pain

A complete assessment of acute pain often consists of little more than some form of pain severity score. The cause of pain is usually obvious (e.g., the broken bone or surgical incision), and the severity of pain is usually proportional to the physical damage. The pain assessment simply shows how effective the pain treatment (usually a short-acting opioid) is.

In contrast, chronic benign pain and many cases of cancer pain include physiologic, neurological, psychological, socio-environmental, and learned behavior components. Some patients with chronic pain will have an obvious cause of pain, but simply relieving that physical abnormality (if it is possible) will not completely relieve the patient's pain. This does not in any way mean that the pain is psychological. Most studies indicate that chronic benign pain, no matter what the original cause, eventually causes abnormalities to develop in the nervous system, vascular system, and/or musculature. Over time, these abnormalities will eventually worsen the patient's pain. Even if the source of the original pain is relieved, these secondary abnormalities are sufficient to cause continued pain.

There are physiologic, neurological, psychological, socio-environmental, and learned behavior components in every case of chronic benign

In addition, most persons with chronic benign pain will have some psychological symptoms (depression, anxiety, etc.) in addition to their pain. Many patients, despite their best intentions, will also have unconsciously learned to use their pain to manipulate others to some extent, as a way to avoid unpleasant situations. Over time, family members become focused on the patient and family life begins to revolve around the affected person's pain. These behavior changes can develop in even the most well-intentioned individuals.

For these reasons, the assessment of chronic benign pain is more complex than the assessment of acute pain. Although the severity of chronic benign pain is assessed in the same way as that of acute pain, the severity score alone is not a very useful measurement for chronic benign pain. In acute pain, the measure gives the physician guidance on how much or what type of pain medication to offer the patient. However, with chronic benign pain, saying "Mrs. Smith has had bad pain" is like saying "Mrs. Smith is awake". It is already clear from the context of the situation that the chronic benign pain is severe enough to be a problem for the patient. Documenting change of

pain severity in a patient with chronic benign pain is more useful as an indicator of how effective a given treatment is for that patient.

Whereas it is usually relatively easy to determine the location of pain, assessing the characteristics, or description, of the pain can be quite difficult. Because many patients find it difficult to describe their pain spontaneously, an adjective checklist (Appendix 2-1) is often used to assess the characteristics of a patient's pain. This description of the pain's characteristics may be the most important information obtained during the initial evaluation. For example, burning, hypersensitivity, and electric shock sensations are associated with neuropathic pain, whereas cramping sensations are associated with visceral pain (see Chapter 1). Aching or throbbing pains are characteristic of somatic damage involving muscles, bones, or tendons. The use of certain adjectives, such as "sickening" or "punishing" are associated with significant emotional distress rather than physical problems. Vague or changing descriptions of the area that hurts may indicate that a large emotional component is involved in the patient's perceived pain. Vague symptom description can also occur with central pain syndromes, such as those that develop in some stroke patients (see Chapter 1).

Vague or changing descriptions of the area that hurts may indicate that a large emotional component is involved in the patient's perceived pain.

Also important is the temporal (over time) course of the pain and its association with certain activities. Pain that is worse in the afternoon and evening or worse after activity, for example, may be associated with inflammation of the joints, muscles, and tendons. The combination of the pain's characteristics with its temporal course provides valuable clues concerning the physical source of the pain. Aching, throbbing pain that is worse in the morning and evening may be associated with arthritis and certain muscular diseases. Tingling pain that shoots down the leg with certain movements may indicate compression or damage to the nerves in the lower spine.

Psychosocial Assessment

Patients with cancer, and most patients with chronic benign pain, have real, physical causes for their pain that are due to their cancer or treatment. However, many also have some psychological factors that modify their perception of pain. Certainly, depression and anxiety are to be expected when a person suffers near constant pain, or sudden, unexpected episodes of severe pain.

Between 20% and 25% of cancer patients meet the psychiatric criteria for major depressive syndrome during at least part of their illness. About 20% also report that they suffer anxiety that is severe enough to interfere with their ability to function. The incidence of both problems is even higher in patients with chronic benign pain.

Whether the psychological factors existed before the patient developed chronic benign pain, or only after they become debilitated by their condition, is not important. However, it is extremely important to identify and treat these factors. If they are not identified and treated, relieving the patient's pain may be impossible. Many patients find it difficult to say (or even feel) that they are depressed, lonely, or sad. Such persons may instead simply ask for more pain medication. They may only recognize the pain or may be attempting to relieve their emotional distress by taking advantage of the sedating or euphoric effect of opioids. This may lead the physician to inappropriately increase the medication dosages, potentially leading to excessive side effects.

A formal psychiatric or psychological evaluation is usually not necessary for the evaluation of patients with chronic pain. Many centers will administer a few brief written questionnaires that accurately detect depression and major psychiatric problems. These brief evaluations depend upon the physician's experience to determine which patients need in-depth psychiatric or psychological evaluation.

Formal psychotherapy is rarely required for chronic pain patients, but treatment with medication to relieve depression and anxiety is often necessary. Support groups or individual counseling to help the patient learn new coping skills may also be helpful. Cancer patients, in particular, often benefit from family counseling or group support.

Somatoform Disorders

Although most patients with chronic benign pain experience some psychological symptoms, in a few cases the psychological problems are actually the primary cause of the chronic pain. These psychological conditions are the somatoform disorders, a group of psychological conditions that produce medically unexplainable physical complaints. These patients do not consciously feign or lie about their symptoms; they truly experience the symptoms and therefore believe they have a physical illness. Somatoform patients often "doctor hop" from physician to physician, undergoing a multitude of repetitive diagnostic tests and even exploratory surgery in an attempt to determine a cause for the pain. As many as 5% of the patients evaluated for chronic benign pain actually have somatoform disorders.

Past Medical History

The past medical history can be quite complex in a patient with chronic benign pain. In addition to the usual information, such as past surgeries, medical illness, and family history of illness and allergies, a complete history of the pain problem should be obtained. This must include past efforts to diagnose the problem and a complete listing of those tests. It is important to know which treatments have been tried, both to avoid repeating unsuccessful treatments and failure to respond to certain therapies may provide clues about the nature of the problem.

Physical Examination

The physical examination should include careful examination of all painful sites described by the patient and a complete neurological evaluation. Palpation (feeling and pressing) of the painful area may help the examiner to determine exactly which anatomical structures are involved in the pain process. Moving the patient's major joints or spine may demonstrate damage to these structures or compression of nearby nerves.

Common sites of pain referral should also be evaluated (e.g., shoulder pain may emanate from abdominal sources; knee and hip pain may be referred from lumbar spine lesions). In addition, the patient should be observed for cues that indicate the source of pain, such as distorted posture, impaired mobility, guarding (bracing against or resisting the touch of the examiner) the painful area, or restricted movement of a

limb. The patient should also be observed for signs of anxiety, attention seeking, or depression.

Pain Behaviors

Because pain is subjective, the examiner will use several clues to help determine if the patient is reporting accurately. One type of clue is the presence of "pain behaviors". Pain behaviors are generally considered dysfunctional behaviors and are common in chronic pain patients. During the physical examination, these behaviors manifest as a magnification of symptoms out of proportion to any possible illness, hyperemotional responses, or exaggerated responses to simple questions. Although these behaviors are emotional in nature, they do not usually indicate psychological problems. Rather, they are learned behaviors, which sometimes develop when patients are convinced that people do not believe how severe their pain is or in order to manipulate others. The presence of these behaviors, however, will alert the physician that the patient may not be reporting symptoms or answering questions accurately.

Pain behaviors usually involve magnification of symptoms out of proportion to any possible illness, hyperemotional responses, or

Behavior Consistency

Another factor evaluated during the physical examination is verbal-behavior consistency. This simply means that the patient's actions and words match up. If the patient says, "I'm in agony" while smiling and talking on a cell phone, that's not consistent. Temporal consistency of behavior means that actions do not change inappropriately over time or in different circumstances. If a patient winces, grimaces, and can barely stand when the nurse is in the room but is chatting amiably while waiting for the elevator 5 minutes later, he or she is not exhibiting temporal consistency of behavior.

Finally, the examiner will note the specificity of requests for treatment to identify patients who are drug seeking. "Nothing but Dilaudid will relieve my pain" or "only injectable medicine works on me" are potential signs of drug-seeking patients, but may in fact be a patient being truthful with their healthcare provider, after trying various medications.

Diagnostic Tests

The purpose of diagnostic tests, such as X-rays, CT or MRI scans, and laboratory tests, differs between chronic benign pain patients and cancer patients. In cancer patients, the major purpose is to visualize the spread of tumor (or absence of tumor), which allows the oncologist to determine what treatment, in addition to symptom management, is needed. Diagnostic tests frequently provide invaluable information for cancer patients. In chronic benign pain, however, the major purpose of diagnostic testing is to rule out the presence of any disease for which there is a curative treatment. In most cases, no curable disease will be found, but it is important to be absolutely certain that this is the case. Once all treatable causes of the pain have been eliminated, the pain specialist can begin to manage the patient's symptoms.

Evaluation of Treatment

Once a therapy has been prescribed, the patient's improvement (or lack of improvement) must be monitored. Although this would seem quite simple, in reality it can be rather complex for two reasons: First, pain treatment rarely results in complete and total pain relief, so patients will rarely volunteer that a treatment worked completely. The question becomes "is the pain improved, and is the improvement sufficient?" Numeric or visual analog pain scores are very useful ways to judge improvement.

Secondly, chronic pain, whether from cancer or benign causes, normally waxes and wanes over time. Therefore, it may be difficult to tell whether improvement is from a recently started medication or is just the normal change in pain severity that occurs over time. The use of a "pain diary" in which the patient marks his or her pain level several times each day can be an effective way of determining how much relief is obtained from a given treatment.

When discussing pain assessment and control with patients, members of the health care team should emphasize the importance of a factual report, avoiding either minimizing or exaggerating symptoms. If anxiety or depression is significant, patients should be asked to rate their emotional distress separately from their pain by using similar scales. When discrepancies between behaviors and self-reports of pain occur, these differences should be discussed with the patient and the pain management plan should then be revised.

Clinicians should be aware of the unique needs and circumstances of patients from different age groups or from various ethnic, cultural, and educational backgrounds. Certain cultures have strong beliefs about pain and its management. Members of some cultures may hesitate to report unrelieved pain, whereas others readily complain about even the most minor unrelieved pain.

It is also important to ask the patient about improved ability to function. Some persons will report that their pain level remains high, but when questioned further, it becomes apparent that they are engaging in activities that were not possible before beginning medication. Family members should also be questioned about changes in activity level and any side effects that they may have observed in the patient.

Summary

The first step in the management of chronic benign pain is a comprehensive clinical assessment. By specifically evaluating the pattern and type of pain and diagnosing the likely specific causes of the pain, the clinician is taking a major step toward relieving the patient's discomfort.

The initial evaluation of pain should include a complete history including assessment of the intensity, location, temporal course, and characteristics of the pain. A psychological assessment, physical examination, and a review of diagnostic tests should be done. During the evaluation, the physician should also evaluate the patient for consistency between the patient's behavior and the patient's subjective complaints.

Once treatment has begun, therapy is evaluated by using numerical or visual scales of pain severity. It is also important to ask the patient and family about side effects and whether the patient's functional status has improved.

Self-Assessment Test

Circle the best response

1). What percent of patients seen in a general practice office suffer from some type of chronic pain?
   a. 10%
   b. 20%
   c. 40%
   d. 60%

2). How many persons in the U.S. have cancer at any one time?
   a. 100,000
   b. 1,000,000
   c. 10,000,000
   d. 3,418

3). The cost of chronic pain in the U.S. is about
   a. 9 billion dollars a year
   b. 19 billion dollars a year
   c. 90 billion dollars a year.
   d. 900 billion dollars a year.

4). What percent of cancer patients with pain meet the criteria for major depression?
   a. 10%
   b. 25%
   c. 50%
   d. 75%

5). Is the number above higher or lower for patients with chronic benign pain?

6). Psychological disorders that can cause a patient to experience physical symptoms and pain are called_____.
   a. Somatoform disorders
   b. Obsessive Compulsive disorders
   c. Malingering
   d. Anorexia

7). Pain behaviors are:
   a. The expected symptoms of a person in chronic pain
   b. Repetitive actions likely to cause injury or pain
   c. Exaggeration or magnification of the severity or effects of pain
   d. Changes in family dynamics that revolve around the pain patient

8). Which of the following types of behavior suggests that a patient's pain complaints are valid?
   a. Temporal consistency in behavior in response to pain
   b. Requests for only specific pain medications
   c. Verbal descriptions of pain that are out of proportion to physical findings
   d. All of the above

Answers to Self-Assessment Test

1). c	5). higher
2). c	6). a
3). c	7). c
4). b	8). a

Appendix 2-1

McGill Adjective Checklist for describing pain

Please circle the appropriate number, telling us how severely you experienced the symptom described by each of the following words over the last week. If the symptom does not describe your pain at all, circle 0 (none).

	none	mild	moderate	severe
throbbing	0	1	2	3
shooting	0	1	2	3
stabbing	0	1	2	3
sharp	0	1	2	3
cramping	0	1	2	3
gnawing	0	1	2	3
hot/burning	0	1	2	3
aching	0	1	2	3
heavy	0	1	2	3
tender	0	1	2	3
splitting	0	1	2	3
tiring/exhausting	0	1	2	3
sickening	0	1	2	3
fearful	0	1	2	3
punishing/cruel	0	1	2	3

CHAPTER THREE

Chronic Pain Treatment

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the commonly used pain therapies.
- Explain the basic principles of pain management.
- Describe 3 types of nonopioid analgesics.
- State the difference between opioid agonists, antagonists, and agonist-antagonists.
- Review the most frequently used opioid agents.
- Understand the advantages and disadvantages of each controlled-release opioid preparation.
- Examine the various conditions in which opioids and nonopioids are most commonly used.
- Discuss the use of adjuvant drugs used to augment opioids.
- Understand the principle of dose titration.
- Discuss the use of nonpharmacologic interventions for pain control.

Terminology

Abuse :	The use of a prescription medication in a manner other than that for which it was prescribed. This can include recreational use of a prescription drug.
Acupuncture:	A procedure that originated in Far Eastern medical traditions that involves inserting needles into specific locations of the body to relieve pain and other symptoms. This is different than dry needling and moxibustion.
Adjuvant	Adjuvant drugs are medications that are not analgesics, but that may reduce pain or improve other symptoms associated with chronic pain. The term adjuvant itself means an aid or assistant and the adjuvant drug is typically given as an additional medication to augment pain control.
Adsorption:	A process by which a thin layer of a material is attached to another, as when molecules of medication are attached to beads. This term is similar in spelling, but different in meaning, to the more familiar term, absorption.
Agonist:	a drug that binds with a receptor on a cell and initiates the same reaction or activity produced by the binding of an endogenous substance.
Agonist-antagonist:	Medication that has one effect at low doses and a different effect at higher doses. For example, at low doses, the drug may act as an agonist, but acts as an antagonist at higher doses. Example: Buprenorphine
Analgesic ceiling effect:	Opioid analgesics theoretically have no limit to the analgesic effects mediated by the mu receptor. However, opioids stimulate additional receptors that cause side effects that limit the maximum dose that can be given. For example, while morphine could theoretically be titrated upward indefinitely to control pain, high doses can cause respiratory depression, thus the actual maximum dose that can be given is limited by the risk of respiratory depression (and/or other side effects).
Anatomical pathology:	The actual physical disturbances in the body. For example, a broken leg is the anatomical pathology and leg pain is the symptom.
Anorexia:	Lack of a desire to eat. (The term is similar to 'anorexia nervosa' but these are different medical conditions.)
Antitussive:	Effective at relieving coughing. Anti-tussive effects associated with opioids are due to μ-receptor and possibly κ-receptor stimulation.
Baseline dose:	A dose of pain medication that is given consistently to achieve an acceptable level of pain control in a given patient. The pain control is effective most of the time in most situations but may require supplementation (e.g., the pain relief is effective during both the peaks and troughs of the serum drug levels).

Biliary colic:	Pain due to an obstruction(and subsequent increases in pressure) in the gallbladder or bile collecting system in the liver. This medical condition can be an adverse effect of opioid drugs. A few opioids, such as meperidine, fentanyl, and butorphanol, produce less pronounced increases in biliary tree pressure than morphine.
Bioavailability:	The degree to which a drug will become available in the system after it is taken orally or injected (parenterally).
Biphasic absorption pattern:	An absorption pattern of a drug that demonstrates two phases, with two distinct and separate serum drug peaks.
Bleeding time:	The amount of time it takes blood to clot.
Circulatory depression:	A reduction in the activity of the heart and normal tone of the blood vessels and can be a side effect of opioids. The clinical findings are low blood pressure and a slow pulse.
Congener:	(also spelled cogener) A substance that is chemically related to another.
Conjugation:	One of the metabolic processes performed by the liver to deactivate drugs in preparation for elimination. A drug changed by this type of metabolism is sometimes referred to as a conjugate.
Controlled-release drug:	The rate at which an oral drug is absorbed depends partly on how quickly it is dissolved in and absorbed from the digestive tract. A drug can be chemically altered (e.g. the pH is altered, causing absorption to be delayed) or placed into a delivery system that alters the rate of release of the drug into the digestive tract in a predictable manner, allowing control over how quickly the drug is absorbed into the system.
Cytochrome P-450 system:	A family of liver enzymes involved in the metabolism of various substances in the body, including drugs. The term is often abbreviated to CYP and then the number of the specific member of the family is given. These enzymes include CYP3A3/4, CYP1A2, and CYP2D6, which are involved in the metabolism of various opioids.
Dealkylation:	To remove a chemical alkyl group from a chemical structure. This is one way the body metabolically alters drugs into inactive forms.
Diversion :	The act of giving one's prescription drugs to others for their use. This may be done in exchange for money.
Drug metabolism:	The process of changing a drug from an active form to a less-active or inert form before it is eliminated from the body. This can occur by means of enzymes in the liver or the kidney.
Elimination half-life:	The amount of time it takes the body to eliminate half of a dose of a drug that has been fully absorbed.

Equianalgesic dose:	The dose of a given drug that is required to reach the same degree of activity as another drug. In the case of opioids, morphine is the standard used to compare potency. Doses of other opioids are often compared to morphine to determine doses that offer equivalent activity.
Excrete:	The process of actively eliminating a molecule from inside a cell into a cavity for the purpose of removing it from the system. For example, a drug molecule may be excreted by a kidney cell into the collecting system of the kidney where it will be transported into the urine.
Formulation:	The form a drug is in for administration. For example, an oral formulation is a form that is meant to be taken orally (by mouth).
Gastric emptying:	The process of the body moving the contents of the stomach into the small intestine.
Genitourinary:	Of or pertaining to the urinary and genital systems.
Hepatic:	By or of the liver.
Hydrophilic:	Literal translation is "water-loving." This refers to the ability of a chemical or agent to easily dissolve into water.
Hypnotic:	Produces drowsiness.
Immediate-release:	A drug (or form of drug) that is absorbed quickly after administration.
Intramuscular:	Into the muscle. This term is used for injections of medications that require administration deep into the muscle tissue.
Kappa receptor:	(also spelled κ receptor) One of the 3 major opioid receptor types in the central nervous system. This receptor is a molecule on the nerve cell that, when activated by an agonist (e.g. morphine), leads to decreased pain signal transmission. This has been named the OP_2 receptor by the International Union of Pharmacology.
Lipophilic:	Literal translation is "fat-loving." This refers to the ability of a chemical or agent to easily dissolve in lipids, fats, or oils. These agents easily cross cell membranes, because cell membranes are composed of lipids and proteins.
Metastatic tumor:	A tumor that has spread to 1 or more distant sites from the original tumor.
Misuse:	Using a prescribed drug for a reason or in a manner other than that for which it was prescribed.
Mu receptor:	(also spelled μ receptor) One of the 3 major opioid receptor types in the central nervous system. This receptor is a molecule on the nerve cell that, when activated by an agonist (e.g. morphine), leads to decreased pain signal transmission. This has been named the OP_3 receptor by the International Union of Pharmacology.
Nerve block:	An injection of anesthetic near a major nerve. A steroid may be added to the injection for therapeutic or diagnostic purposes.
Neuropathic :	Generated by the nerves. Neuropathic pain is that which is generated as a result of damage to a nerve.

NMDA receptor:	A subtype of glutamate receptor on neurons. Binding with N-methyl-D-aspartate (NMDA) to these receptors opens calcium channels, allowing signal transmission (e.g. pain signal transmission).
Nociception :	The perception of pain.
Nociceptive:	Relating to the perception of pain. A nociceptive receptor is a pain signal receptor.
Nonopioid analgesic:	A medication that reduces pain through mechanisms other than through stimulating or blocking opioid receptors on nerve cells in the central nervous system. The mechanisms of action of various nonopioid analgesics differ. Barbiturates, such as butalbital, inhibit the gamma-aminobutyric acid neurotransmitter receptors to block signal transmission. Acetaminophen is conjugated with arachidonic acid to form N-arachidonoylphenolamine, a compound known as an endogenous cannabinoid (Bertolini 2006) which is responsible for its analgesic effect. Acetaminophen has also been thought to exert its analgesic effect by inhibiting prostaglandin synthesis in the brain (the prostaglandin inhibition results in a minimal amount of anti-inflammatory effect that is not clinically significant and does not contribute to the analgesic effect). The release of phospholipid from injured cell membranes is converted to arachidonic acid, which in turn is metabolized by a cyclooxygenase or lipoxygenase to produce prostaglandins and other chemicals that mediate inflammation. Non-steroidal anti-inflammatory drugs, such as naproxen sodium, inhibit prostaglandin production, thereby reducing pain signal transmission, and reducing inflammatory responses that contribute to pain.
Opioid:	A drug that is chemically similar to or derived from opium. These drugs act at opioid receptors on nerve cells in the central nervous system to reduce transmission of painful stimuli/impulses.
Opioid Naïve:	This refers to a patient who is not currently or who has not recently been treated with opioids. Opioid-naïve patients have not developed tolerance to the effects of opioids and therefore are started at the low recommended doses.
Opioid receptors:	A receptor is group of cell membrane proteins in nerve cells that cause certain responses in the cell when stimulated or blocked by ligands. Opioid receptors are stimulated or blocked by opioids. There are different classes of opioid receptors, including delta opioid receptors (also known as OP_1 receptors), kappa opioid receptors (also known as OP_2) receptors, and mu opioid receptors (also known as OP_3). Activation of these receptors stimulates specific activities within the activated cell, causing effects such as analgesia, nausea, or somnolence. Blockage of the effects of some types of receptors can cause effects such as anorexia or decreased prolactin release.
Opioid Tolerant:	This refers to a patient who has been taking opioids and has developed physical tolerance to some of the effects of opioids, such as respiratory depression.
Oralet:	Medication in a lozenge form.
Paralytic ileus:	A side effect of opioids that manifests as a functional stoppage of the bowel. The bowel stops all contractions in response to the drug and

	rather than being digested, the contents build up, leading to severe bloating, constipation, and vomiting. In rare cases of severe paralytic ileus with massive dilation of the colon, decompression with colonoscopy and selective use of neostigmine may be necessary. (Saunders 2003, Cowlam 2007) In select patients who cannot be treated with decompression, percutaneous endoscopic colostomy or other invasive procedures may be necessary.
Parenteral:	A non-oral route of administering medicine. This includes intravenous, intramuscular (an injection), rectal suppository, or transcutaneous (through the skin, as with a skin patch).
Partial agonists:	Agents that are only partly effective as agonists. Partial opioid agonists have actions at the opioid receptors that are not as strong as agonists.
pH:	A logarithmic scale used to measure the degree of acidity or alkalinity of a given substance. A lower pH is associated with acidity and a higher pH is associated with alkalinity.
Pharmacodynamics:	Describes the effects of a drug on the body and the relationship between the size of a dose and the degree of these effects. These effects would include therapeutic effects as well as side effects.
Pharmacokinetics:	The collective information about how a drug is absorbed, metabolized by the body, distributed in body tissues, and eliminated from the body.
Plasma terminal half-life:	The amount of time it takes for the drug levels that are already present plus the drug added by a recent dose to fall to half of the peak level. This is applied to drugs for which a steady level is intermittently augmented with additional breakthrough doses.
Platelets:	Independent cell-like bodies in the blood that help form clots. They are actually cell fragments that break off a parent cell (megakaryocyte) and form clots by adhering to damaged tissue.
Polypharmacy:	Taking multiple drugs concurrently. Polypharmacy may be necessary to manage a patient's medical condition(s), however, it increases the potential for side effects and drug interactions.
Potency:	The strength of a drug's effects. This is not to be confused with a higher dose. A very potent drug can have powerful effects at very low doses, whereas a drug with low potency will require large doses to have any effect.
Pro-drug:	A drug that must be metabolized by the liver before it becomes active in the body.
Psychotomimetic effects:	Side effects of drugs that affect mood and thinking.
Pulmonic:	Pertaining to or of the lungs.
Renal:	By or of the kidney.

Rescue (breakthrough) dose:	An additional dose of pain medication above the usual baseline dose for times when pain is worsened (e.g., when a patient with otherwise well-controlled pain overexerts himself or the disease/condition has periodic "flares" of symptoms or breakthrough pain).
Respiratory depression:	A reduction in the amount of respiratory effort that can be a side effect of opioids in the CNS. If this worsens, it can lead to respiratory arrest (the patient ceases to breathe).
Serum half-life:	The amount of time it takes for a drug level in the blood to decrease to one-half of the maximum amount reached. This term is sometimes shortened to "half-life."
Sigma receptors:	Receptors in the central nervous system that appear to be involved in antidepressant effects and antianxiety effects. These receptors also attenuate the pain response in experimental settings, thus these receptors were originally classified as opioid receptors. They are now felt to constitute a distinct class of receptors.
Subcutaneous:	Beneath the skin. This term is used for injections of medications that require administration into the looser tissue under the skin.
Suppository:	A formulation of a drug that can be given rectally.
Titration:	Adjusting the amount to achieve a desired effect.
Vertigo:	Dizziness.

Introduction

Chronic pain is frequently untreated, undertreated, or incorrectly treated. Many patients receive inadequate pain relief because doctors are unwilling to manage chronic pain or do not have sufficient knowledge to treat it properly. Many different therapies are available to treat chronic pain, however. This chapter describes some common strategies of effective pain management and, particularly, the place of opioid medications in these strategies.

Common Pain Therapies

The treatment of chronic benign pain is a diverse topic, because different causes of pain require different therapies. Certain conditions may be almost entirely relieved by a few nerve blocks or injections. Other conditions may require a combination of many different treatments to achieve even a moderate amount of relief. Several basic therapies exist that are frequently used in pain treatment. Most patients are managed through one or a combination of these basic techniques.

Even if we consider a group of patients with the same diagnosis, the treatment of these patients must be individualized. What may be appropriate for a 20 year old may not be appropriate for a patient who is 70. Similarly, a medication that may be quite effective in one person may have unacceptable side effects in another. One individual with severe arthritis may remain cheerful and outgoing, whereas in another person the same disease results in depression that is so severe it becomes more limiting than the arthritis itself.

A basic principle of treating chronic pain is that multimodal therapy, the use of several different types of treatment all focused on relieving the patient's

A basic principle of treating chronic benign pain is that multimodal therapy, that is, the use of several different types of treatment all focused on relieving the patient's symptoms may be required. In small offices and rural settings, the therapies are frequently administered under the guidance of a single healthcare professional. In larger pain clinics, a team of several healthcare providers may each contribute to the patient's care.

Commonly used therapies include:

- nerve blocks
- rehabilitation and physical therapy
- pharmacologic therapy (medications)
- acupuncture
- psychotherapy such as stress management (biofeedback)
- neurosurgical procedures
- and others

In most cases, however, pharmacotherapy provides the mainstay of pain relief. Basic pharmacotherapy usually loosely follows the World Health Organization's guidelines for treating cancer pain, which are discussed in more detail in Chapter 4. In general, these guidelines include using nonopioid analgesics as a foundation of therapy, supplementing them with opioid analgesics as needed, and adding adjunctive medications when appropriate.

General Principles of Pain Management

The basic principles of chronic pain management are as follows:

- The first step in managing pain is a thorough assessment of the patient, including a medical history, a history of the patient's pain, and a physical exam.
- Proper therapy depends on recognizing the source or sources of pain and treating each separately.
- Treatable underlying conditions that are causing or contributing to pain should be managed appropriately.
- If it is not possible to resolve the underlying condition, treatments to relieve the patient's symptoms should be initiated.
- Multimodal therapy (using several different types of therapy) is generally more effective than any single therapy.
- Treatment for each patient must be individualized depending on anatomical pathology, the presence of other diseases, age, social and economic status, emotional state, gender, ethnic background, and other factors.
- The use of nonopioid analgesics and adjuvant agents should be explored.

- Pure opioid agonists, such as morphine, should be used when appropriate. **Mixed agonist-antagonist opioids** may induce a withdrawal syndrome in patients tolerant to opioids.
- Analgesic medications should be prescribed in low doses initially, then titrated upwards as necessary.
- Oral medications should be used whenever possible. Oral opioids are relatively inexpensive and allow the patient to control their own medication.
- When patients have constant, or nearly constant pain, analgesics should be given "ATC" (around the clock), not "PRN" (when necessary). Fixed, regular dosing intervals maintain continuous control of pain. Breakthrough medications are allowed, but frequent episodes of breakthrough pain indicate that the regular "around-the-clock" dosing should be increased.
- There are no "standard" or set doses of opioids. Individuals vary greatly in their metabolism of opioids and different individuals require different doses of the medications.
- Care should be exercised when converting from one analgesic to another, or changing from one route of administration to another, to avoid overdosing or underdosing. Conversion tables are notoriously inaccurate and contradictory.
- Nonpharmacologic therapies should be investigated and used when appropriate.

Review of Key Pharmacologic Agents

Pharmacologic agents provide the mainstay of pain relief for most patients with either chronic benign pain or cancer pain. Pharmacologic agents include both nonopioid analgesics and opioid analgesics. The nonopioid and opioid medications have distinct benefits and drawbacks and these are taken into consideration when choosing a therapy for a patient.

Nonopioid Analgesics

There are 3 general types of nonopioid agents:

- Acetaminophen
- Nonsteroidal anti-inflammatory agents (NSAIDs)
- Aspirin

Acetaminophen (APAP)

Acetaminophen is the most widely used nonopioid analgesic, because it has a low incidence of side effects. Acetaminophen also has a high oral and rectal bioavailability and is available in multiple preparations. The major disadvantage of this drug is that it has no significant anti-inflammatory properties. Toxicity of acetaminophen is limited, but in doses of more than 4 grams per day (two Extra StrengthTylenol® is 1 gram), or 2 grams per day for the elderly. In patients with liver abnormalities (e.g., cirrhosis), liver toxicity is a potential problem. Because acetaminophen is included in many preparations of low-dose opioids (Lortab®, Vicodin®, Percocet®, etc.), patients who take such medications AND additional acetaminophen are at risk of liver toxicity.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The nonsteroidal anti-inflammatory drugs (NSAIDs) are used alone for mild to moderate pain or in combination with opioids for more severe pain. NSAIDs reduce pain largely by suppressing the inflammatory process (although they have some other analgesic effects), so they are most effective when the pain is at least partially caused by inflammation. NSAIDs also inhibit bone nociception (pain generation) by reducing prostaglandin synthesis and are therefore quite effective for the pain caused by metastatic bone cancer.

Individual NSAIDs vary widely in both their ceiling doses and dose-related toxicities. If the NSAID chosen proves ineffective with an adequate trial, another NSAID should be substituted, because individuals often respond differently to different NSAIDs. Like aspirin, the most important side effects of NSAIDs are gastrointestinal: pain, bleeding, ulceration of the stomach and duodenum. The COX-2 specific agents have fewer gastrointestinal effects than do the nonselective agents, but may have a higher incidence of other side effects, particularly on the cardiovascular system. NSAIDs prolong the bleeding time by inhibiting blood platelets, which can contribute to bleeding complications. Additionally, they can have toxic effects on the kidney. The potential toxicity of NSAIDs limits their dose and, to some extent, the duration of therapy. They should only be taken short term.

Aspirin (ASA)

Aspirin is an analgesic, anti-inflammatory, and antipyretic (fever-reducing) drug. Like the NSAIDs, and for the same reasons, aspirin is especially useful for reducing

pain associated with inflammation and metastatic bone disease. However, aspirin, like the NSAIDs, can cause pain, bleeding, and ulceration of the stomach and duodenum (the first part of the small intestine). The risk of these complications increases with prolonged use and the use of higher doses as well as in the elderly. Aspirin also increases bleeding time through its inhibitory actions on blood platelets, which are involved in the formation of blood clots.

Opioid Analgesics

The treatment of moderate to severe pain may require the addition of opioids such as morphine. Opioids relieve pain primarily by binding to opioid receptors throughout the nervous system, activating pain-suppressing pathways.

All opioids stimulate pain-suppressing receptors in the nervous system called "mu" receptors. Partial agonists stimulate the mu receptor but also stimulate a different receptor, called "kappa." Stimulation of the kappa receptor produces analgesic effects as well as unpleasant side effects. Mixed agonist-antagonists both stimulate and suppress responses from receptors on nerve cells. Due to the fact that they are associated with effects other than pure analgesia (stimulation of the mu receptor), partial agonists and mixed agonists-antagonists produce side effects and have a more limited ability to produce analgesia. This limitation is referred to as a ceiling effect. In addition, the antagonist action of the agonist-antagonist agents can potentially block the effects of a pure agonist (like morphine) that a patient may already be taking, potentially precipitating withdrawal symptoms. For these reasons, mixed-agonist-antagonists may have little use in chronic benign pain management.

Three major categories of opioids are available for clinical use:

Agonists

- morphine
  - Sustained released oral forms: KADIAN®, Oramorph®, Avinza®, MS Contin®,
  - Immediate-release oral tablet: MSIR®
  - Short acting (infusion/injection): Astramorph™ PF, Duramorph®, Infumorph®
  - Long-acting Epidural: DepoDur™
  - Suppository: RMS®
  - Liquid (immediate acting): Roxanol™, Roxanol-T™, MSIR® Oral Solution

- fentanyl
  - Oral form: Actiq® Fentora®
  - Transdermal: Duragesic®, Fentanyl Transdermal System, Ionsys™
  - Injection: Sublimaze®, Fentanyl PF Solution
- sufentanil
  - Sufenta® (used as an adjunct to surgical anesthesia and for intubation), Chronogesic™ (in phase III trials for use in chronic pain, not yet FDA approved)
- hydromorphone
  - Oral: Dilaudid® tablets, Dilaudid® liquid
  - Extended-release oral capsules: Palladone™
  - Infusion/Injection/epidural: Dilaudid-HP
- meperidine
  - Oral: Demerol® tablets, Demerol® liquid, Meperitab™, Pethidine
  - Injection/infusion: Demerol®, Mepergan Fortis®
- methadone
  - Oral: Dolophine®, Methadose®, Diskets®
- oxycodone
  - Oral tablets: Percocet®, Tylox®, Roxilox®, Endocet®, OxyIR®, Endocodone®, Percolone®
  - Controlled-release oral tablets: Roxicodone®, OxyContin®,
  - Oral solution: Oxy-Fast®, Roxicodone® Intensol, Eth-OxyDose™
- hydrocodone
  - Oral tablets or liquid: Hycodan®, Mycodone®, Vicodin®, Lortab, Hydromet®, Hydropane®, Tussigon®, Norco
- levorphanol
  - Oral and parenteral: Levo-Dromoran®
- codeine (available in various combinations with acetaminophen, aspirin, cold medication preparations, and promethazine)
  - Oral tablets or solution: Tylenol® with codeine, Capital® with codeine, Tussi-Organindin® NR, Phenergan® with codeine, Fiorinal® with Codeine, Fiorital® with Codeine, Esgic, Fioricet® with Codeine, Phrenilin with Caffeine and Codeine, Phreno-Care™, Ty-PAP with Codeine, Tyalgesic™, Vopac™, Ascomp® with Codeine, Soma® compound with Codeine, Ambenyl®, Bromanyl®, Codeprex™ Pennkinetic® Suspension, Decohistine™ DH, Dihistine® DH, Novahistine® DH, Phenylhistine® DH, Ryna-C®, etc.
- propoxyphene
  - Oral tablets: Darvocet® (propoxyphene compounded with acetaminophen), Darvon® (propoxyphene compounded with aspirin)
- tramadol
  - Oral tablets: Ultram®, Ralivia™ ER, Ralivia™ FlashDose®, Ultram® ER.

- oxymorphone
  - Injection: Numorphan®
  - Oral tablet: Opana®
  - Oral extended-release: Opana® ER
  - Rectal suppository: Numorphan®

Mixed agonist-antagonists

- butorphanol
  - Parenteral: Stadol®
  - Nasal spray: Stadol® NS®
- buprenorphine
  - Parenteral: Buprenex®
  - Sublinqual tablets: Subutex®, Suboxone® (buprenorphine plus naloxone)
- dezocine
  - Parenteral: Dalgan®
- nalbuphine
  - Parenteral: Nubain®
- pentazocine
  - Oral tablet: Talwin®, Talwin®NX (pentazocine plus naloxone)
  - Parenteral: Talwin®

Commonly Prescribed Potent Opioids

Many opioid agonists are used to treat chronic benigh pain. For most opioids, both generic and proprietary preparations are available. Many opioids are available as both immediate-release and controlled-release preparations.

For the last decade, most patients have been prescribed a long-acting or controlled-release "baseline" opioid, with a short-acting "rescue" opioid added for breakthrough pain. In recent years, the use of large amounts of breakthrough medication in chronic benign pain has been questioned, and while still used, it is now administered less frequently.

A number of commonly prescribed opioids are discussed below, because an overview of these medications is appropriate at this time. However, some of the information listed below, such as pharmacokinetics and metabolism, are more completely discussed in Chapter 8. Please plan to review this section again after reading that chapter. Because the emphasis of this manual is on the use of KADIAN®, the controlled-release morphine preparations are discussed together at the end of this section.

Morphine (Immediate Release)

Morphine is considered the "gold standard" for measuring the potency of an opioid for the treatment of pain, because most patients (85% to 95%) respond adequately to regular administration of morphine. Morphine is effective orally and is also available in parenteral and suppository forms. It has no ceiling effect on analgesia and it has known and predictable side effects.

Key abbreviations:

SC - subcutaneous
IM - intramuscular
IV - intravenous
PO - by mouth (per os)
Q - every (Latin "quaque")
mg - milligrams
ml - milliliter
ug-microgram

Table 3-1. Available Morphine Products

Formulation	Product Strengths Available	Dosing Interval
Injection	0.5-25mg/ml	q2 to 6 hr
Liquid	2-20mg/ml	q4 hr
Suppository	5mg, 10mg, 20mg, 30mg	q4 hr
Tablet/Capsule	15mg, 30mg	q4 hr

Dosage

- The usual starting oral dosage is 5-30mg every 4 hours.
- The average maintenance dose is 150 to 200mg daily. Patients with very severe pain may require a higher dose.
- When giving SC or IM injections, 10mg/70 kg body weight provides satisfactory analgesia in most patients with moderate to severe pain.

Pharmacology

- Morphine is a strong opioid agonist.
- The potencies and performances of all other analgesics are measured against morphine.
- Duration of action of morphine is 4 to 5 hours for IM or SC injection, or 4 hours (depending on formulation) for oral administration.
- Morphine is rapidly, but not always predictably, absorbed from the gastrointestinal tract
- After SC, IM, or IV injection, morphine is readily absorbed into the blood.

Pharmacokinetics

- Maximum plasma concentrations of morphine are reached on average 45 minutes after administration of oral morphine sulfate solution.
- It undergoes extensive and variable first-pass metabolism: bioavailability of oral preparations of morphine is only about 15-40%. As a result, morphine has a low oral-to-parenteral potency ratio (1:6 with single doses, improving to 1:2 or 1:3 with repeated dosing), meaning that it is more completely absorbed and is more effective when given parenterally (IV), but that potency improves with repeated oral doses (as the serum levels increase).
- The terminal serum half-life is 2 to 4 hours.
- It is distributed to the skeletal muscle, kidneys, liver, gastrointestinal tract, and brain.
- It is secreted into breast milk and crosses the placenta. Morphine is a Category C drug, as adequate animal studies have not been performed.
- Morphine is conjugated (metabolized) to M3G-and M6G-glucuronides (metabolized forms of morphine) in the liver; M6G has significant analgesic activity.
- About 90% of a dose is excreted through the urine, mainly as conjugates. The remainder is excreted through the bile into the feces.
- Morphine does not accumulate in tissues when given in normal doses.
- The pharmacokinetics are altered in hepatic and renal disease, so that adjustment of doses may occasionally be necessary in hepatically or renally impaired patients
- Obesity may lessen absorption

Side Effect Profile

- Most common side effects in normal doses are constipation (which can generally be managed with appropriate therapy), drowsiness (usually transient), nausea and vomiting (usually transient), dizziness and lightheadedness (usually transient).
- Other side effects include: Respiratory depression, headache, pruritis, etc.
- Cardiovascular alterations: flushing of the face, bradycardia (slow heart rate), tachycardia (fast heart rate), palpitations
- Central nervous system effects: confusion, hallucinations, restlessness, vertigo
- Gastrointestinal tract effects: anorexia, biliary colic
- Genitourinary tract effects: urinary retention, hesitancy
- Inappropriate antidiuretic hormone secretion

- Visual disturbances: blurred vision, diplopia, nystagmus, miosis
- Hypothermia
- Dermatological effects: urticaria and pruritus
- Allergic and anaphylactic reactions
- Withdrawal (abstinence) syndrome
- Major hazards in large doses are respiratory depression, circulatory depression, respiratory arrest, cardiac arrest and/or shock.

Advantages

- Morphine sulphate (MS) is the gold standard analgesic for moderate to severe pain.
- Morphine has no apparent analgesic ceiling effect.
- Easy to administer, allows rapid escalation of dose, widely available and relatively inexpensive. Available in oral, parenteral, and suppository forms.
- Antitussant, antianxiety, and hypnotic properties of morphine can also be very useful in patients with severe cancer pain.

Disadvantages

- Wide variability in metabolism of and response to morphine means doses must be titrated to patient's needs.
- Physical dependence to morphine is inevitable with continuous use. Patients physically dependent on morphine will experience withdrawal (abstinence) syndrome if the drug is withdrawn abruptly.

Potential for abuse.

- More likely to be associated with adverse effects than weak opioids. Adverse events are more likely to occur in opioid naïve patients.
- Acute morphine overdosage can cause life-threatening respiratory depression and other adverse effects, although this occurs rarely, in patients taking morphine for severe pain.

Fentanyl

Fentanyl is a synthetic opioid that was first introduced as an alternative to morphine in 1960. For the next thirty years, it was available only in an injectable form, and was used primarily in anesthetic situations. It is not effective orally because the liver breaks it down too quickly after absorption. In 1990, it was introduced in a transdermal formulation skin patch (Duragesic®) that delivers a steady level of

medication for 72 hours. The fentanyl patch has the advantage of being useful for people who cannot take their medications orally. In 1998, it was introduced as a flavored lozenge on a stick. This form of fentanyl (Actiq®) is placed inside the cheek where it is rapidly absorbed directly into the bloodstream (often within 15 seconds), making it very useful for episodic pain.

Table 3-2. Available Fentanyl Products

Formulation	Products	Dosing Interval
Injection	Sublimaze® or Fentanyl PF solution, 50mcg/ml or Ug	IM/IV/SC injections may be repeated in 30 to 60 minutes. It may also be given as a continuous infusion
Transdermal Patch	Duragesic®, Fentanyl Transdermal System, or Ionsys™ 12mcg/hr, 25mcg/hr, 50mcg/hr, 75mcg/hr, 100mcg/hr	q 48 to 72 hr
Lozenge	Actiq® 200mcg, 400mcg, 600mcg,800mcg, 1200mcg, 1600mcg Fentora® transmucosal 100 mcg	Dose can be repeated 15 minutes after completion of the first dose. Consumption limited to 4 units/day

Therapeutic Use

The injectable form is used for sedation, relief of pain, as a preoperative medication, and an adjunct to general or regional anesthesia. The transdermal product is used in the management of chronic or cancer pain that: 1) cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteroidal analgesics, or PRN dosing with short-acting opioids, and 2) requires continuous opioid administration.

Actiq® is indicated only for the management of breakthrough cancer pain in patients who are tolerant to and currently receiving opioid therapy for persistent cancer pain.

Pharmacology

- Very potent opioid agonist with actions similar to those of morphine. Fentanyl is lipophilic and therefore crosses the blood/brain barrier quickly.
- Approximately 50 to 100 times more potent than morphine; 0.1mg IM is equivalent to morphine 10mg IM.

Duragesic®

Duragesic® (and the generic forms) are dermal patches that contain a reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose. They deliver fentanyl to the skin forming a depot of drug in the upper layers, from which it enters the circulation. An ethylene-vinyl acetate copolymer membrane controls the rate of delivery of fentanyl to the skin surface. Serum fentanyl concentrations are proportional to the dose, thus allowing for accurate individual dose titration. The product is available in 5 strengths (patch sizes); the rate of fentanyl delivery is proportional to the surface area of the patch (See Table 3-3). The Fentanyl Transdermal System by Mylan uses the same mechanism used by Duragesic®. The Ionsys™ transdermal system is composed of a housing that contains a battery and two hydrogel reservoirs with a polyisobutylene skin adhesive. The system is a patient-controlled iontophoretic transdermal system that uses an electrical charge to release a dose from the reservoir.

Table 3-3. Duragesic® Equivalency to PO Morphine

Patch Size	Fentanyl Content	Rate of delivery (µg/hr)
10 cm2	2.5 mg	25µg/hr
20cm2	5.0mg	50µg/hr
30cm2	7.5mg	75µg/hr
40cm2	10mg	100µg/hr
50cm2	12.5mg	125µg/hr

The transdermal patch has a broad range of doses that are equivalent in potency to doses of oral morphine. See Table 3-4 for corresponding morphine doses. In

controlled clinical trials in non-opioid-tolerant patients, 60mg/day IM morphine was considered to provide analgesia approximately equivalent to Duragesic® 100µg/hr. Duragesic® should not be administered to children under 12 years of age or patients under 18 years of age who weigh less than 50kg (110lbs) except in an authorized investigational research setting because it has not been well studied in this patient population. Duragesic® carries the following black box warning regarding use in children: The safety of Duragesic® has not been established in children under 2 years of age. Duragesic® should be administered to children only if they are opioid-tolerant and 2 years of age or older.

Table 3-4 Dose Conversion Guidelines for Duragesic®

Current Morphine Dose	Daily Dosage (mg/dL)			
Oral Morphine	60-134	135-224	225-314	315-404
IM/IV Morphine	10-22	23-37	38-52	53-67
Recommended Duragesic dose	25 mcg/h	50 mcg/h	75 mcg/h	100 mcg/hr

Pharmacokinetics

- Injection and lozenge forms have a very quick onset of action. The lozenge is almost as quick as an injection with an onset of action in 5-15 minutes. Peak analgesia is reached within minutes of IV administration.
- The transdermal patch takes much longer to reach analgesic efficacy. Serum fentanyl concentrations increase slowly after application of the fentanyl patch (usually about 12-18 hours), level off after 12 to 24 hours, and remain relatively constant for the remainder of the 72-hour application period. (Peak serum drug levels occur 24 to 72 hours after applying the patch).
- It is rapidly metabolized, primarily by dealkylation to inactive metabolites in the liver and excreted mostly as metabolites in the urine.

Drug Interactions

- Fentanyl is a CYP3A3/4 enzyme substrate. Medications that inhibit these enzymes (eg. erythromycin, ketoconazole, itraconazole, and protease inhibitors) may increase serum concentrations of fentanyl.
- Drugs that increase metabolism through CYP3A3/4, including carbamezapine, phenobarbital, and rifampin, may decrease serum levels of fentanyl by increasing

its metabolism.

- It is unknown whether these interactions are clinically significant, but should be monitored.

Side Effect Profile

- At high doses, can produce marked muscular rigidity. This side effect is typically associated with rapid IV infusion.
- Skin rash around the patch is a common side effect. However, this may often be prevented by pretreating the skin with a steroid spray (e.g. the kind that is used in steroid inhalers for asthma) or skin prep applications.
- Adverse effects can persist for up to 36 hours after removal of the patch because of continued absorption of drug in the skin.

Advantages

- Very potent opioid.
- Less likely than morphine to cause nausea and vomiting when used in equivalent doses.
- Good alternative for those who cannot take oral medications.
- Physicians believe the transdermal patch is less abusable than OxyContin® and MS Contin®.

Disadvantages

- No tablet or capsule formulation of fentanyl is available at this time.
- Analgesic effect cannot be evaluated during the first 18-24 hours due to delay of onset of fentanyl patch.
- With the fentanyl patch, patients often require short-acting analgesics for the first 24 hours.
- There is no opportunity for proper dose titration in the management of acute or postoperative pain, including use in outpatient surgeries.
- Must rotate application site.
- Large dose strength patches are quite wide (2-3 inches across).
- Patients with adverse reactions to fentanyl should be monitored for at least 12 hours after patch removal.
- Patients should be advised to avoid exposing the fentanyl patch application site to direct external heat sources (e.g., heating pads, heat lamps, hot tubs, etc.) while wearing the patch. There is a potential for temperature-dependent increases in fentanyl release from the patch.

- There has been no systematic evaluation of fentanyl as an initial opioid in the treatment of pain.

Hydromorphone

Hydromorphone is a synthetic opioid with somewhat fewer side effects than morphine. Hydromorphone is commonly used as an injectable agent in the hospital and is also available in oral and suppository forms. There is currently no long-acting hydromorphone product on the market, which limits its usefulness in chronic pain (a previously available long-acting form, Palladone™, was removed from the market in 2005). It is a good alternative to morphine, but has a higher abuse potential.

Table 3-5. Available Hydromorphone Products

Formulation	Products and doses available	Dosing Interval
Tablet, immediate-release; Capsule, controlled-release	Dilaudid® 1mg, 2mg, 3mg, 4mg, 8mg	q 4-6 hr; FDA approval pending
Liquid	Dilaudid® 5mg/ml	q 4-6 hr
Suppositories	3mg	q 6-8 hr
Injection	1-4mg/ml IM, SC Dilaudid HP® 10mg/ml	q 4-6 hr

Pharmacology

- Very potent opioid, morphine-derivative
- 1.5mg IM or SC or 7.5mg PO equivalent to morphine 10mg IM or 60mg PO.
- High solubility means large quantities can be given IM in small volumes.
- Duration of action similar to morphine.

Pharmacokinetics

- Similar to morphine.
- Serum terminal half-life is 2 to 3 hours.

Side Effect Profile

- Same as for morphine, but it produces slightly more euphoria.

Advantages

- Alternative to morphine for moderate to severe pain.
- Usually given by injection; large quantities can be given IM in small volumes.

Disadvantages

- Injection can cause local pain and tissue irritation.
- No long-acting product available.
- High abuse potential and high street value.

Meperidine

In its oral form, meperidine is a very short-lived opioid. One of its breakdown products, normeperidine, can cause euphoria, agitation, and decrease the seizure threshold. Prolonged use can cause personality changes and epileptic seizures. For these reasons, meperidine is relatively contraindicated for the treatment of chronic benign pain. This recommendation, however, does not prevent its use in chronic benign pain. It is only available in short-acting formulations either as meperidine alone or in combination with 25mg of promethazine.

Table 3-6. Available Meperidine Products

Formulation	Products	Dosing Interval
Syrup	50mg/5ml)	q 4 hr
Tablet; Liquid	Demerol® 50mg, 100mg	q 4 hr
Tablet with promethazine	Mepergan Fortis® 50mg/25mg Meperitab™ 50mg	q 4-6 hr
Injection with promethazine	Mepergan®25mg/25mg ml	q 4-6 hr

Pharmacology

- Oral meperidine 300mg is equivalent to approximately 30mg of oral morphine.

Pharmacokinetics

- When given orally, 50% of the meperidine dose is metabolized in the first pass through the liver to several metabolites.
- One of the active metabolites, normeperidine, can last in the body for over 15 hours after every dose. Normeperidine levels, therefore, will continuously increase whenever meperidine is used steadily for more than 3 or 4 days. This effect is even greater in persons with renal dysfunction.
- Normeperidine is potentially toxic, causing euphoria, agitation, personality changes, and epileptic seizures. The effects of normeperidine are not reversible by opioid antagonists such as naloxone.
- This metabolite is more likely to accumulate in patients with renal dysfunction, if doses are greater than 600mg per day, and with continuous dosing for longer than 48 hours.

Side Effect Profile

- As with morphine, but may cause more nausea.

Advantages

- None

Disadvantages

- Potential accumulation of toxic metabolite with chronic dosing.
- Not available in a long-acting formulation.

Methadone

Methadone was first synthesized in Germany at the end of World War II and was specifically designed for the treatment of severe chronic cancer pain. In the middle 1960s it became widely used to treat drug addicts because it can suppress drug craving in this population with one daily dose. Because of this, it has developed a reputation as a medication that is linked to addiction. Actually, it is an excellent pain medication. Because of its long duration of action, it may be dosed only 2 or 3 times a day.

Because it has effects on other receptors (NMDA receptors) in addition to opioid receptors, methadone is sometimes effective for treating pain that does not respond to other opioid medications. The major advantage of methadone is its low cost compared with the time-release opioids.

One danger that is specific to methadone is delayed-onset sedation. The other opioids cause their strongest sedating effects within the first day or two of use. Methadone, however, may actually cause more sedation up to 2 weeks after the start of therapy. This makes methadone particularly difficult to titrate or for use in elderly patients.

Table 3-7. Available Methadone Products

Formulation	Products (Manufacturers)	Dosing Interval
Tablets	Dolophin® 5mg, 10mg, 40mg Methadose® 5mg, 10mg Methadose Dispersible Tablet 40mg Diskets® Orodispersable Tablet 50 mg	q 3-8 hr
Oral solution	1-10mg/ml	q 3-8 hr

Therapeutic Uses

- Indicated for the management of severe pain.
- Also used in detoxification and maintenance treatment of narcotic addition. If used for detoxification and maintenance treatment of narcotic addiction, it must be part of an FDA-approved program.
- Strong opioid agonist. Considered by some to be the best alternative for morphine-intolerant patients.
- In single doses, methadone is only marginally more potent than morphine: 10mg IM or 20mg PO equivalent to morphine 10mg IM or 60mg PO.
- In repeated doses, methadone is several times more potent than morphine; oral doses of 20-30mg daily are equianalgesic to 60-90mg or more of morphine PO.
- Duration of action of methadone is 4 to 5 hours after IM injection and 4 to 6 hours after oral administration (i.e., similar to morphine). Duration extends up to 6 to 8 hours after repeated administration.

Pharmacokinetics

- Readily absorbed from the gastrointestinal tract, reaching peak concentrations after about 4 hours.
- Widely distributed in tissues and diffuses across placenta. Extensively metabolized in the liver, mainly by *N*-demethylation. Metabolites excreted in bile and urine.
- Terminal half-life is extremely variable (15 to 40 hours), therefore, accumulation is possible and dosing interval needs to be carefully monitored.

- Accumulation more likely in patients with impaired renal or hepatic function, because both organs are involved with the metabolism of methadone.
- Like morphine, methadone displays wide variability between individuals in concentrations of drug achieved in the blood and rate of elimination of drug from the body. Dosage schedules of methadone must therefore be individualized for each patient.

Drug Interactions

- Methadone is a CYPIA2, 2D6, and 3A3/4 enzyme substrate and a CYP2D6 enzyme inhibitor. CYP3A3/4 and CyP2D6 enzyme inhibitors increase serum methadone concentrations. Enzyme inducers decrease serum methadone concentrations via enhanced hepatic metabolism. Drugs that induce hepatic enzymes and lower methadone serum levels include carbamazapine, St. John's Wort, rifampin, rifapentine, and barbiturates.

Side Effect Profile

- Similar to morphine but with a greater respiratory depressant effect.
- Pulmonary edema after overdosage is a common cause of fatalities among addicts.

Advantages

- Extended duration of action advantageous for patients with chronic benign pain except for tendency of drug to accumulate.
- Tolerance may develop more slowly to methadone than to morphine in some patients.
- Better antitussive and stronger sedative properties than morphine.
- Very effective in suppressing withdrawal symptoms in patients dependent on opioids.

Disadvantages

- Repeated administration may lead to accumulation of the drug (with potential for significant toxicity) because of very long half-life.
- Produces less intense but more prolonged withdrawal symptoms than morphine.
- Use should be restricted to patients intolerant of opioids, and should be used with great caution in elderly patients and patients with hepatic or renal dysfunction, all of whom are more likely to experience accumulation of the drug. Methadone can cause urinary retention and oliguria, which are more likely to occur in patients with bladder obstruction or renal disease. Drug accumulation can develop in patients with hepatic disease due to decreased metabolism. In patients with

hepatic disease, doses may need to be reduced and the patients should be monitored closely for symptoms and signs of toxicity.

- Should also be used with great caution in patients whose compliance or communication with the prescribing physician is in question, such as the confused or demented patients.

Oxycodone

Oxycodone is a synthetic opioid that is roughly 50% more potent than morphine per milligram. Since 1994, it has been available as a long-acting medication (OxyContin®), which is dosed every 8 or 12 hours. The short-acting forms of oxycodone are usually manufactured in combination with acetaminophen (e.g. Percocet®, Tylox®, Roxicet®) or aspirin (e.g. Percodan®).

Therapeutic Use

Oxycodone is used for the management of moderate to severe pain. OxyContin® is indicated for around the clock management of moderate to severe pain when an analgesic agent is needed for an extended period of time.

Table 3-8. Available Oxycodone Products

Formulation	Products	Dosing Interval
Short-acting capsules and tablets with acetaminophen	Percocet® 2.5/325,5/325/7.5/325/10/325/; Tylox® 5/500, Roxilox®, Roxicet®, Endocet®, OxyIR	q 4-6 hr
Short-acting capsule with aspirin	Percodan® 5/500	q 4-6 hr
Capsule, immediate-release	OxyIR® 5mg	q 4-6 hr
Tablet, immediate-release	Roxicodone® 5mg, 15mg, 30mg	q 4-6 hr
Tablet, controlled-release	OxyContin® 10mg, 20mg, 40mg, 80mg	q 8-12 hr
Liquid	Roxicodone® 5mg/ml; Roxicodone Intensol® 20mg/ml Oxyfast Solution 20 mg/mL	q 4-6 hr

Pharmacology

- Oxycodone is a potent opioid agonist derived from morphine and resembling codeine in structure.
- The oral equianalgesic dose of morphine is approximately 1 to 2 times the oral oxycodone dose. For example, 20mg of oral oxycodone is equivalent to 20 to 60mg of morphine.
- Like codeine, oxycodone is about one-half as potent orally as parenterally.

OxyContin®

OxyContin® is a controlled-release product with a biphasic method of action designed to deliver up to a third of its contents in the first hour and then to slowly release the remainder over 8 to 12 hours. Because of this, it has a much quicker onset of action than some controlled-release medications. This may also explain the increase in side effects that sometimes occur when patients are taking higher dosages of this medication.

Pharmacokinetics

- Oxycodone release from OxyContin® is pH independent.
- The absorption of oxycodone is greater than that of morphine.
- Oxycodone is well absorbed from OxyContin® tablets with an oral bioavailability of 60% to 87%. This high oral bioavailability is due to low presystemic and first-pass metabolism.
- In normal volunteers, the absorption half-time (time to half of the total absorption) is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin® exhibits a biphasic absorption pattern with 2 apparent absorption half-lives of 0.6 and 6.9 hours. This describes the initial release of oxycodone from the tablet followed by a prolonged release. However, oxycodone is not released continuously over the dosing interval. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours.
- Dose proportionality or bioavailability has been established for the 10-mg, 20-mg, 40-mg, and 80-mg strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC).
- Approximately 7% of whites, 8% of blacks, and 1% of Asians are poor metabolizers of CYP2D6 and produce no CYP2D6 or undetectable levels of it. Some authorities have reported reduced clinical response to oxycodone in individuals who are CYP2D6 deficient, possibly because of a reduced level of or complete absence of active metabolites (namely oxymorphone and alpha- and

beta-oxymorphol). However, other research suggests that the parent drug, rather than metabolites are responsible for the central effects of oxycodone. (Lalovic 2006, Susce 2006, Tyndale 1997)

- Oxycodone is metabolized to primarily oxymorphone and noroxycodone. Noroxycodone is the major circulating metabolite of oxycodone. Oxymorphone possesses analgesic activity but is present in low plasma concentrations.
- Oxycodone and its metabolites are excreted primarily by the kidney.
- The apparent elimination half-life of oxycodone after the administration of OxyContin® is 4.5 hours compared with 3.2 hours for immediate-release oxycodone.

Drug Interactions

- Medications that interfere with cytochrome P450 2D6 liver enzyme (including some antidepressants such as Prozac® and Paxil®) may reduce the effectiveness of oxycodone. Blockade of this pathway by concomitant medications has not yet been shown to be of clinical significance.

Side Effect Profile

Similar to morphine but with fewer gastrointestinal side effects.

Advantages

- An effective oral alternative to morphine for moderate to severe pain.

Disadvantages

- Deaths from overdose have been reported due to misuse or abuse after crushing or altering the delivery system of OxyContin®.
- OxyContin® serum levels fluctuate because of the early release of 33% of the dose. This peak may be associated with increased side effects.
- Oxycodone used in combination with acetaminophen or aspirin is limited by the maximum dose of the nonopioid product.

Less Commonly Prescribed Potent Opioids

Oxymorphone

Oxymorphone is used for moderate to severe pain. It is available in parenteral, oral, and rectal formulations and offers a potent alternative to morphine.

Table 3-9. Available Oxymorphone Products

Formulation	Products	Dosing Interval
Injection	1 mg/ml, 1.5 mg/ml	q 4-6 hr
Suppository	Numorphan® 5 mg	q 4-6 hr
Oral Tablet	Opana® 5 mg and 10 mg	q 4-6 hr

Pharmacology

- Very potent opioid agonist; 1 mg IM or SC or 6mg rectally equivalent to morphine 10mg IM or 60mg PO.
- Duration of action of oxymorphone is 4 to 6 hours after IM or SC injection (e.g., similar to morphine).
- Duration of action of oral dose is 4 to 6 hours.

Pharmacokinetics

- Similar to morphine.
- Terminal half-life of 2 to 3 hours.
- Steady-state of the oral formulation is reached after 3 days of multiple dose administration.

Side Effect Profile

- Similar to morphine

Advantages

- Potent alternative to morphine injections and suppositories for moderate to severe pain.

Disadvantages

- No antitussive activity.
- Must be taken one hour prior or two hours after eating.

Levorphanol

Levorphanol is occasionally used for moderate to severe pain. It is also used parenterally for preoperative sedation and as an adjuvant to anesthesia.

Table 3-10. Available Levorphanol Products

Formulation	Products (Manufacturers)	Dosing Interval
Injection SC (IV not recommended)	2mg/ml	q 6-8 hr
Tablet	Levo-Dromoran® 2mg (Roche Pharmaceuticals)	q 6-24 hr

Pharmacology

- Very potent opioid agonist: 2-3mg IM or SC or 4mg PO equivalent to morphine 10mg IM or 60mg PO.
- Levorphanol is almost as effective by mouth as by injection.
- Duration of action of levorphanol is 4 to 8 hours after oral administration (i.e., longer than morphine).

Pharmacokinetics

- The metabolism of levorphanol is similar to that of morphine.
- It is rapidly conjugated with glucuronic acid in the liver.
- Plasma levels of the glucuronide conjugate (the metabolized form of the drug) are 5 to 10 times as great as levels of the unconjugated drug.
- The terminal half-life is 12 to 16 hours, which is much longer than that of morphine. This long half-life may lead to accumulation of the drug in tissues in a manner similar to that for methadone.

Side Effect Profile

- Same as for morphine, but less likely to cause nausea, vomiting, and constipation than morphine and has greater sedative effects.
- Levorphanol accumulates in the tissue in a mechanism similar to methadone.
- Frequent monitoring is required to minimize side effects.

Advantages

- Effective orally.
- More potent and has longer duration of action than morphine.
- Greater sedative effect than morphine (sometimes could be advantageous).
- Antitussive

Disadvantages

- Like methadone, repeated administration leads to accumulation of the drug with potential for significant toxicity-because of very long half-life.
- Greater sedative effect than morphine.
- Same precautions should be used with this drug as with methadone.

Less Potent Opioids

Hydrocodone

Hydrocodone is very commonly used to treat mild to moderate pain. It is typically given to chronic pain patients for breakthrough or incident rescue pain. It is available in several different strengths, all combined with acetaminophen, aspirin, or ibuprofen (Lortab®, Vicodin®, Vicoprofen®, Norco, etc.) and is generally effective for 3 to 4 hours. It is also available in antitussive syrup (Tussionex®) which is dosed every 12 hours.

In addition to its use in mild to moderate pain, hydrocodone is also frequently used as a rescue medication in patients with chronic benign pain. All hydrocodone analgesic formulations have a ceiling effect due to the nonopioid content. Acetaminophen and aspirin dosing should not exceed 4 grams per day. Ibuprofen is limited to 3200mg/day for otherwise healthy individuals. Less than 4 grams per day (2 grams for the elderly) of acetaminophen or aspirin may be the limit for the elderly population

Codeine

Codeine is probably the most commonly prescribed opioid in the world. Because it is a fairly weak medication that lasts for only 3 or 4 hours, it is most appropriate for mild pain. It is associated with a greater incidence of side effects (especially nausea, hives, itching) than some other opioids. It is primarily available in combination with acetaminophen and aspirin. It may be used to treat mild pain from conditions such as mild injuries or mild dental pain. It is also used as in combination with expectorants and/or decongestants as an anti-tussive.

Propoxyphene

Propoxyphene (Darvon®, Darvocet®) is a very weak opioid medication that in some studies has not been shown to be any more effective than acetaminophen. At the

same time, some patients can get 3 to 6 hours of relief from mild to moderate pain with this medication. Propoxyphene is also only available in combination with nonopioid products.

Tramadol

Tramadol is a synthetic pain reliever with weak opioid effects. It also inhibits the reuptake of norepinephrine and serotonin. It is not a controlled substance although some states have imposed regulations on the medication. It is generally considered to be less potent than codeine, which is one of the weaker opioids. Nevertheless, tramadol has proven to be useful for some people with mild to moderate pain levels. Tramadol is dosed every 4 to 6 hours and must not exceed 400 mg/day. Doses above this limit are associated with an increased risk of seizure. Tramadol causes less constipation and sedation than the other opioids but can cause considerable nausea.

U.S. Drug Enforcement Administration Schedule of Controlled Substances	
Schedule I	A) The drug or other substance has a high potential for abuse. (B) The drug or other substance has no currently accepted medical use in treatment in the United States. (C) There is a lack of accepted safety for use of the drug or other substance under medical supervision.
Schedule II	(A) The drug or other substance has a high potential for abuse. (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. (C) Abuse of the drug or other substances may lead to severe psychological or physical

	dependence.

U.S. Drug Enforcement Administration Schedule of Controlled Substances *continued*	
Schedule III	(A) The drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.
Schedule IV	(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule III. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.
Schedule V	A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule IV. (B) The drug or other substance has a currently accepted medical use in treatment in the United States. (C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV.

Mixed Agonist-Antagonist Opioids

Traditional opioids stimulate the mu receptor. Mixed agonist-antagonists stimulate the kappa receptor and at least partially block the mu receptor. They were originally believed to cause less respiratory depression. However, at therapeutic doses, the risk of respiratory depression is equivalent to that of traditional opioids. The agonist-antagonists do have a ceiling effect to respiratory depression, just as they have a ceiling effect for analgesia. Basically, this means at very high doses the risk of respiratory depression does not increase any further.

Mixed opioid agonist-antagonists are usually not recommended for use in chronic benign pain. In addition, if a chronic pain patient who has been on mu agonists is given a mixed agonist-antagonist, opioid withdrawal may result. This occurs because the mixed opioid may block the mu receptor which was previously stimulated by the mu agonist.

Butorphanol

Butorphanol is used in the management of moderate to severe pain including migraine headache.

Table 3-11. Available Butorphanol Products

Formulation	Products	Dosing Interval
Injection	Stadol® 1-2mg/ml	q 6 hrs
Nasal Spray	Stadol® 1mg/inhalation	Initial may be followed by a second dose in 90—120 minutes. This sequence can be repeated every 3 to 4 hours

Pharmacology

- Mixed agonist-antagonist morphine congener with profile of actions similar to pentazocine.
- Far more potent than morphine; 2-3mg IM equivalent to morphine 10mg IM or 60mg PO.
- Duration of action of butorphanol is 3 to 4 hours after intramuscular administration (slightly less than morphine).

Pharmacokinetics

- Absorbed from the gastrointestinal tract but undergoes extensive first-pass metabolism.

- Extensively metabolized through hydroxylation and *N*-dealkylation; less than 5% excreted unchanged.
- Butorphanol and metabolites are excreted mainly in the urine.
- Plasma half-life is 2.5 to 3.5 hours.

Side Effect Profile

- Same as for morphine, although less likely to produce respiratory depression at high doses.
- Can produce prominent psychotomimetic effects (e.g., confusion, sedation, hallucinations, disorientation, euphoria, bizarre feelings, and psychosis), although to a lesser degree than pentazocine.
- May also increase pulmonary and aortic blood pressure as well as increase cardiac work.

Advantages

- Potent analgesic agent, less likely than morphine to produce respiratory depression.

Disadvantages

- As a mixed agonist-antagonist at opioid receptors, butorphanol is not recommended for continuous treatment of chronic cancer pain.
- Ceiling analgesic effect and an associated increased risk of psychotomimetic side effects
- Potential to reduce analgesia or precipitate withdrawal symptoms when administered to patients already taking opioid agonists.
- Can also have serious adverse hemodynamic effects, such as increased pulmonary artery pressure and systemic blood pressure.
- No oral formulation available.

Pentazocine

Used to treat moderate to severe chronic pain; better suited for relief of acute rather than chronic pain.

Table 3-12. Available Pertazocine Products

Formulation	Products	Dosing Interval
Injection	30mg/ml	q 3-4 hr
Tablet	Talwin® 50mg	q 3-4 hr
Tablet with acetaminophen	Talacen® 25mg/650mg	q 3-4 hr
Tablet with aspirin	Talwin Compound® 12.5mg/325mg	q 3-4 hr
Tablet with aspirin and caffeine	Talwin Compound 50® 50mg/390mg/32mg	q 3-4 hr
Tablet with naloxone	Talwin NX® 50mg/0.5 mg (	q 3-4 hr

Pharmacology

- Strong mixed agonist-antagonist opioid.
- Far less potent than morphine; 30-60mg IM or SC or 150-180mg PO equivalent to morphine 10mg IM or 60mg PO.
- Oral 50mg dose results in analgesia equivalent to that produced by 60mg codeine.
- Duration of action of pentazocine is 2 to 3 hours after intramuscular administration (e.g., less than morphine).

Pharmacokinetics

- May be erratically absorbed from the gastrointestinal tract and undergoes significant first-pass metabolism after oral administration.
- Metabolized chiefly in the liver and excreted mainly as metabolites in the urine.
- Plasma half-life is 2 to 4 hours.
- Displays wide variability among individuals in the concentrations of drug achieved in the blood and rate of elimination of drug from the body after parenteral administration. Appropriate dosing schedules must therefore be individualized for each patient.

Side Effect Profile

- Similar to morphine, although less likely to produce vomiting or respiratory depression.
- Its use may be associated with marked delays in gastric emptying and thus the potential to alter absorption of other orally administered drugs. Also associated with rapid development of tolerance. Of all the mixed agonist-antagonist opioids, pentazocine has the greatest potential to produce prominent psychotomimetic

effects (e.g., confusion, sedation, hallucinations, disorientation, euphoria, bizarre feelings, and psychosis).

- May also increase pulmonary and aortic blood pressure as well as increase cardiac work. Abrupt discontinuation of drug after prolonged use causes severe withdrawal syndrome, often worse than that caused by morphine or other opioids.
- Injections may be painful; local tissue damage, including fibrosis (subcutaneous tissue scarring), may occur at injection sites, particularly after SC injection or multiple doses.

Advantages

- Effective orally.
- Less likely than morphine to produce respiratory depression and physical dependence.

Disadvantages

- Pentazocine is not recommended for continuous treatment of chronic cancer pain because of a ceiling analgesic effect, associated increased risk of psychotomimetic side effects, and a potential to reduce analgesia or precipitate withdrawal symptoms when administered to patients already taking opioid agonists.
- May be absorbed erratically.
- Can have serious adverse hemodynamic effects. Hypotension, hypertension, and tachycardia have been reported.
- May be associated with pain and tissue damage with repeated injections.
- Rapidly induces tolerance and may cause very severe withdrawal syndrome when administration is terminated abruptly.

Nalbuphine

Nalbuphine is used in the relief of moderately severe pain. It is also used for preoperative analgesia and in anesthesia.

Table 3-13. Available Nalbuphine Products

Formulation	Products	Dosing Interval
Injection	Nubain® 1.5-20mg/ml	q 3-6 hr

Pharmacology

- Analgesic potency similar to morphine; 10mg IM equivalent to morphine 10mg IM or 60mg PO.
- Duration of action of nalbuphine is 4 to 6 hours after intramuscular administration (e.g., similar to morphine).

Pharmacokinetics

- After IM administration nalbuphine is metabolized chiefly in the liver and excreted predominantly in the feces.
- Considerable first-pass metabolism after administration by mouth.
- Plasma half-life 2 to 5 hours.

Side Effect Profile

- Similar to morphine, although less likely to produce respiratory depression and physical dependence.
- Substantial potential (although less than pentazocine) to cause psychotomimetic effects (e.g. confusion, sedation, hallucinations, disorientation, euphoria, bizarre feelings, and psychosis).

Advantages

- Opioid analgesic with similar potency and duration of analgesic action to morphine.
- Less likely to produce respiratory depression and physical dependence than morphine.
- Less potential to cause psychotomimetic and hemodynamic adverse effects than pentazocine.

Disadvantages

- As a mixed agonist-antagonist at opioid receptors, nalbuphine is not recommended for continuous treatment of chronic cancer pain because of its ceiling analgesic effect, associated increased risk of psychotomimetic side effects, and potential to reduce analgesia or precipitate withdrawal symptoms when administered to patients already taking opioid agonists.

- No oral formulation is available.

Controlled-Release Morphine Compounds

Conventional, immediate-release formulations of opioids have been available for many years. The challenge in improving chronic pain management has not been in the development of new drugs with new actions or better potency, but rather improvements in the way in which the drug is delivered. This section provides information concerning KADIAN® and other sustained-release or controlled-release formulations of morphine. Specifically, the differences between the products are addressed.

KADIAN®

(Alpharma Pharmaceuticals, LLC)

Modified-Release Composition

KADIAN® capsules contain polymer-coated, extended-release pellets of morphine sulfate. The gelatin capsule dissolves quickly in the stomach, freeing the polymer-coated pellets. As the pellets pass into the less acidic small intestine, morphine release is greatly accelerated. The pellets develop minute holes through which the morphine diffuses. The pellets are formulated so that morphine is released over several hours, resulting in plasma morphine concentrations which are maintained for up to a 24-hour period.

Product Strengths

- Color-coded gelatin capsules in 8 strengths: 10mg (light blue);20mg (yellow), 30mg (blue violet), 50mg (blue), 60mg (pink), 80 mg(light orange) 100mg (green) and 200mg(light brown).*Pharmacokinetics*
- Up to 24-hour release profile.
- Minimally affected by presence of food.
- Absorption: extent comparable, but rate slower than all other oral morphine formulations.
- The minimum peak serum concentration (C_{min}) for KADIAN® is higher than for MS Contin®, thus producing less fluctuation in plasma levels.
- The time to maximum plasma levels (*T*max) is 8.6 hours.

Indications

- Prolonged relief of moderate to severe chronic pain where treatment with an opioid analgesic is indicated for more than a few days.

Contraindications

- Hypersensitivity to morphine, morphine salts or any of the capsule components. True hypersensitivity is rare, most untoward effects are side effects of the medication.
- Patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings)
- Patients with acute or severe bronchial asthma or hypercardia.
- Patients who have or are suspected of having paralytic ileus.

Precautions

- As for morphine, plus only for chronic use (more than several days) and should be withdrawn within 24 hours of cordotomy or similar surgery.

Dosage and Administration

- Administer q12h to q24h.
- Patients who do not have a proven tolerance to opioids should be started only on the 20mg strength.
- Dosage titration should generally be increased by 48 hour increments.
- Breakthrough pain may require supplementation with short-acting (immediate-release) morphine.
- Morphine supplementation allows treatment with the same compound for both chronic pain management and breakthrough pain.
- In general, capsules (and pellets) should be swallowed whole and should not be chewed, crushed, or dissolved.
- As an alternative to ingesting whole capsules, the capsule may be opened and the pellets can be ingested with a small amount of applesauce (sprinkle administration) or the pellets may be mixed with a small amount of water and administered through a 16 French or larger gastrostomy tube (a tube going into the stomach for the purpose of feeding a patient; also known as a G-tube).
- The administration of KADIAN® pellets through a nasogastric tube (a tube that goes through the nose, down the esophagus and into the stomach) should not be attempted.

MS Contin®

Modified-Release Composition

MS Contin® tablets are film-coated and contain wax-coated controlled-release granules of hydroxyalkyline cellulose to which morphine sulfate is adsorbed. Gastric juices dissolve the tablet surface and expose the wax-coated granules. The wax coating slowly dissolves and exposes the cellulose carrying the morphine. Morphine then diffuses from the cellulose and is absorbed into the bloodstream. Thus morphine release is controlled as a result of the extra time it takes the tablet to disintegrate, the wax to dissolve, and the morphine to diffuse from the cellulose.

Product Strengths

- Sustained-release tablets in 5 strengths: 15mg, 30mg, 60mg, 100mg, 200mg. (Note: 200mg tablets are for use in opioid-tolerant patients only.)
- Generic products are also available.

Pharmacokinetics

- Unaffected by food.
- Does not release morphine continuously over the dosing interval.
- Absorption: extent comparable but rate slower than oral immediate-release morphine sulfate.
- Time to maximum plasma levels is 2.5 hours.

Indications

- For management of moderate to severe chronic pain when a continuous, around-the-clock, opioid analgesic is needed for an extended period of time.

Contraindications

- Same contraindications as for morphine.
- Paralytic ileus.

Precautions

- Same precautions as for morphine.
- Only for chronic use (more than several days).
- Should be withdrawn within 24 hours of cordotomy or similar surgery .This is because severe pain antagonizes the subjective and respiratory depressant actions of morphine and abrupt removal of the pain may allow these actions to become manifest.

Dosage and Administration

- Approved for 12-hour administration; but clinical experience suggests that 8 hour

administration is necessary for some patients.

- There has been no systematic evaluation of MS Contin® as an initial opioid in the treatment of pain.
- Breakthrough pain may require supplementation with short-acting (immediate-release) morphine or shortening of the dosing-interval of MS Contin® from 12-hour to 8-hour.
- Tablets should be swallowed whole and should not be broken, chewed, or crushed.
- 200mg tablets are for use in opioid-tolerant patients only.

Oramorph® SR

Modified-Release Composition

Oramorph® SR tablets contain sustained-release granules of hydroxypropyl methylcellulose to which morphine sulfate is adsorbed.

Product Strengths

White tablet embossed in 4 strengths: 15mg, 30mg, 60mg, 100mg.

Pharmacokinetics

- Pharmacokinetics of Oramorph® SR shows considerable intersubject variation.
- Pharmacokinetics unaffected by food.
- Oramorph® SR does not release morphine continuously over the course of the dosing interval.
- Absorption: extent comparable but rate slower than oral immediate-release morphine sulfate.
- Less fluctuation between single dose peak plasma morphine concentrations compared with immediate-release morphine or MS Contin®.

Indications

- Relief of pain in patients who require opioid analgesics for more than a few days.

Contraindications

- As for morphine, plus paralytic ileus.

Precautions

- As for morphine, plus only for chronic use (more than several days).

Dosage and Administration

- Considerations as for morphine plus:
  - Administer 12-hourly.
  - The dosing interval should not be extended beyond 12 hours or shortened to less than 8 hours.
  - The 30mg tablet strength is recommended for the initial titration period.
  - There has been no systematic evaluation of Oramorph® SR as an initial opioid for the treatment of pain.
  - Tablets should be swallowed whole and should not be broken, chewed, or crushed.

Avinza®

Modified-Release Composition

Avinza® Capsules contain polymer-coated, sustained-release pellets of morphine sulfate. The capsules use the proprietary SODAS (Spheroidal Oral Drug Absorption System) technology to produce an extended-release component of Avinza®. The preparation consists of 2 components, an immediate-release component that rapidly achieves plateau morphine concentrations and an extended-release component that maintains plasma concentrations throughout the 24-hour dosing interval.

As the capsule passes through the GI tract, soluble polymers of ammonio methacrylate dissolve leaving pores within the outer membrane. Fluid enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the dissolution phase. This is mediated by fumaric acid, which acts as an osmotic agent and a local pH modifier. Doses above 1600mg per day contain a quantity of fumaric acid which has not been demonstrated to be safe and which may result in serious renal toxicity.

Product Strengths

- Capsules available in 4 strengths: 30, 60, 90, or 120mg.

Pharmacokinetics

- Up to 24-hour release profile.
- Minimally affected by presence of food.
- The extent of absorption is comparable with other extended-release morphine formulations.

- Plasma *T*max is approximately 0.5 to 1 hour.

Indications

- Intended for once daily administration.
- Indicated for the relief of moderate to severe pain requiring continuous, around the clock opioid therapy for an extended period of time.
- Not intended for use as a PRN analgesic.

Contraindications

- Known or hypersensitivity to morphine, morphine salts or any components of the product
- In patients with respiratory depression in the absence of resuscitative equipment and in patients with acute or severe bronchial asthma
- In patients who have or are suspected of having paralytic ileus.

Precautions

- Same as for morphine.
- Only for chronic use (more than several days).

Dosage and Administration

- Avinza® should not be given more frequently than every 24 hours.
- The 30mg capsule strength is recommended for the initial titration period.
- There has been no systematic evaluation of Avinza® as an initial opioid in the treatment of pain.
- Capsules should be swallowed whole and should not be broken, chewed, sprinkled on food, or crushed.

Adjuvant Drugs

Adjuvant drugs are medications that are not analgesics, but that may reduce pain or improve other symptoms associated with chronic pain. In some cases, such as the use of antidepressants, the adjuvant medications are used "as indicated" to treat a symptom associated with pain. In other cases, such as the use of antiseizure medications to treat neuropathic pain, the mechanisms of benefit are not clearly understood. The most commonly prescribed adjuvants are antidepressants (for depression or neuropathic pain), anticonvulsants (particularly for neuropathic pain), benzodiazepines (for anxiety, muscle spasm, and muscle pain), and corticosteroids (for metastatic cancer pain and some types of inflammation).

Tricyclic Antidepressants

Antidepressant medications have been used as analgesics for chronic pain for over 25 years. The older, tricyclic antidepressants (TCA), such as amitriptyline, appear to work better for this purpose than the newer antidepressant medications (SSRIs). TCAs can stimulate the body's natural pain-relieving pathways and thus potentiate the analgesic effects of opioid medications. (Dick 2007) The analgesic effects of amitriptyline and morphine are synergistic. The sedation caused by the tricyclics may be used to help chronic pain patients sleep. (Luccarini 2004) Currently, more than half of the prescriptions for tricyclic antidepressant medications are given for pain rather than for depression.

The peak effects of tricyclic antidepressants are not reached until several weeks after starting on the medication. The dosage needed to relieve pain is generally less than the dosage required to treat depression. Amitryptaline (Elavil®) is the most commonly used TCA adjuvant. Nortriptyline (Pamelor®), imipramine (Tofranil®) and doxepin (Sinequan®) are alternatives. Desipramine (Norpramine®) has been found to be especially useful in neuropathic pain and may have less sedative effects than the other tricyclics. The side effects of the TCAs include morning sedation, a drop in blood pressure on standing (postural hypotension), weight gain, and dry mouth.

Other Antidepressants

The newer class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), have largely replaced the tricyclic medications for the treatment of depression because they work more rapidly and have fewer side effects. Identifiable depression occurs in up to 25% of chronic pain patients; therefore, these agents are frequently prescribed. Unlike the tricyclics, the SSRIs have not been clearly demonstrated to have any pain-relieving effects. It should be noted that some SSRI's might reduce the effectiveness of certain opioids, such as oxycodone and hydrocodone, which must be activated in the liver before they become effective.

Anticonvulsants

Anticonvulsants are medications used to control neurological conditions such as epilepsy (seizures). They are also frequently used to treat neuropathic pain conditions. Gabapentin (Neurontin®) is the anticonvulsant used most frequently for this purpose. Patients with neuropathic pain sometimes find the relief they get from

gabapentin is better than the relief they get from opioids. It also improves the quality of sleep and in some people has mild mood-elevating effects. Gabapentin is not metabolized; it is excreted by the kidneys in its unchanged form. Because of this, it has no interactions with other medications and can be safely used even by persons with severe liver disease.

Pregabalin (Lyrica®) is structurally similar to gabapentin and has antiepileptic, analgesic, and anti-anxiety properties. It is indicated for the treatment of neuropathic pain associated with peripheral diabetic neuropathy, postherpetic neuralgia, and for treatment of moderate somatic pain (such as post-operative dental pain). It is taken orally, reaching a peak plasma concentration within 1.5 hours of ingestion. Pregabalin undergoes minimal metabolism. The primary route of excretion is renal. Dose adjustments are needed in patients with renal impairment.

Carbemazepine (Tegretol®, Epitrol®), phenytoin (Dilantin®), phenobarbital (Primidone®), and valproate (Depakote®) are also used to treat neuropathic pain. Lamotrigine (Lamictal®) is a new anticonvulsant that has been effective in the treatment of stubborn neuropathic pain, at least in a few cases. However, it has been associated with severe and even dangerous skin rashes if the dose is escalated too quickly, so many doctors prefer to limit its use.

Benzodiazepines

The benzodiazepine class of medications includes the minor tranquilizers such as diazepam (Valium®), lorazepam (Ativan®), alprazolam (Xanax®), and oxazepam (Serax®), as well as many of the commonly used sleeping pills. All of these medications work at GABA-A receptors in the brain. There is considerable controversy over the use of benzodiazepine medications for the treatment of chronic benign pain. Some physicians feel that benzodiazepines are inappropriate because they are habit forming. However, they can be helpful in treating anxiety and insomnia that sometimes accompany chronic benign pain. They may also be used to treat muscle spasms and certain types of pain originating in muscles.

Corticosteroids

Corticosteroids are more potent inhibitors of inflammation than the NSAID medications and may have an additional analgesic effect. They are frequently used to treat cancer pain arising from bony metastases or tumor infiltration and are sometimes

used to treat acute episodes of benign pain. However, they have significant side effects if used for a prolonged period.

Stimulants

Stimulants such as amphetamine (Dexedrine®) and methylphenidate (Ritalin®) have found limited use as adjuvants. Their primary indication in chronic pain is to counteract sedation in cancer patients who require very high-dose opioids. The side effects of stimulants include anxiety, tremulousness, loss of appetite and, rarely, psychological effects including delirium (severe mental disturbance, sometimes including hallucinations) or paranoia.

Dose Titration

Dose titration to effect is an important principle in both opioid and adjuvant medication therapy. For most of these medications, the dose should be gradually increased until pain relief is satisfactory or intolerable side effects occur. The lowest dose that produces analgesia is best, because this is less likely to produce side effects. Usually, the dose, rather than the frequency of dosage, is increased when titrating, with increases made every 2 to 3 days. .

Titration of drugs (sustained release increases) should be carried out as quickly as possible, (2-3 days), to prevent the patient from experiencing pain or side effects for longer than necessary. However, the time course of action of the medication must be considered when doing so. An adjunctive medication that is expected to take days to develop an effect (such as anticonvulsants) may only be titrated upward every week or two.

Upward titration of pure opioid agonists can theoretically be continued indefinitely, because there is no absolute ceiling effect to

Upward titration of pure opioid agonists can theoretically be continued indefinitely, because there is no absolute ceiling effect to these medications. In practice, however, although this is sometimes performed in cases of cancer pain, most physicians will try an alternative medication once they have exceeded their own comfort level with a given drug. When the opioid is combined with another medication (such as Lortab® or Percocet®) or if the delivery vehicle contains potentially toxic agents (such as Avinza®) the ability to titrate upward may be limited. Additionally, side effects, and costs of medications, become issues when very high doses of opioids are required.

Tapering doses

Morphine therapy should be withdrawn slowly in patients on doses higher than 30mg/day to prevent signs and symptoms of opiate withdrawal. The daily dose should be reduced by 50% for the first two days and then by 25% every two days thereafter until the total dose is equal to the initial dose recommended for opiate-naïve patients (15 to 30 mg/day). Once the 15 to 30 mg/day range is reached, therapy can be discontinued.

Nonpharmacologic Treatment of Pain

Although medication alone can effectively control chronic pain in many patients, several other strategies can and should be used in more difficult cases. Nonpharmacologic strategies are commonly used in patients with chronic benign pain and are indicated in cancer patients who continue to have pain despite optimal medical management.

Neural Blockade (Regional Analgesia)

Peripheral transmission of pain can be interrupted temporarily by the injection of local anesthetic agents near nerves, providing immediate relief of uncontrolled pain. In some cases, anesthetic blocks may provide partial or complete pain relief for prolonged periods, although the mechanism by which this occurs is not clear. Anesthetic nerve blocks can be performed at nerve endings in painful tissues, at various target points along the course of peripheral nerves, or at nerve roots near their attachment to the spinal cord.

Nerve blocks are most commonly used for problems involving the spine or when peripheral nerves are irritated or compressed. They can be used for diagnostic or therapeutic purposes. They are also used to treat painful conditions involving the sympathetic nervous system and can be used for diagnostic and therapeutic purposes. Nerve blocks using neurodestructive chemicals, such as phenol, are sometimes used to destroy nerves carrying pain messages in rare cases of terminal cancer pain.

Physical Therapy

Physical therapy is most commonly used to help restore physical strength and functioning after injury or surgery. Physical therapists can also provide pain relief for patients with musculoskeletal (involving the bones and muscles) pain, some types of neuropathic pain, and sympathetically mediated pain through stretching, movement,

water therapy, heat and cold therapy, etc. Many pain centers have their own physical therapy programs designed specifically to treat persons with chronic pain.

Acupuncture

Acupuncture has been practiced in China for over 5000 years. It has been claimed to treat many conditions, including several causes of pain. Much of the evidence in support of acupuncture is anecdotal (based on individual patient's reports of benefit, rather than from controlled studies). However, some studies have shown benefit. In a small, recent study, acupuncture at the most painful point was shown to relieve back pain. In other studies, a combination of acupuncture with massage offered additional relief over standard pain management alone and acupuncture appeared to be beneficial in treatment of migraine. Another study demonstrated effectiveness for patients with pain due to osteoarthritis. An additional benefit of acupuncture is the relative safety and lack of side effects. (Mehling 2007, Michalek-Sauberer 2007, Linde 2007, Weidenhammer 2007, Eisenberg 2007, Inoue 2006, Witt 2006)

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS stands for transcutaneous (meaning across the skin) electrical nerve stimulation. A TENS device applies a controlled, low-voltage electrical current through electrodes placed on the skin. Theoretically, the current will interfere with the ability of nerves to transmit pain signals to the spinal cord and brain. However, even after several decades of research, it still is not clear whether TENS provides any better pain relief than placebo.

Biofeedback

Biofeedback uses monitoring electrodes placed on the body or scalp and connected to amplifiers. During biofeedback sessions, a therapist helps the patient learn how to mentally control and change the signals from the electrodes, gaining conscious control over normally unconscious functions. Biofeedback is most commonly used to relax spasmed muscles and reduce stress. It has the advantages of being noninvasive, inexpensive, and safe, but usually requires between 5 and 15 sessions before effective control is achieved.

Drug Infusion Pumps

Drug infusion devices (also called implanted infusion pumps) have been available since the 1980s. An electrical or mechanical pump containing a drug reservoir is totally implanted under the skin, infusing the drug through a small catheter directly

into the patient's intraspinal space 24 hours a day. The medication reservoir is filled at the healthcare professional's office every few weeks, and the rate of infusion can be changed as conditions require. Very small quantities of drug are given in the spinal fluid (ug vs. mg). This provides the same relief as larger doses given by mouth or intravenously; so patients have potentially fewer side effects.

Intraspinal infusion devices have their own set of concerns, including device malfunction, catheter obstructions, and the possibility of developing infections. Most pumps run on an internal battery that must be changed (requiring a surgical procedure) every 7-10 years. They are also not effective in every case, so a trial of intraspinal medication must be given before deciding if an infusion pump is indicated. In a small study of patients receiving intraspinal morphine (12 patients) with an implanted pump, patients overall reported a 42% reduction in pain. In a study of the use of polyanalgesia (morphine mixed with additional pain medications), 19 out of 26 patients reported excellent or good long term efficacy. (Valentino 1998, Rainov 2001)

Neurostimulation

Neurostimulation involves implanting a computerized generator and electrodes near the spinal cord, peripheral nerves, or within the brain. Neurostimulators have been used successfully for a variety of pain syndromes. These devices are effective in treating neuropathic pain and pain associated with central neurologic diseases. Implantation of spinal cord stimulators has been shown to relieve refractory angina pectoris pain, intractable headaches, and even chronic pelvic pain. The vast majority of neurostimulators are placed in the epidural space near the spinal cord. Complications from spinal cord stimulation are less common than with implanted infusion pumps, but are still significant. Infections, migration of a lead, spinal fluid leaks, and spinal cord injuries may all occur. Stimulation can only be used for pain involving an isolated area of the body, such as a leg or hand. For this reason, the technique is not useful in cancer patients whose pain may spread as the tumor grows. (Ansari 2007, Weiner 2007, Birknes 2006, Kapural 2006)

Summary

Treatments that resolve the painful condition should be explored whenever possible. If it is not possible to resolve the condition, treatments to relieve the patient's symptoms should be explored.

Multimodal therapy (using several different types of therapy) is generally more effective than any single therapy. The use of nonopioid analgesics and adjuvant agents should always be explored first.

Pharmacologic treatment is the primary therapy for most pain patients, especially cancer patients.

Pure opioid agonists, such as morphine, should be used in most cases. Mixed agonist-antagonist opioids may induce a withdrawal syndrome in patients tolerant to opioids. Analgesic drugs may need to be prescribed in low doses initially for opioid-naïve patients and then be titrated upward as necessary. Patients with severe pain may require higher initial dosing.

Oral medications should be used whenever possible. Oral opioids are relatively inexpensive and allow the patient control of their own medication.

Nonpharmacologic interventions for pain include neural blockade, physical therapy, acupuncture, TENS, biofeedback, infusion pumps, and neurostimualation.

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Self-Assessment Test

Circle the best response

1). Which of the following are used as adjuncts to opioid medication in the treatment of chronic pain?
   a. Nerve blocks
   b. Physical therapy
   c. Counseling
   d. All of the above

2). Which statement concerning the management of a chronic benign pain patient is FALSE?
   a. The first step in managing pain is to prescribe pain medication.
   b. Proper therapy depends on recognizing the source or sources of pain.
   c. Multimodal therapy is generally more effective than any single therapy.
   d. Treatment for each patient must be individualized.

3). When using opioids to treat chronic benign pain, agonist-antagonist or partial agonist medications should not be used because they might:
   a. Cause withdrawal syndrome in patients on chronic pain therapy with agonist agents
   b. Result in seizures
   c. Counteract the effect of nerve blocks
   d. Increase depression

4). Patients with constant pain should receive opiates:
   a. At fixed doses, around the clock
   b. Whenever they need them
   c. About every two weeks
   d. With meals

5). Which of the following types of medication have a ceiling effect, i.e., a dose level above which additional increases produce no further analgesic effect?
   a. Opioid agonist/antagonist or partial agonist analgesics
   b. Antiseizure medications
   c. Tranquilizers
   d. Nonopioid analgesics

6). Which medications largely reduce pain by suppressing the inflammatory process?
   a. Opioids
   b. Tricyclics
   c. NSAIDs
   d. Acetaminophen

7). How long does it take Duragesic® to approximately achieve a steady blood level?
   a. 4 hours
   b. 8 hours
   c. 12 hours
   d. 24 hours

8). What portion of a dose of OxyContin® is delivered within the first hour after taking the drug?
   a. One tenth
   b. One third
   c. One half
   d. Two thirds

9). What types of antidepressant drugs have pain-relieving effects?
   a. Selective Serotonin Reuptake Inhibitors (SSRIs)
   b. Monoamine Oxidase Inhibitors (MAOs)
   c. Tricyclic Antidepressants (TCAs)
   d. Benzodiazepines (BZDs)

10). The class of medications commonly used to treat neuropathic pain is:
   a. Anticonvulsants
   b. NSAIDs
   c. Opioids
   d. Stimulants

11). The principle of adjusting the dose of a medication until the desired effect is obtained is known as:
   a. Overprescribing
   b. Dosage Titration
   c. Ceiling Effect
   d. Multimodal Therapy

12). Meperidine (Demerol®) should not be used for chronic pain management because:
   a. It has a high abuse potential
   b. It's only available as an injectable
   c. It's too expensive
   d. Its metabolites may cause mental status changes and seizures

13). Disadvantages associated with the use of methadone include:
   a. Delayed-onset sedation may occur up to 2 weeks after onset of therapy.
   b. Due to a long half-life, repeated administration may lead to accumulation of the drug with a potential for significant toxicity
   c. It causes a prolonged but less severe withdrawal syndrome than morphine
   d. All of the above.

14). Which of the following is a mixed agonist-antagonist?
   a. Nalbuphine
   b. Levorphanol
   c. Propoxyphene
   d. Tramadol

15). Which of the following is NOT a disadvantage of Duragesic®?
   a. Higher doses come in very large patches
   b. Higher incidence of nausea and vomiting
   c. Can take 24 hours to become effective
   d. Relatively high cost

16). Which of the following products have both an immediate-release and a time-release component?
   a. KADIAN® and Lortab™
   b. Duragesic® and OxyContin®
   c. OxyContin® and Avinza®
   d. Oramorph® and MS Contin®

17). Which of the following drugs is NOT available in controlled-release form?
   a. Morphine
   b. Hydromorphone
   c. Oxycodone
   d. Fentanyl

Answers to Self-Assessment Test

1). d	7). d	13). d
2). a	8). b	14). a
3). a	9). c	15). b
4). a	10). a	16). c
5). d	11). b	17). b
6). c	12). d	

CHAPTER FOUR

Cancer Pain and Palliative Care

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the 6 general principles of treating cancer pain.
- Describe the role of anticancer therapies in treating cancer pain.
- Describe the 4 steps of the WHO pain treatment ladder.
- Describe the drugs commonly used in each step of the ladder.
- Discuss the use of potent opioids as step 3 of the WHO ladder.
- Discuss the phenomena of opioid tolerance and dependence.
- Discuss the use of adjuvant drugs to augment opioids.
- Discuss the use of nonpharmacologic interventions for cancer pain management.

Terminology

Adjuvant medications:	Medications used to help analgesics work better or that treat other symptoms associated with pain.
Catheter:	Any small tube used to carry fluids.
Ceiling effect:	For certain medications, when an increase in dose past a certain level does not result in any further effect.
Gamma knife:	Specialized machine that projects a very tightly focused beam of radiation.
Linear accelerator:	A machine that projects a beam of radiation.
Metastases:	Tumor that has spread to a new location.
Neurotoxic:	Damaging to nerve tissue.
Oncologist:	A physician specializing in cancer treatment.
Palliative:	Attempting to relieve symptoms without curing the disease.
Pathological fractures:	Fractures caused by tumor invading and destroying bone.
Radiotherapy:	General term for all types of radiation used to treat cancer.
Syndrome:	A group of findings or symptoms that commonly occur together.

Introduction

Pain is one of the most common symptoms experienced by cancer patients. Unfortunately, despite improvements during the last decade, cancer pain is often poorly managed. As a result, many patients experience needless suffering. Cancer pain, however, can be simpler to manage than chronic benign pain. In most patients, it can be effectively decreased with a simple medication regimen. This chapter describes some common strategies of effective cancer pain management, and particularly how opioid medications contribute to this plan.

General Principles of Pain Management

Almost all cancer patients will suffer significant pain at some point during the course of their disease. Many of these patients will respond very well to the routine medical management prescribed by their oncologist. A minority, however, will suffer persistent pain not relieved by such routine measures. These patients require a comprehensive clinical assessment, as described in Chapter 2, and therapy that is more intensive.

Whether the patient is managed with a simple prescription or with several different therapies, 6 general principles will always apply:

1) The patient must have an informed role in the management of the disease. The patient's condition and treatment options should be explained in understandable terms. Keeping the patient involved reduces anxiety and feelings of hopelessness and helplessness, increases compliance, and ensures that the patient's views remain paramount.

2) Involvement of the patient's family is important. The effects of cancer and cancer pain are almost as disruptive to the family as to the patient. The family will therefore require advice and support. At the same time, the family is a part of the patient's therapy and should be included in planning treatment.

3) A team approach is optimal. A collaborative effort between the patient, family, physicians, nurses, social workers, physiotherapists, dietitians, clergy, etc., provides the best possible care. When pain is not relieved by routine means, inclusion of a pain specialist in the team is helpful.

4) Treating the cancer is the first priority. Curative or palliative surgery, radiation therapy, hormonal therapy, and chemotherapy can remove or diminish the source of cancer pain, rather than just treat the symptoms.

5) All symptoms that cause distress, such as nausea, diarrhea, cough, constipation, insomnia, bedsores, incontinence, etc., should be treated.

6) The patient's environment is important. A comfortable and supportive setting reduces distress. Home is the best environment for most patients, as long as adequate support is available.

Anticancer Therapies

The initial focus of cancer treatment is to cure the patient of disease. Even when the cancer is not curable, appropriate chemotherapy, radiotherapy, or surgery may all be used to extend the patient's life and to reduce pain and other symptoms caused by the tumor. When the patient's pain is believed to result directly from the tumor invading the tissues of the body, anticancer therapy is the first priority.

When the pain is the result of tumor invading the tissues, anticancer therapy is the first priority.

These therapies all take time to work, however, and the patient's symptoms must be treated until the primary therapy becomes effective. Radiation or chemotherapy, for example, may take several months to shrink a tumor significantly. In terminal cases, the patient may have already received maximal doses of anticancer treatments. Control of symptoms is then the primary goal of therapy.

Radiation treatments relieve pain in several ways. Large tumors can cause pain by stretching or compressing surrounding tissues. Shrinking a large tumor with radiation can relieve much of this pain. Additionally, when tumors invade normal tissue they cause irritation, swelling, and destruction of the normal cells. Radiation not only slows cancer growth in such areas, it also reduces the inflammation and tissue irritation relieving much of the pain.

Radiation is usually delivered as a beam from an external radiation source, such as a linear accelerator or a "gamma knife". It can also be delivered to cancer cells by temporarily inserting radioactive material into a body cavity or an organ. This can be done by surgically implanting "seeds" of radioactive material, such as Cesium-137 or Iridium-192 directly into the area of tumor growth. Certain radioactive substances can also be injected into the bloodstream or taken by mouth. In these cases, the substance used is one that is selectively taken up by tissue that is the target of treatment. Orally ingested Iodine-131, for example, is selectively taken up by the thyroid gland and metastatic deposits of thyroid cancer. Strontium-89, another radioactive chemical, is taken up primarily by bone tissue, so it can selectively destroy metastatic cancer invading the bones.

Radiotherapy is most commonly indicated for localized pain from cancer invading a bone. It can also be effective when a tumor has nearly blocked a hollow structure in the body, such as the bowel or a bronchial tube. It is less effective for tumors invading nerves or soft tissues.

Palliative Therapy

Palliative means to provide relief without curing. When used specifically in discussing cancer pain, palliative usually refers to using treatments that are sometimes curative, such as radiation or chemotherapy, to provide relief from symptoms without trying to cure the disease. For example, a surgeon may open a patient's abdomen to find an incurable tumor nearly obstructing the intestines. He may perform a palliative procedure to reroute the intestines around the tumor, relieving the obstruction without curing the disease.

Palliative usually refers to using treatments that are sometimes curative, such as radiation or chemotherapy, to provide relief from symptoms

Chemotherapy and radiation therapy are sometimes prescribed for patients with incurable cancer in order to extend their life expectancy. They may also be used later in the course of the cancer to provide pain relief, even when it is obvious they will not help the patient live longer. Palliative therapy is often used to shrink large tumors that are causing pain by pressing on other structures or to relieve pain from tumors eroding into bone.

Radiation therapy is more commonly used for pain control than is chemotherapy for several reasons. Radiation therapy is often more acceptable to the patient, who may have had unpleasant experiences with chemotherapy. It can also be used to treat only specific areas, such as pain arising from a single metastatic tumor in a bone.

The WHO Analgesic Step-Ladder

In 1986, the World Health Organization (WHO) published guidelines for cancer pain management based on the "three-step ladder" (Figure 4-1). The WHO guidelines for managing cancer pain have since become the standard most oncologists follow for routine cancer pain management.

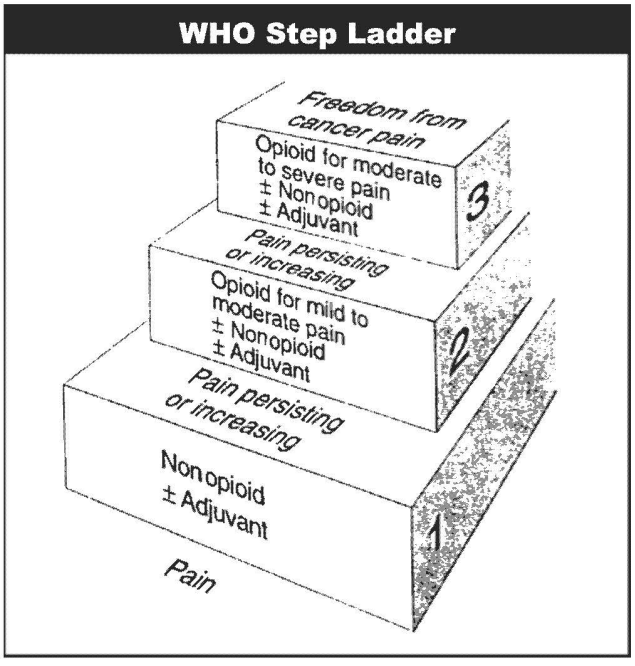
It should be noted, however, that the WHO steps have been changing, at least unofficially. Many practitioners consider that there is a fourth step: more invasive therapies that are used for terminal patients who do not respond well to medical management. Some consider Step 2 to include all opioids and Step 3 to be adjuvant medications. Others regard Steps 2 and 3 to be weaker and more potent opioids, respectively, with adjuvant medications considered an unwritten step. In any regard,

the "Steps" are not rigid, but rather provide a general guideline. In general, the steps consist of:

1) Nonopioid analgesics
2) Opioid analgesics
3) Adjuvant medications
4) Invasive therapies

In all cases, the WHO guidelines call for all medications to be dosed "around the clock" and "by the clock", although breakthrough medications are allowed. The 3 steps of the classic WHO analgesic ladder are discussed in the following sections. When using this format, adjuvant medications can be added at any step.

Figure 4-1.



Step 1

For mild pain, a nonopioid analgesic is administered and an adjuvant drug added if a specific indication for one exists.

As discussed in Chapter 3, nonopioid analgesics include acetaminophen, salicylates (e.g., aspirin), and nonsteroidal anti-inflammatory drugs (NSAIDs). Adjuvant drugs

are, strictly speaking, those that enhance the effects of other drugs; although in this context the term also refers to agents that have specific actions in their own right.

Nonopioid analgesics share the following important characteristics:

- They have a ceiling analgesic effect, i.e., a dose above which additional increases produce no further analgesic effect
- They do not induce tolerance, physical dependence, or psychological dependence
- They do not cause respiratory depression

Except for acetaminophen, all of these drugs relieve pain in the peripheral tissues, primarily by inhibiting the synthesis of prostaglandins. Prostaglandins stimulate the painful inflammation that commonly surrounds tumors. They also enhance pain perception by stimulating nociceptors (pain sensing nerve endings) and by increasing the breakdown of bone (in the case of bone metastases).

The analgesic effects of nonopioid analgesics tend to be underestimated. These drugs are useful for reducing the pain associated with surgery, trauma, arthritis, and cancer, especially of tumors invading bone. Nonopioid analgesics may be used alone when pain is mild, or in combination with opioids when pain is moderate or severe. Nonopioid and adjuvant drugs are discussed in greater detail in the Pharmacologic Agents section of Chapter 3.

Step 2

If a Step 1 regimen fails to control pain, an oral opioid is administered in combination with a nonopioid analgesic.

This combination attacks pain through central and peripheral neural mechanisms. Many practitioners prescribe a combination product containing an opioid and nonopioid analgesic, such as codeine, hydrocodone, or oxycodone combined with aspirin or acetaminophen. Such agents are relatively inexpensive and are generally perceived to be weaker than morphine or the other potent agents. In reality, they are simply low-dose preparations that cannot be taken in great quantity because of the combined nonopioid medication.

Although these agents may be acceptable in patients with mild or intermittent pain, they have the distinct disadvantage of a short duration of action. This leads to their

being used PRN, rather than being taken on a schedule. For these reasons, most cancer patients proceed to Step 3 of the WHO ladder.

Step 3

If Steps 1 and 2 do not control the patient's pain, a strong oral opioid is administered, with or without a nonopioid analgesic or adjuvant drug.

(**Note:** many authors consider this to be Step "2B" and adjuvant medications Step 3.)

An opioid with flexible routes of administration and wide variation in available doses is used at this level. Long-acting or time-release preparations are suggested, because these medications are taken on a timed schedule, not PRN. A short-acting opioid may be added as rescue medications for breakthrough pain.

Morphine is the first choice as a potent opioid in most countries and is the WHO's opioid of choice. Methadone, hydromorphone, fentanyl, and oxycodone are also used. Some of the important characteristics that differentiate opioid analgesic agents from the nonopioid agents are listed below:

- They have no ceiling effect on analgesia.
- They do not have a set dose that is automatically safe or effective.
- They relieve pain primarily by activating opioid receptor sites in the brain and spinal cord.
- Their most common side effects are sedation, constipation, nausea, vomiting, and respiratory depression.

Step 4

If the above steps do not control the patient's pain, invasive therapies, such as implanted infusion pumps, destruction of nerves, or spinal cordotomy may
be indicated.

The Steps in Practice

In actual practice, the first step of cancer pain management is usually administering a nonopioid analgesic, with an adjuvant drug (antidepressant, sleeping pill, etc.) added if a specific indication for one exists. If this is not sufficient to control the patient's pain, a mild opioid is added. This combination attacks pain through both central and

peripheral neural mechanisms. Should the patient still have pain, a stronger, long-acting opioid is administered and the dose adjusted until the patient obtains relief. Should the patient develop side effects from one opioid, others are tried until an effective agent is found.

The principles of this therapy include taking medication on a routine schedule "around the clock" to prevent severe pain.

The principles of this therapy include taking medication on a routine schedule around the clock to prevent severe pain. For this reason, long-acting agents are preferred in most cases. A short-acting agent may be added if the patient experiences some episodes of pain not controlled by the long-acting medication. The oral route is preferred because of its simplicity and lack of complications. This simple pharmacologic approach can provide relief in 80% of cancer patients with pain. If they are not effective, referral to a pain center for reevaluation and possible Step 4 therapy should be considered.

Surgical Treatments for Pain

Palliative forms of general, orthopedic, and other surgery can relieve cancer pain in many situations. Examples include relief of bowel or urinary obstruction, repair and fixation of pathological fractures, drainage of abscesses, and debulking (reducing the size of) large tumors.

Neurosurgery is not usually necessary for treating cancer pain, but is required in a few cases for one of 2 reasons: spread of the disease and/or control of severe localized pain. In some patients, spread of tumor to the bones of the spine compresses the spinal cord. This requires emergency neurosurgery to relieve the compression or paralysis will result.

In some cases, neurolytic (nerve destroying) operations are needed to control severe localized pain. These are considered one of the Step 4 therapies and are only used in a few specific cases—usually, patients with severe localized pain that does not respond to any conservative treatment. In patients who are suitable, destroying the pain pathways may provide long-lasting relief with minimal side effects. A number of different neurolytic procedures can be performed.

Percutaneous cordotomy is the most commonly performed palliative neurosurgical procedure. It can be carried out using only a small incision or needle puncture, through which a small area of the spinal cord is destroyed. It is indicated when

unilateral (one-sided) pain below the head and neck cannot be controlled by other means. In this operation, the spinothalamic tract (which carries pain and temperature information to the brain) is severed on one side of the spinal cord at the neck level, producing loss of pain and temperature sensation below that level. The remainder of the spinal cord remains intact, and no other function is lost (hopefully).

Trigeminal nerve root rhizotomy (pronounced 'rye-zot-oe-mee') means destroying the large trigeminal nerve, which carries sensation directly from the face to the brain. A special microwave needle is inserted underneath the cheekbone to destroy the trigeminal nerve where it exits the skull. The procedure is used only for patients whose pain is confined to the trigeminal nerve distribution (i.e., the face, teeth, mouth, and nose).

Sympathectomy (destroying part of the sympathetic nervous system) may be performed when cancer pain originates from certain tumors of the internal organs. Usually, a temporary sympathetic nerve block is performed first to be certain destroying the nerve will relieve the patient's pain. Then a neurolytic (nerve destroying) block or a surgical sympathectomy (cutting the sympathetic nervous system tracts) is performed to provide permanent pain relief. This is usually used for tumors involving the pancreas or other abdominal organs.

Surgical hypophysectomy (pronounced 'hi-pof-is-eck-toe-mee') means the removal of the pituitary gland. The pituitary, which is situated at the base of the brain, regulates much of the normal hormonal activity of the body. Surgical hypophysectomy may be appropriate for patients with severe generalized pain caused by metastatic disease. How removal of the pituitary gland reduces pain is unclear, but the effect is fairly well documented.

Surgical disruption of thalamic sites (areas in the upper brainstem) can also often relieve slow, suffering types of pain while preserving the patient's appreciation of acute pain. This procedure requires specialized equipment and is rarely used.

Nonsystemic Administration of Opioids

Drug infusion pumps, as discussed in Chapter 3, allow 24-hour-a-day infusions of opioids and other medications directly into the cerebrospinal fluid bathing the spinal cord. They are used in a few cancer patients when oral opioids are ineffective or

cause severe side effects. However, these devices are extremely expensive and therefore are usually reserved for patients who are expected to live at least 6 months.

This technique is generally not effective for pain involving the head and neck region. There have been a few reports of inserting a catheter directly into the skull in such cases, delivering morphine directly to the fluid around the brain. This route of administration is still considered experimental, however.

Management of Some Cancer Pain Syndromes

For each individual patient, the therapies discussed above are used together, in various combinations, to achieve the best possible pain control with the lowest incidence of side effects. Which therapies are appropriate for an individual depends on many factors. These include the severity of symptoms, amount of family support, and patient finances (unfortunately, many therapies are not covered by insurance plans). Most important, however, is the type of cancer the patient has, and the way that the cancer is causing pain.

Several cancer pain syndromes (a group of findings and symptoms that commonly occur together) are quite common, and standard protocols for treating them have been developed. These common syndromes include

- bone metastases
- peripheral neuropathies
- postmastectomy syndrome

Bone Metastases

Cancer of the breast, prostate, lung, and multiple myeloma (a cancer of the blood-forming cells inside of bones) are the most common causes of bone metastases. The most common locations of bone metastasis include the vertebrae (bones of the spine), pelvis, femur (thigh bone), and skull. The most frequent symptom is pain, although 25% of patients with bone metastases have no symptoms. In addition to pain from the bones, patients may also experience pain from compression of adjacent nerves, vascular structures, and soft tissue.

Multiple areas of deep, aching pain that is worse with movement are the most common symptoms. However, spine metastases may compress nerve roots, resulting in radicular (radiating neuropathic) pain that can be shooting or burning in character.

Besides pain and immobility, complications of bone metastases include fractures, hypercalcemia (very high calcium levels in the blood, causing seizures), and spinal cord compression. When pathologic fractures occur, they are most likely to involve the spine, femur, or hip. X-rays, nuclear medicine scans, and magnetic resonance imaging (MRI) are used to confirm the diagnosis of bone metastasis.

Radiation treatments, and sometimes chemotherapy, are given to directly kill the invading tumor. Radiation is particularly effective for treating most forms of bone pain, sometimes relieving the pain in a matter of days. Patients with several different bony metastases may benefit from radiation given internally, rather than standard X-ray radiation (which is considered external radiation). A radioactive chemical, Strontium-89, that collects in the bones is given in these situations. However, Strontium-89 destroys some of the blood-forming cells of the bone marrow, so it cannot be used in patients receiving chemotherapy. It can take weeks or more to effectively remove the tumor, so immediate efforts are made to treat the pain. These efforts usually include opioid medications and NSAIDs. In some cases, particularly when spinal bones are involved, cortisone either taken by mouth or injected into the area is beneficial. Some other kinds of medication reduce the pain of bone metastasis by slowing the destruction of bone. Bisphosphonate drugs or calcitonin, a naturally occurring hormone, are used for this purpose, although they may have significant side effects.

Peripheral Neuropathies

Peripheral neuropathies result when nerves are compressed or infiltrated by tumor, damaged by neurotoxic chemotherapy, or injured by the retraction of tissues during surgery. Some specific types of cancer, such as myeloma, may cause a progressive painful neuropathy by mechanisms we do not understand.

Neuropathy is characterized by sensory loss, burning, or tingling sensations and sometimes by weakness and muscle wasting. There may also be sudden episodes of shooting or shocking pain. Neuropathy may involve a specific area of the body, but often (especially when caused by chemotherapy) involves the most distal body parts: the hands and feet.

There is no test to find or diagnose neuropathic pain because the damage is microscopic and does not show up on an MRI or CT scan. A nerve conduction study may show the damage if it is severe, but most physicians rely on the patient's description of the pain to make the diagnosis.

In about half of cases, neuropathic pain does not respond well to any opioid medication. The primary treatment involves using the adjunctive medications such as antidepressants, antiseizure medications, and benzodiazepines to stop the damaged nerve fibers from sending out abnormal messages. Neurostimulation (see Chapter 3) may be beneficial, but is usually reserved for patients with a long life expectancy.

Postmastectomy Syndrome

This condition occurs in up to 5% of women who have had a mastectomy, even if the cancer was entirely removed. It is more common in those who have also had radiation and therapy to the area. The pain is usually described as a burning pain located in the armpit, back of the arm, and chest wall. There is usually a tight sensation that makes moving the shoulder difficult, and movement of the arm tends to make the pain worse. Swelling of the arm often occurs and is made worse by the lack of movement.

Although medications can be helpful, the most important therapy for postmastectomy syndrome is an aggressive physical therapy to restore movement and motion. This not only relieves pain (eventually); it will reduce swelling and prevent the condition from becoming worse. The therapy can be quite painful at first, however, so it is important that potent opioid medications are available to provide sufficient relief so that the patient can complete therapy. Nerve blocks can be very helpful, especially if there is a trigger area that causes radiating pain.

Summary

- Effective cancer pain management involves the individualized use of several different types of medications, sometimes in association with other therapies.
- Medications should be used in a sequential fashion, always attempting to relieve the patient's pain with minimal side effects and complications.
- Although many patients can be managed with a simple regimen of oral medications, a few will require the use of several different therapies to achieve pain control.

Self-Assessment Test

Circle the best response

1). The initial focus of cancer treatment is to:
   a. Restore the patient's ability to function
   b. Relieve pain
   c. Treat depression
   d. Cure the disease

2). Which route of opioid administration should be used whenever possible?
   a. Oral
   b. Injectable
   c. Transdermal
   d. Opioids should be avoided until the disease is terminal

3). Opioid analgesics should be administered to cancer patients:
   a. On a schedule, around the clock
   b. Every 4 hours on an as needed basis
   c. Only after the disease has become terminal
   d. As the first medication used

4). The first step in all versions of the WHO ladder is:
   a. Antidepressants
   b. Adjunctive medication
   c. Nonopioid analgesics
   d. Opioid analgesics

5). Which medications reduce pain by suppressing the inflammatory process, reducing prostaglandin-induced chemical stimulation of nociceptors?
   a. Opioids
   b. NSAIDs
   c. Tricyclics
   d. Antiepileptics (antiseizure medications)

6). The first choice of a potent opioid used for cancer pain is usually:
   a. Hydrocodone
   b. Morphine
   c. Tylenol
   d. Meperidine

7). To be considered a candidate for a drug infusion pump, a cancer patient must have a life expectancy of at least:
   a. 3 months
   b. 6 months
   c. 1 year
   d. 3 years

8). The definitive treatment of bone metastases is usually:
   a. Radiation
   b. Chemotherapy
   c. Surgery
   d. Opioids

9). Until this therapy is effective, however, patients with bone metastases are usually treated with:
   a. Radiation and surgery
   b. Chemotherapy and opioids
   c. Antidepressants and NSAIDs
   d. NSAIDs and opioids

10). Postmastectomy syndrome is usually treated with aggressive physical therapy. However, opioids are useful to:
   a. They are really not useful, since it is neuropathic pain
   b. Allow the patient to tolerate physical therapy
   c. Provide relief until radiation therapy is completed
   d. Help with postoperative pain.

11). Percutaneous_____ is an operation performed through the skin in which a particular area of the spinal cord is cut to relieve pain in certain desperate cases.
   a. Hypophysectomy
   b. Opioid therapy
   c. Cordotomy
   d. Pump implantation

Answers to Self-Assessment

1). d	7). b
2). a	8). a
3). a	9). d
4). c	10). b
5). b	11). c
6). b	

CHAPTER FIVE

Management of Chronic Benign Pain

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Understand the differences between cancer pain and chronic benign pain.
- Name 6 common causes of chronic benign pain.
- Describe the modifying factors that often exist in chronic benign pain.
- Understand the usefulness of opioids in chronic benign pain.
- State the risks of opioid therapy to patients with chronic benign pain.
- State the risks physicians face in prescribing opioids for chronic benign pain.
- Discuss the techniques used to minimize those risks.

Terminology

Anxiolytic:	Reducing or preventing anxiety.
Carpal tunnel syndrome:	Entrapment of a large nerve at the wrist, causing pain and numbness in the palm and fingers.
Coping skill:	A means of dealing with difficult or stressful situations.
Incidence of abuse:	The frequency that a certain drug is reported by legal agencies to be abused. Overdoses, overdose deaths, and arrests for illegal sales are the usual sources of such numbers.
Neuropathic pain:	Pain resulting from damage to the nerves.
Street value:	The price for which a drug is commonly sold illegally or for illegal use.(i.e., "on the street").
Secondary gain:	A gain (financial, emotional, or social) resulting from (or secondary to) what would appear to be an unpleasant situation.
Somatic pain:	Sharp, localized pain originating from the skin, muscles, tendons, ligaments, and bones.
Subjective:	Cannot be seen, felt, or shown on laboratory test. A subjective diagnosis is one that is made on the basis of the patient's history rather than a finding on physical exam or by testing.
Therapeutic regimen:	All of the combined treatments used for a certain condition.

Introduction

Patients with chronic pain include those with pain due to cancer and those with pain due to all other causes (chronic benign pain, or CBP). This distinction arose from obvious observations: cancer pain is considered more severe, worsens more rapidly, and the underlying cause of pain is in plain sight. Perhaps most important, most patients with chronic cancer pain succumb to their illnesses within a few years. The causes of CBP, on the other hand, are often difficult to determine, the symptoms do not change rapidly, and the patient usually survives to a normal life expectancy.

These differences are reflected in the goals of therapy and type of treatment the patients receive. As discussed in the last chapter, persons with cancer pain are treated primarily with opioids and with therapies directed at fighting the cancer. The primary goal of cancer pain treatment is to relieve symptoms and provide comfort.

The primary goal of CBP treatment is to restore the person's ability to function; relief of the pain is only one of the treatments required to restore function.
Relief of the subjective pain is important, but treatment is not considered successful if the person's ability to function is not improved. Persons with CBP are treated with a variety of different therapies, depending on the conditions involved. Opioid medications have a place in that therapeutic regimen, but the exact nature of that place varies widely depending on the individual patient and the practitioner involved.

The general principles of evaluation (Chapter 2) and pain treatment (Chapter 3) are applied to every patient with CBP. This chapter provides an overview of how those tools are actually used to manage these patients and the decisions a practitioner must make in treating them.

Differences in Treating Chronic Benign Pain and Cancer Pain

Treating chronic benign pain is often more problematic to treat than cancer pain. Some of the features of chronic benign pain that make it more challenging to treat than cancer pain include:

- Difficulty estimating the severity of the pain
- Subjective diagnosis
- Presence of pain behaviors
- Presence of potential or realized secondary gains
- Normal life expectancy
- Potential for spurious claims
- Potential for underlying psychiatric or psychological pathology

The cause of CBP is usually less clear than the cause of cancer pain. The severity of pain the patient is experiencing is also often unclear, because it is difficult or impossible to actually see the cause of pain on a diagnostic image or test. When an MRI scan shows a tumor invading the bones of a cancer patient's spine, one assumes the patient has significant pain. When an MRI shows scar formation in the spine after surgery for a ruptured disc, the conclusion is less clear. Many patients with such scars feel normal and return to work. Others have severe pain that prevents them from even walking far enough to get the mail. Few physicians will flatly deny that the patient has pain, but some will wonder if the pain is as severe as the patient describes. Many of the conditions that cause CBP are subjectively diagnosed, meaning there is no test or finding the physician can use to say "this test shows the diagnosis is X". Subjective diagnoses are made largely on the basis of the symptoms the patient describes. For example, there is no test to show whether a person does, or does not, have fibromyalgia. The diagnosis is made on the basis of the symptoms the patient tells the physician about.

> Patients with CBP often suffer depression and anxiety, as severe as that experienced by cancer patients. However, they often have a history of these problems before they developed chronic pain.

Patients with CBP often suffer depression and anxiety, similar to that experienced by cancer patients. However, they often have a history of these problems existing before they developed chronic pain. Additionally, as discussed in Chapter 2, some of these patients show "pain behaviors", exaggerated symptoms, and descriptions of their pain. Additionally, many CBP patients have unconsciously learned to use their pain to avoid unpleasant situations or emotional stress. In some cases, they have lost the normal coping skills that they once used to face normal life stresses.

Additionally, some patients with CBP may have "secondary gains" involved in their pain. This may involve litigation over the injury that caused their pain. In other cases, patients are fighting to receive disability for their condition. In either case, the patient may be aware that should their pain go away, so will their settlement or disability payment. Cancer patients do not typically have such issues. Perhaps the most significant difference between cancer pain and CBP, however, is life expectancy. Most cancer patients who require significant pain management have a terminal illness and are expected to live a few years or less. CBP patients have a near normal life expectancy and therefore their treatment is expected to last for many years or even decades.

Finally, the clinician must always be aware of patients who for various reasons claim an injury or illness that does not really exist. It has been estimated that as many as 10% of patients seeking treatment for CBP do not actually have a physical problem. In many of these cases, the patient has a psychological illness that produces physical symptoms. In others, the patient is actually feigning an illness to receive financial reward or to obtain medications. Whatever the cause, the clinician must always remain alert to the possibility that the patient does not actually have a physical problem.

All of these features make CBP more difficult to diagnose and treat than cancer pain. However, the majority of CBP patients have a real, physical illness and are not exaggerating their symptoms. These patients deserve effective treatment of their symptoms.

Chronic Benign Pain Syndromes

Although the number of diseases and syndromes that cause CBP are far too numerous to mention individually, the following 6 broad categories of problems account for most patients seen in offices and clinics.

Back or Spine Problems are the most common source of CBP. The vast majority of low back pain results from muscular injuries and degenerative arthritis of the spine, but these tend to be self-limited or intermittent problems that don't really cause chronic pain. "Failed surgery syndrome" or "multiple laminectomy syndrome" is a more common cause of severe chronic pain. Such patients have usually had two or more surgeries for ruptured discs, resulting in scar formation around spinal nerves, as well as degeneration of the bones and joints of the spines. The condition is most common in the lumbar (low back) region, but can also occur in the neck. Such patients usually have both somatic pain (which is felt in the back or neck) and neuropathic pain (which radiates into the leg or arm). Other spinal conditions that cause chronic pain are stenosis (narrowing of the spine or the openings the spinal nerves travel through), spondylosis (degeneration of the joints of the spine), and spondylolisthesis (instability of the bones of the spine).

Connective Tissue Diseases refer to conditions involving the joints, tendons, and muscles. Degenerative arthritis is a common painful connective tissue disease in older adults. Rheumatoid arthritis, lupus erythematosus, and other autoimmune diseases (the immune system attacks the body's tissues) are also common connective tissue diseases that cause chronic pain. All of the connective tissue diseases cause somatic pain.

Peripheral Neuropathy and Neuralgia result when damage to peripheral nerves causes neuropathic pain. Neuralgia often occurs when nerves are compressed by other structures in the body, as is the case with carpal tunnel syndrome. Peripheral neuropathy results when a disease causes generalized damage to long nerve fibers, resulting in pain of the feet and hands. Diabetes is the most common cause of peripheral neuropathy.

Central Pain Syndromes result from damage to the central nervous system. This may occur after a stroke, from damage to the spinal cord, or as "phantom limb pain",

a rare condition that sometimes follows amputation. Central pain syndromes are considered a form of neuropathic pain.

Sympathetically Mediated Pain Syndromes have a number of names including reflex sympathetic dystrophy (RSD), causalgia, and complex regional pain syndrome (same as RSD). Although these conditions are each fairly rare, they cause extremely severe pain and are difficult to treat.

Headaches are quite common, and although most headache sufferers do not become chronic pain patients, a large number do. About 3% of the population suffers from chronic daily headache. (Stovner 2007). Most headache specialists, however, feel that chronic opioid therapy should be avoided in patients with headaches, because "opioid rebound" (a new headache developing when the opioid wears off) is common. For this reason, they will not be discussed further.

It should be noted that many patients with CBP suffer more than one condition and more than one type of pain. For example, a patient with rheumatoid arthritis (a somatic pain) is likely to develop carpal tunnel syndrome or other conditions causing peripheral neuralgia (neuropathic pain).

Treatment of Chronic Benign Pain

The basic strategies of CBP management follow those discussed in previous chapters. A careful clinical assessment is required in every case to determine the possible causes of pain and correct them if possible. At the same time, the clinician must be alert for consistency of behavior and the presence of pain behaviors that may indicate whether a patient is exaggerating or making up symptoms.

In CBP, adjunctive medications are considered even more important than they are in managing

Once a diagnosis is made, the treatment plan is individualized for the condition. In CBP, adjunctive medications are considered even more important than they are in managing cancer pain. Most patients with CBP will receive one or more adjunctive medications. NSAIDs, muscle relaxants, tricyclic antidepressants, serotonin-selective antidepressants, and antiepileptic medications are all used frequently.

Patients with connective tissue disease, for example, may receive NSAID medications, opioids to relieve somatic pain, and occasional short courses of cortisone to treat flare-ups of their disease. A person with peripheral neuropathy will receive trials of several antiepileptic medications and tricyclic antidepressants.

In addition to medications, CBP patients usually receive other types of therapy. Because many of them have been inactive or even immobile, physical therapy or an exercise program may be needed to restore function. Nerve blocks or other invasive therapies may be helpful in certain conditions. Antidepressant medications, psychotherapy, or anxiolytic medications may help relieve secondary psychological symptoms. Treatments such as acupuncture and TENS (transcutaneous electrical nerve stimulation) units are sometimes used because they have few side effects and can be continued safely for many years.

Depending upon the individual practice and practitioner, opioid medications may be used in a small percentage or the vast majority of CBP patients. To some degree, this variation reflects the type of patients seen. Those with primarily somatic pain are likely to obtain relief from opioids, whereas those with neuropathic pain are far less likely to benefit. Other factors, including the practitioner's specialty training, the geographic location, and personal prejudices of the practitioner may also affect the frequency of opioid prescription.

As discussed in Chapter 2, the effects of each treatment must be monitored and evaluated. It is quite common for the treatment plan to be adjusted several times before it becomes effective. The medications used to treat neuropathic pain, for example, frequently have side effects and each may take several weeks to show benefit. It may take several months before an effective medical regimen is found.

Although the effect of the therapy in reducing the patient's pain is of primary importance, the improvement in the patient's ability to function is considered the gold standard of chronic pain treatment. Being able to perform more household tasks, walk longer distances, or even return to work are usually considered the key measurements in treating CBP. It is also important to confirm improvement with family members. Too often, a patient reports that their treatment relieves their pain quite effectively, but a spouse complains that the patient is sedated or even intoxicated from their medication.

Opioid analgesics for Chronic Benign Pain

There remains no question that opioids effectively reduce the severity of most types of CBP. They are most effective when the pain is somatic in origin, but are somewhat less effective in the treatment of NCP.

When used in CBP, opioids are generally dosed in a manner very similar to the WHO ladder used in cancer pain: a nonopioid analgesic is used initially, with opioid medications added if this is not effective, and stronger opioids prescribed when necessary. As with cancer pain, opioids for CBP are used "by the clock" on a scheduled basis, with breakthrough medication sometimes (but not always) made available.

As with cancer pain, the dose of opioids is titrated upward if the initial dose is insufficient. Unlike in cancer pain, however, most practitioners will not continue to titrate opioid dosage upward indefinitely for CBP. Rather, they have a "comfort level" that they are not willing to exceed in patients with chronic benign pain. There are several reasons for this. Because CBP patients may require opioid medications for many years, physicians may be concerned that high doses used early may make opioids less effective when or if the disease progresses.

Controversy and disagreement between clinicians continue regarding the appropriate use of opioids in CBP. Some clinicians prescribe them for the majority of their patients, whereas others use them only occasionally and in very limited quantities. There are several reasons some clinicians are hesitant to prescribe large quantities of opioids for patients with CBP:

- *Development of Tolerance and Physical Dependence* is a major reason some clinicians feel opioid therapy should be limited for patients with CBP. Most clinicians do not consider this a major issue, however. Although tolerance and dependence do occur with long-term use of opioids, many studies have shown that tolerance is limited in most patients with CPB. Physical dependence simply requires a tapered withdrawal should the opioid medication no longer be needed.
- *Sedation and somnolence* are more significant side effects in patients with CBP (who are expected to function) than in patients with cancer pain. However, these side effects are usually self-limited or can be managed by changing to a different opioid.

- *Substance Abuse* will be seen in a few patients in every CBP practice, perhaps largely because patients attempting to obtain opioids will eventually end up at a pain management practice. However, despite the continued unscientific beliefs of some clinicians, there is no evidence that simply taking opioids for a period of time will cause substance abuse or addiction. It appears likely that most substance-abusing patients in pain management practices had an abuse problem before entering the practice. This topic is so important, and so much misinformation exists, that it is discussed separately in Chapter 6.
- *Regulatory Criticism for Inappropriate Prescribing* has become an increasing problem since 1999, largely because of the problem with OxyContin® abuse and diversion. Many persons working to curtail substance abuse, including some medical professionals, are outspoken in opposition to the use of chronic opioid therapy in CBP because of the abuse and diversion of prescription opioids.

  Clinicians are also concerned about how regulatory agencies view prescribing high-dose opioids to patients with CBP. Should a patient be diverting the medication for illicit resale, the prescribing clinician may come under investigation. Should the patient later be found to have a substance abuse problem (see Chapter 6), the clinician could be sued for failure to diagnose the problem.

Guidelines for Opioid Use in Chronic Benign Pain

With increasing regulatory efforts and high profile arrests of clinicians for overprescribing, many clinicians are understandably reluctant to prescribe opioids. However, clinicians often do not have a clear understanding of why certain clinicians have been arrested, and do not have a working knowledge of what is expected of them when they write opioid prescriptions. Educating clinicians about these guidelines will help to ease their fears of prescribing for patients with CBP.

Three national guidelines have been published concerning the use of opioids in CBP. The American Academy of Pain Medicine and American Pain Society have published a consensus statement – "The Use of Opioids for the Treatment of Chronic Pain". Although supportive, the document is very broad and does not provide clinicians with specific instructions for the appropriate use of opioids.

The Federation of State Medical Boards has developed Model Guidelines for the Use of Controlled Substances for the Treatment of Pain (Appendix 5-1), which has in turn been adopted by numerous state medical boards. The model guidelines do set standards regarding the minimum acceptable documentation a physician should maintain when prescribing opioids. It should be noted that no guidelines, including this one, give an appropriate "dosage range" for using opioids in CBP. Rather, they simply discuss the steps a physician should take to document proper medical decision-making and monitoring of the patient.

No guidelines give an appropriate "dosage range" for using opioids in CBP

The American Society of Anesthesiology Task Force on Pain Management has published an even more in-depth set of practice guidelines. These apply only to Board Certified Pain Specialists, but this group makes up the largest number of physicians who treat CBP. These guidelines are more limiting with regards to opioid use than the Federation of State Medical Boards Guidelines, stating:

> *"Opioid therapy may be considered when analgesia provided by other modalities is no longer adequate to manage chronic pain. Delivery of opioids should occur within the context of a logistic system that provides the resources and availability of personnel to respond to patient needs and according to applicable local, state, and federal regulations. The analgesic benefits of opioids should be balanced against the potential adverse sequelae of long-term opioid use."*

Following these and other guidelines minimizes the clinician's risk when prescribing opioids for CBP, but does not eliminate the risk altogether. Some clinicians remain so concerned about the possibility of regulatory action that they are unwilling to prescribe opioids for CBP. Others find that the paperwork and other efforts needed to follow the suggested guidelines are so burdensome they are also not willing to prescribe opioids.

However, many clinicians do not realize that certain opioids are far more likely to be diverted and abused than others and are therefore more likely to attract the attention of regulatory agencies. Pointing out the lower frequency of diversion and lower street values of agents such as KADIAN® may be beneficial in such cases.

Summary

- Chronic benign pain requires more diverse and more complex treatment than does the management of cancer pain.
- Opioid medications can be a beneficial part of that treatment for many patients with CBP. However, fear of regulatory effort, controversy regarding the long-term effects of opioids, and poor understanding of addictive disease prevent some clinician from using opioid therapy effectively.

Literature Cited

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Self-Assessment Test

Circle the best response

1). The biggest difference between patients with chronic benign pain and cancer pain is the difference in:
   a. Opioid requirement
   b. Life expectancy
   c. Rate of return to work
   d. Incidence of depression

2). The primary goal in the treatment of CBP is to:
   a. Restore ability to function
   b. Provide pain relief
   c. Prevent depression
   d. Return the patient to work

3). The diagnosis of the cause of CBP is often made by:
   a. Laboratory tests
   b. X-rays or other imaging studies
   c. Subjective complaints and symptoms
   d. Family history

4). Compared with cancer patients, those with CBP are more likely to have all of the following situations EXCEPT:
   a. Loss of job or income
   b. Psychological problems
   c. Secondary gains
   d. Symptom exaggeration

5). What percent of persons seeking treatment for CBP do not have any physical problem?
   a. 1%
   b. 10%
   c. 20%
   d. 50%

6). The most common source of benign pain are problems originating:
   a. From the back
   b. From nerve damage
   c. From arthritic joints
   d. From diabetes

7). When dosing opioids for CBP (as compared to cancer pain), physicians are more likely to have a _____ with dosing.
   a. Comfort level or ceiling
   b. Tolerance
   c. 4 Step ladder
   d. Lack of education

8). Which of the published guidelines for opioid use in CBP provides an "appropriate dosage range"?
   a. American Academy of Pain Medicine /American Pain Society joint consensus statement
   b. Federation of State Medical Boards "Model Guidelines"
   c. American Society of Anesthesiology Task Force on Pain Management Guidelines
   d. None of them give an appropriate dosage range.

True or False

Mark **True** if the statement is a common reason clinicians are uncomfortable prescribing opioids; **False** if it is not a common reason.

9). Developing tolerance or dependence

10). Oversedation

11). Chronic nausea

12). Possibility of substance abuse

13). Worry over regulatory criticism

Answers to Self-Assessment

1. b	8. d
2. a	9. true
3. c	10. true
4. a	11. false
5. b	12. true
6. a	13. true
7. a	

Appendix 5-1

Model Guidelines for the Use of Controlled Substances for the Treatment of Pain

The recommendations contained herein were adopted as policy by the House of Delegates of the Federation of State Medical Boards of the United States, Inc., May 1998.

Section 1: Preamble

The (name of Board) recognizes that principles of quality medical practice dictate that the people of the State of (name of state) have access to appropriate and effective pain relief. The appropriate application of up-to-date knowledge and treatment modalities can serve to improve the quality of life for those patients who suffer from pain as well as reduce the morbidity and costs associated with untreated or inappropriately treated pain. The board encourages physicians to view effective pain management as a part of quality medical practice for all patients with pain, acute or chronic, and it is especially important for patients who experience pain as a result of terminal illness. All physicians should become knowledgeable abut effective methods of pain treatment as well as statutory requirements for prescribing controlled substances.

Inadequate pain control may result from physicians' lack of knowledge bout pain management or an inadequate understanding of addiction. Fears of investigation or sanction by federal, state and local regulatory agencies may also result in inappropriate or inadequate treatment of chronic pain patients. Accordingly, these guidelines have been developed to clarify the Board's position on pain control, specifically as related to the use of controlled substances, to alleviate physician uncertainty and to encourage better pain management.

The Board recognizes that controlled substances, including opioid analgesics, may be essential in the treatment of acute pain due to trauma or surgery and chronic pain, whether due to cancer or non-cancer origins. Physicians are referred to the U.S. Agency for Health Care and Research Clinical Practice Guidelines for a sound approach to the management of acute and cancer-related pain. The medical management of pain should be based on current knowledge and research and include

the use of both pharmacologic and nonpharmacologic modalities. Pain should be assessed and treated promptly, and the quantity and frequency of doses should be adjusted according to the intensity and duration of the pain. Physicians should recognize that tolerance and physical dependence are normal consequences of sustained use of opioid analgesics and are not synonymous with addiction.

The (name of board) is obligated under the laws of the State of (name of state) to protect the public health and safety. The Board recognizes that inappropriate prescribing of controlled substances, including opioid analgesics, may lead to drug diversion and abuse by individuals who seek them for other than legitimate medical use. Physicians should be diligent in preventing the diversion of drugs for illegitimate purposes.

Physicians should not fear disciplinary action from the Board or other state regulatory or enforcement agency for prescribing, dispensing or administering controlled substances, including opioid analgesics, for a legitimate medical purpose and in the usual course of professional practice. The Board will consider prescribing, ordering, administering or dispensing controlled substances for pain to be for a legitimate medical purpose if based on accepted scientific knowledge of the treatment of pain or if based on sound clinical grounds. All such prescribing must be based on clear documentation of unrelieved pain and in compliance with applicable state or federal law.

Each case of prescribing for pain will be evaluated on an individual basis. The Board will not take disciplinary action against a physician for failing to adhere strictly to the provisions of these guidelines, if good cause is shown for such deviation. The physician's conduct will be evaluated to a great extent by the treatment outcome, taking into account whether the drug used is medically and/or pharmacologically recognized to be appropriate for the diagnosis, the patient's individual needs-including any improvement in functioning-and recognizing that some types of pain cannot be completely relieved.

The Board will judge the validity of prescribing based on the physician's treatment of the patient and on available documentation, rather than on the quantity and frequency of prescribing. The goal is to control the patient's pain for its duration while effectively addressing other aspects of the patient's functioning, including physical, psychological, social and work-related factors. The following guidelines are not intended to define complete or best practice but rather to communicate what the Board considers to be within the boundaries of professional practice.

Section II: Guidelines

The Board has adopted the following guidelines when evaluating the use of controlled substances for pain control:

1. Evaluation of the Patient

A complete medical history and physical examination must be conducted and documented in the medical record. The medical record should document the nature and intensity of the pain, current and past treatments for pain, underlying or coexisting diseases or conditions, the effect of the pain on physical and psychological function, and history of substance abuse. The medical record also should document the presence of one or more recognized medical indications for the use of a controlled substance.

2. Treatment Plan

The written treatment plan should state objectives that will be used to determine treatment success; such as pain relief and improved physical and psychosocial function, and should indicate if any further diagnostic evaluations or other treatments are planned. After treatment begins, the physician should adjust drug therapy to the individual medical needs of each patient. Other treatment modalities or a rehabilitation program may be necessary depending o the etiology of the pain and the extent to which the pain is associated with physical and psychosocial impairment.

3. Informed Consent and Agreement for Treatment

The physician should discuss the risks and benefits of the use of controlled substances with the patient, persons designated by the patient or with the patient's surrogate or guardian if the patient is incompetent. The patient should receive prescriptions from one physician and one pharmacy where possible. If the patient is determined to be at high risk for medication abuse or have a history of substance abuse, the physician may employ the use of a written agreement between physician and patient outlining patient responsibilities, including:

- Urine serum medication levels screening when requested;
- Number and frequency of all prescription refills; and
- Reasons for which drug therapy may be discontinued (i.e., violation of agreement).

4. Periodic Review

At reasonable intervals based on the individual circumstances of the patient, the physician should review the course of treatment and any new information about the etiology of the pain. Continuation or modification of therapy should depend on the physician's evaluation of progress toward stated treatment objectives, such as improvement in patient's pain intensity and improved physical and/or psychosocial function, i.e., ability to work, need of health care resources, activities of daily living and quality of social life. If treatment goals are not being achieved, despite medication adjustments, the physician should reevaluate the appropriateness of continued treatment. The physician should monitor patient compliance in medication usage and related treatment plans.

5. Consultation

The physician should be willing to refer the patient as necessary for additional evaluation and treatment in order to achieve treatment objectives. Special attention should be given to those pain patients who are at risk for misusing their medications and those whose living arrangement pose a risk for medication misuse or diversion. The management of pain in patients with a history of substance abuse or with a comorbid psychiatric disorder may require extra care, monitoring, documentation and consultation with or referral to an expert in the management of such patients.

6. Medical Records

The physician should keep accurate and complete records to include:

- The medical history and physical examination
- Diagnostic, therapeutic and laboratory results
- Evaluations and consultations
- Treatment objectives
- Discussion of risks and benefits
- Treatments
- Medications (including date, type, dosage and quantity prescribed)
- Instructions and agreements
- Periodic reviews

Records should remain current and be maintained in an accessible manner and readily available for review.

7. Compliance with Controlled Substances Laws and Regulations

To prescribe, dispense or administer controlled substances, the physician must be licensed in the state and comply with applicable federal and state regulations. Physicians are referred to *the Physicians Manual of the I.S. Drug Enforcement Administration* and (any relevant documents issued by the state medical board) for specific rules governing controlled substances as well as applicable state regulations.

CHAPTER SIX

Drug Abuse and Chronic Pain

Learning Objectives

After reading this chapter and completing the self-assessment test, the student should be able to:

- Describe the frequency of substance abuse.
- Define what substance abuse is and is not.
- Differentiate between tolerance and dependence.
- List the criteria for diagnosing substance abuse.
- Describe common signs of substance abuse.
- Differentiate pseudoaddiction from substance abuse.
- List the factors that are associated with substance abuse.
- Describe what steps a clinician must take if he or she diagnoses substance abuse.
- Explain the documentation guidelines required when clinicians prescribe chronic opioids.
- Describe the abuse risks of different categories of opioids.

Terminology

Craving:	An extremely strong psychological desire to use a substance.
Crossover abuse:	Shifting patterns of abuse from one substance to another, for example, an individual stops using cocaine but starts drinking heavily.
Demographics:	Distribution throughout the population.
Detoxification:	Tapering a medication to prevent withdrawal symptoms.
Epidemic:	Affecting a large number of individuals within a population.
Matrix:	The substances, other than the active drug, contained in a pill or capsule.
Naloxone/naltrexone:	Two opioid antagonists; medications that reverse the effects of opioids.
Polysubstance abuse:	Abusing several different types of drugs, i.e., alcohol and cocaine and opioids, either together or at different times.
Recovering:	An ex-abuser who now abstains. Such individuals remain at increased risk of relapse for at least several years.
Relapse:	Returning to substance abuse after a period of abstinence.
Substance abuse:	Continued use of a mood-altering substance despite repeated problems associated with its use.
Substance dependence:	Substance abuse associated with tolerance and withdrawal symptoms.

Introduction

The regulation of controlled substances to prevent their diversion and abuse has been an area of controversy since federal regulation began in the 1930s. Today, the problem is perhaps more difficult for the practitioner treating patients with chronic benign pain than ever before. Medical ethics and previous court decisions state that clinicians must adequately prescribe for their patient's pain control. However, criminal investigations and state medical board sanctions are possible if clinicians prescribe excessive amounts or with excessive frequency. Fortunately, such interventions are rarely needed.

> Lay persons, law enforcement personnel, and even clinicians do not understand exactly what substance abuse is.

To understand the problem, one must first understand what substance abuse actually is. Unfortunately, many laypersons, law enforcement personnel, and even clinicians do not understand exactly what substance abuse is. This chapter will review what substance abuse is and the steps clinicians are expected to take to prevent diversion of prescription drugs.

> Fifty percent of all primary care clinicians state that they have no knowledge concerning substance abuse, and 75% of all clinicians feel their knowledge is, at best, inadequate.

NOTE: When calling on clinicians, especially primary care clinicians, one should not assume that they understand the topics covered in this chapter. Fifty percent of all primary care clinicians state that they have no knowledge concerning substance abuse, and 75% of all clinicians feel their knowledge is, at best, inadequate. This lack of knowledge allows a golden opportunity to educate clinicians about substance abuse. However, the subject must be approached carefully. Approximately 1 in every 10 clinicians will have experienced the problems of substance abuse personally, or in a close family member, and may therefore have strong feelings on the subject.

Additionally, one must always remember that every opioid has at least some abuse potential. Avoid stating broad conclusions. Other pharmaceutical firms have lost credibility by stating that their product is "less abusable" or, even worse, has a "low abuse potential." Instead, always provide factual data. Statements such as "has a lower street value" or "is more difficult to remove active drug from the matrix," when accompanied by reprints of factual articles, are more accurate and more credible.

Substance Abuse and Chronic Pain

Until the 1980s, medical (and particularly state board of medical examiners) dogma was that the long-term use of opioids for chronic benign pain was always inappropriate. Practitioners who prescribed long-term opioid therapy, other than for cancer patients, were frequently investigated and sanctioned.

Beginning in the late 1980s, it became apparent that many patients with chronic pain improved markedly when given sufficient opioids for pain control and that they continued to benefit for years without significant problems. Many clinicians were surprised to find that the dosage requirements of these patients did not continually increase but rather remained stable. Clinicians who had been incorrectly trained to believe that taking opioids for a prolonged period would always result in addiction were surprised that most of these patients never exhibited any signs or symptoms of addictive disease.

The use of opioids to control chronic benign pain became even more common in the 1990s, as long-acting opioid preparations became readily available. The Joint Commission on Accreditation of Healthcare Organizations has issued guidelines on how to assess and manage pain. These guidelines require assessing the nature and intensity of the pain, establishing and using pain management procedures, and monitoring patient response to the pain intervention. A "Bill of Rights" asserting that patients had a right to effective pain control was adopted in many states. In most other states, the medical examiner boards eased prescribing guidelines. Some clinicians were even sued successfully for failing to prescribe sufficient opioid medications to control a patient's pain.

At the end of the 1990s, however, the increasing frequency of diversion and abuse of opioid medications, particularly OxyContin®, drew widespread public attention. Successful criminal prosecution of clinicians for indiscriminately prescribing opioids occurred, and federal and state drug enforcement agencies actively investigated many clinicians who prescribed large quantities of opioids. As a result, many clinicians became afraid to prescribe opioids for chronic
benign pain.

Most clinicians have only a superficial understanding of what substance abuse really is, are not skilled at recognizing the symptoms of the problem, and have no knowledge of the diversion and illicit resale of controlled medications. Most

clinicians do not know the laws and statues regarding prescribing controlled substances, because the subject is rarely covered in medical school or in continuing medical education courses. Similarly, many are unaware of their legal responsibilities when they become aware that patients in their practice have a substance abuse problem.

The responsibility for knowing state and federal regulations regarding prescribing, dispensing, or administering controlled substances ultimately lies with the clinician. However, the Federation of State Medical Boards specifically states that clinicians should not fear disciplinary action for ordering, prescribing, or administering controlled substances for a legitimate medical purpose in the course of professional practice. Prescribing and administering controlled substances for pain are legitimate if prescribed for a medical purpose. Prescribing should be done in the context of a diagnosis and documentation of unrelieved pain as part of a physician-patient relationship. (Federation of State Medical Boards 2004)

Demographics of Substance Abuse

The epidemic of drug abuse that exists today is a relatively modern phenomenon, first beginning in the mid 1800s and accelerating rapidly during the 1960s. Despite perennial declarations of a "war on drugs," since that time, the epidemic of drug abuse has continued. During the past 20 years, data have consistently shown that about 7.5% (7.9% in 2005) of the U.S. adult population has a significant substance abuse problem. The national Institute on Drug Abuse (NIDA) found that between 1990 and 1996 there was no change in the number of Americans (about 15 million) who were considered substance abusers. However, in the most recent NIDA report in 2005, a reported 19.7 million Americans reported current or recent (past month) illicit drug use.

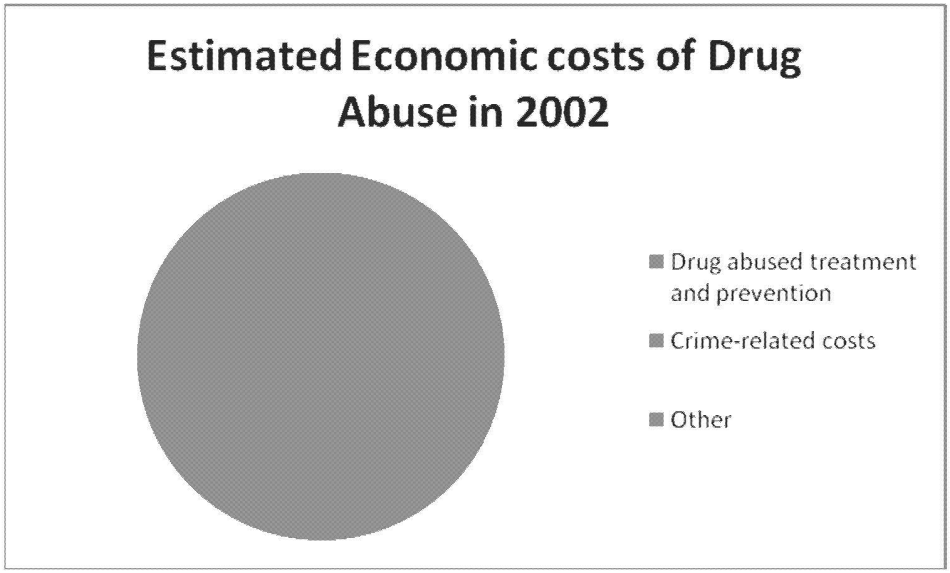
Marijuana has remained the most commonly used illicit drug since the 1960s, with about 2.4 million Americans beginning marijuana use each year. However, the use of other illicit drugs shows distinct historical trends. During the 1960s, abuse of hallucinogens, such as lysergic acid diethylamide (LSD) and peyote was common. In the 1970s, opioids and amphetamines were the most frequently abused drugs. During the 1980s, powder cocaine became the most commonly abused drug, reaching a peak of 5.7 million American users in 1985, then slowly falling in popularity. During the late 1980s and early 1990s, "crack" cocaine use reached epidemic proportions with

more than 600,000 users in 1997. In 2005, an estimated 900,000 individuals reported using cocaine. Recently, methamphetamine use has grown in popularity, with approximately 512,000 persons reporting use in 2005.

In recent years, the frequency of opioid abuse has increased dramatically. Heroin use in the United States increased from 68,000 persons in 1992 to 216,000 in 1996. According to the National Survey on Drug Use and Health (NSDUH), the number of current heroin users was steady at about 136,000 during 2004 and 2005. The number of current heroin users increased to 338,000 in 2006. Estimated lifetime use of heroin was 2,506,000 in 2005 and 3,947,000 in 2006. (Substance Abuse and Mental Health Services Administration;SAMHSA 2006)

Diverted prescription opioids, while always a problem, have become the predominant source of opioids in many areas of the country. The NSDUH estimates that the incidence of lifetime OxyContin® abuse was 3.1 million in 2004. In the month before the 2004 NSDUH survey of nonmedical use of prescription drugs, 4.4 million individuals used pain relievers, 1.6 million used tranquilizers, 1.2 million used stimulants, and 0.3 million reported using sedatives. The severity of the problem of prescription drug abuse has made opioid diversion the focus of both the lay press and law enforcement agencies in recent years.

The financial cost of substance abuse to society remains high. The U.S. government estimates that the economic cost of drug abuse in 2002 was $180.9 billion, representing the use of resources for health and crime consequences as well as loss of productivity, disability, and death. Approximately $9 billion dollars are spent each year on drug abuse treatment and prevention. In 2002, the U.S. government estimated that crime-related costs of drug abuse were estimated to be $107 billion.



Definitions of Substance Abuse and Dependence

Scientific efforts to understand substance abuse began only during the epidemic of drug abuse that began in the 1960s. Concepts and terminology in the field are constantly changing to reflect the improved understanding of substance abuse. The term *narcotic* is rarely used by addictionologists (although it remains in use by law enforcement agencies and court systems). Medically, *narcotic* refers to a drug of the opioid class; legally, the term refers to any illicit drug.

Although the term *addiction* or the *disease of addiction* remains in widespread use among clinicians and the lay public it is no longer used by the American Psychiatric Association or by addictionologists. Currently, the terms *substance abuse* and *substance dependence* are used for medical diagnosis.

Substance abuse is defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders as a maladaptive pattern of chemical substance use that significantly interferes with a person's life as indicated by at least one of the following:

- Neglect of work, school, or home obligations
- Use of the substance in a hazardous situation (e.g., driving, operating machinery)
- Repeated substance-related legal problems

- Continued use of the substance despite harmful, recurrent social or interpersonal problems associated with its use.

Although no single cause of substance abuse exists, substance abuse has definite associations with certain psychological and social factors. Abusers are more likely than nonusers to have a history of depressive illness or bipolar disorder. They are also more likely than others to have a family history of psychiatric illness or substance abuse or to have suffered traumatic or disruptive events during childhood. Abuse or neglect as a child is a strong predictor of substance abuse as a young adult. (Lo 2007, Hussey 2006)

Substance dependence is defined as opioid use that is associated with tolerance to the substance's effect or withdrawal symptoms if the substance is discontinued. Care should be taken to differentiate physical withdrawal symptoms from substance craving. Craving is an extremely strong psychological desire to use the substance, but is not a physical symptom.

Craving is an extremely strong psychological desire to use the substance, but is not

Withdrawal symptoms vary according to the substance in question. Although all patients are different, opioid withdrawal symptoms typically begin to appear within 8 to 16 hours of the last dose of opioid; many abusers, for example, wake up each morning in mild withdrawal. Peak withdrawal effects, which occur within 36 to 72 hours, include nausea, vomiting, diarrhea, watery eyes, runny nose, and coughing. Muscle aches and twitching, including abdominal cramps and jerking of the legs, are common. Chills, profuse sweating, and "goose bumps" occur in most cases. (The chills and goose bumps lead to the phrase "cold turkey" that is sometimes used to describe going through opioid withdrawal.) Irritability and mild elevations of body temperature, blood pressure, and respiratory rate also occur.

Physical withdrawal generally, but not always, resolves within 5 to 8 days and is not considered life-threatening. Nonetheless, these withdrawal symptoms are uncomfortable and unpleasant, and management of the symptoms is desirable. Medically, treatment of withdrawal symptoms is a straightforward process that can usually be accomplished with minimal difficulty. Detoxification is usually performed by reducing the opioid dosage by 10% to 20% each day, with the entire process requiring 5 to 10 days for completion. Almost any opioid can be used for detoxification because they all have some degree of cross-tolerance. The alpha-2 agonist clonidine (Catapres®) has been shown to reduce the severity

of withdrawal symptoms and is often used in conjunction with the above medications.

An alternative method for treatment of withdrawal, which is available only in certain centers, involves heavily sedating the patient (to a near anesthetic level) and administering naloxone or naltrexone to precipitate withdrawal while the patient is unconscious. Although this method is quite expensive and is not covered by insurance plans, it shortens the course of withdrawal to less than 48 hours. Antagonist-induced withdrawal done under sedation also has an increased risk of serious or even life-threatening adverse events without clear benefit. (Gowing 2006)

Approximately 95% of substance abusers who "detoxify" (overcome withdrawal symptoms) will relapse within 3 months unless they receive other treatment.

Although the physical withdrawal symptoms are largely resolved within a week, it is extremely important to realize that simply overcoming withdrawal does not stop drug dependence. Approximately 95% of substance abusers who "detoxify" (overcome withdrawal symptoms) will relapse within 3 months unless they receive other treatment. Because they do not suffer from severe psychological drug cravings, most chronic pain patients can be tapered from their opioid medications at home, even though they may experience some withdrawal symptoms. Substance abusers, on the other hand, can rarely detoxify except in a controlled environment where it is absolutely impossible for them to obtain their drug of choice. Lifestyle changes must accompany the withdrawal process to help the individual maintain sobriety/abstinence.

Complications of Substance Abuse

The most common complications of substance abuse are accidents caused by intoxication. Studies have shown that as many as 50% of all hospital trauma admissions have positive urine drug screens. Impaired motor coordination, decreased inhibition, and altered reasoning ability occur with most forms of intoxication but are most pronounced with sedatives and alcohol. (McGeary 2000) Opioid intoxication also interferes with normal bodily functions such as breathing and swallowing. With chronic use, nearly all side effects diminish or stop, with the notable exceptions of miosis and constipation.

Suicide is also a frequent cause of death among substance abusers but accidental overdose is probably a more common cause of death. Opioid overdose causes

pinpoint pupils, slowed respirations (often only 2 to 4 breaths per minute), slowed heart rate, and sedation. If untreated, the overdose will progress to coma and respiratory arrest, followed by cardiac arrest and death.

Diagnosis of Substance Abuse

Substance abuse is a surprisingly common condition. The lifetime prevalence of substance abuse (which includes alcoholism and drug abuse) among the adult population is almost 15%. At any given time, about 7.5% of adults have a substance abuse problem. In 2005, the NSDUH survey found that approximately 8.1% of the population of the United States had abused an illicit drug during the month before the survey interview. More than one-half of all substance abusers use prescription drugs, sometimes in addition to alcohol or illicit substances. Given the high fatality rates among substance abusers, getting them to proper treatment can be a life-saving measure.

More than one-half of all substance abusers use prescription drugs, sometimes in addition to

Unfortunately, many clinicians fail to investigate the possibility of substance abuse thoroughly and do not make appropriate referrals when they do discover it. When the diagnosis of substance abuse is not considered, these patients are often thought to have primary psychological problems or are simply considered "difficult patients."

Too often, even when the diagnosis becomes obvious, the clinician's response is simply to "fire" the patient rather than to suggest substance abuse treatment. This may be because most clinicians are not fully aware of the success rates of substance abuse treatment and the potential savings, both in dollars and lives, which it offers. Nevertheless, the standards established by the American Medical Association and the American Society of Addiction Medicine state that referral to a treatment program is the minimal acceptable standard of care once substance abuse is diagnosed. Simply discharging a patient with an abuse problem from the practice can place the clinician at risk of "failure to diagnose" and "failure to treat" lawsuits.

Detecting Substance Abuse in a Chronic Pain Practice

Although patients rarely admit that they have substance abuse problems, there are some consistent signs associated with substance abuse that the clinician should watch for. These include changes in mental status, recent accidents or trauma, a history of

poor impulse control (legal difficulties, gambling, losing jobs), and a history of poor or unpredictable response to standard pain therapies. Patients with a past history or strong family history of substance abuse (including alcohol abuse) are far more likely to have a substance abuse problem than
others are.

Similarly, patients with substance abuse problems are likely to have a history of "allergy" or adverse side effects to many different opioids, leaving only 1 or 2 that they say they can take. Substance abusers tend to claim that extended-release medications, such as KADIAN®, are ineffective, whereas immediate-release medications such as hydromorphone or OxyContin® (which becomes immediate-release if broken or swallowed) are effective.

In a few cases, it is obvious the patient has a problem. Patients who have altered a prescription or have obtained opioid prescriptions from multiple clinicians, no matter how valid their reasons for doing so, have committed a felony. A clinician in such circumstances should not continue to prescribe for the patient, and may have a legal obligation to report the patient's actions to law enforcement authorities. Informing the patient of the criminal possibilities involved may break through any denial and get the patient to acknowledge the problem.

Factors Associated with Opioid Abuse

The cause of opioid abuse has been debated for many years. Although there is no single cause, certain predisposing factors are well documented. Family dysfunction during childhood and a family history of drug or alcohol abuse are common among opioid abusers. Up to 90% of opioid abusers have some form of psychiatric illnesses, including major depressive disorder, anxiety disorder, and personality disorder. A family history of depression or psychiatric illness is also common. Recent research also indicates that there may be a genetic predisposition to opioid abuse, because abusers have different central nervous system responses to opioids than do nonabusers. (Kreek 2007)

Practical Issues with Chronic Opioid Use

Chronic opioid therapy for properly selected chronic pain patients appears to be an obvious and medically appropriate treatment option because such therapy offers pain

control and improved quality of life. However, there is disagreement about how appropriate this therapy is. Some clinicians feel the vast majority of chronic benign pain patients should receive long-term opioid therapy. Others feel it is rarely indicated because the risks outweigh the benefits.

Most clinicians agree that the incidence of opioid abuse is low. A few poorly designed studies in the early 1990s even suggested that chronic pain patients "almost never" developed opioid abuse problems. In reality, these studies usually reflected the experience of a single, rather exclusive pain center, or used very superficial definitions of abuse, such as "percent of patients arrested." Many other studies show significantly higher rates of abuse. Some have claimed that as many as 20% of patients requesting chronic opioid therapy have a substance abuse problem. The true incidence of abuse probably varies widely in different practices, depending on factors such as the geographic location, the type of patients seen, and the vigilance of the practitioners involved.

The clinician is left, therefore, to make decisions based on his or her best medical judgment in each individual case. Most pain practitioners agree that when dealing with benign pain the problem is simplified if the decision to initiate and then continue chronic opioid therapy is based on improvements in the patient's ability to function rather than change in subjective pain level. A patient who has wild mood swings when taking medications or who has frequent falls or accidents cannot be considered to have improved quality of life on chronic opioid maintenance.

On the other hand, most chronic benign pain patients do have markedly improved ability to function when maintained on chronic opioid therapy. Being able to perform simple tasks like cleaning the house or being able to shop can make a huge difference in lifestyle and the patient's sense of self worth. Determining if the patient's ability to function is improved should involve questioning not only the patient but also close family members.

Differentiating Use from Abuse

Rarely does any single sign clearly identify a patient with substance abuse problems during the initial evaluation. Rather, a pattern consistent with substance abuse may become evident as the clinician works with the patient over time (Table 6-2). Those patients with past histories or strong family histories of substance abuse and psychiatric illness are more likely to suffer from the disease of addiction. Similarly, a

social history of personal and familial dysfunction or personality disorder is associated with a high incidence of substance abuse.

It must always be remembered, however, that most substance abusers manage to hide their problem for months or years before it becomes evident to outsiders. For this reason, it is strongly recommended that input from the patient's spouse or close relatives be obtained whenever possible. Many practices require not only the patient but also the patient's spouse sign the controlled substances agreement. This not only involves the spouse with the clinician, it provides some protection should a claim later be made by the same spouse that the doctor "should have known" the patient had a substance abuse problem.

Note that persons who are not themselves opioid abusers but who obtain prescriptions for illicit resale are keenly aware of which clinicians in any area are willing to prescribe medications with a high street value. Often, these persons appear to be model patients, answering every question in a manner that will ensure their continued supply. Random urine drug screens are the most effective tool for detecting such individuals, because an appropriately chosen screening panel will be negative for the opioid that is being prescribed.

Table 6-1

Signs Associated with Substance Abuse
Repeated requests for short-acting medications (Hydrocodone is considered short-acting when abused by chewing or breaking the tablet).
Repeated incidences of early refill requests, especially when the patient has "typical" excuses such as "the pills fell in the toilet," "the dog ate them," or "someone stole my medicine."*
Frequent telephone calls, particularly after hours or on weekends.
Frequent requests to change medication because of side effects or lack of efficacy.
More than a single incidence of other clinicians prescribing opioids.
Patient's past history of substance or alcohol abuse.
History of preexisting psychiatric illness, especially bipolar disorder, schizophrenia, or personality disorder.
Family history of substance or alcohol abuse or strong family history of psychiatric illness.
Social history of dysfunctional or high-risk behaviors, including multiple arrests, multiple marriages, abusive relationships (either abuser or victim), inability to maintain employment, and multiple accidents.

* *Such excuses require a police report to substantiate the facts. Even with a police report, most practitioners are unwilling to refill more than one "incident" per year.*

Table 6-2

Signs and Symptoms Consistent with Pseudoaddiction
Complaints that pain medication is ineffective.
Hoarding or repetitively counting medications.
One or possibly 2 incidences of running out of medications early, especially if the patient states honestly that he or she took more than prescribed.
Obsessing about the duration of time until medication refill.
A single incidence of obtaining opioids from another source, not repeated after the patient is warned of the consequences.

The classic signs and symptoms of drug abuse may be difficult to differentiate from the symptoms of chronic pain, especially when depression or other psychological illness is present. Pseudoaddiction is a set of behaviors that are often exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors (Table 6-2) should not be considered signs of abuse in a chronic pain patient, but rather should be considered symptoms of inadequate treatment unless they are accompanied by other signs of abuse.

Pseudoaddiction is a set of behaviors that are often exhibited by patients with inadequately treated pain, including patients with

Documentation and Monitoring

Although what constitutes appropriate prescribing of opioids remains a frequently debated topic, the guidelines requiring proper medical documentation of controlled substances are quite clear. As with every other aspect of medicine, if the medical record does not contain the proper documentation, it will be assumed by regulating authorities that the clinician did not obtain or act on the information in question. In fact, clinicians are more likely to be sanctioned by state medical boards for poor documentation than for overprescribing.

The Federation of State Medical Boards produced guidelines for the use of controlled substances in 1998, which have become a standard for the use of chronic opioids. A similar document was endorsed by the American Academy of Pain Medicine and the American Pain Society in 1999 (see Appendix 6-1). The American Pain Society has since published additional updates for management of arthritis pain (2002), for fibromyalgia syndrome (2005), and for cancer pain patients (2005). In general, the following guidelines, which are similar to those presented in earlier chapters, are consistent with both of these group's guideline requirements for documentation.

Evaluation

The patient evaluation should include a description of the pain, including its effect on the patient's ability to function; any current or past treatments and their effects; the indication for opioid therapy; and whether the patient has a past or family history of substance abuse. The Federation of State Medical Boards suggests the following steps in the evaluation of a patient with chronic pain. 1) Evaluation of the patient. This should include a physical examination and a medical history. The medical record should contain documentation about the nature and intensity of the pain, current and

past treatments, and any history of substance abuse or risk factors for abuse. 2) Treatment plan. This should include the goals of management. 3) Informed consent and agreement for treatment. The physician should discuss the risks and benefits of opioid treatment and outline the patient responsibilities including follow up and prescription management (e.g. refills). 4) Periodic review. The physician should periodically review the progress toward treatment objectives and modify the plan accordingly. 5) Consultation. Patients should be referred as necessary to achieve treatment objectives. 6) Medical records. The physician should keep accurate, current, and complete medical records regarding all aspects of patient management. (FSMB 2004)

Treatment Plan

The treatment plan should include not only the agents to be used, but also the expected effects and side effects. The treatment plan must include how frequently the clinician will modify agents or dosing regimens and what the goals of therapy are, including what would be considered sufficient improvement to continue therapy (improvement should be defined as change in function, not simply "pain relief").

Informed Consent

An informed consent should be obtained before initiating chronic opioid therapy. At a minimum, the consent must make the patient aware of the possibility of the potential for physical dependence and the possibility of withdrawal symptoms. It should also include a warning that opioid therapy could trigger relapse among ex-abusers or substance abuse among those with a strong family history of the disease.

Opioid Agreement

An opioid or controlled substance agreement should be part of the medical record (an example is included in Appendix 6-2). The agreement should include the informed consent, the rules regarding medication use, and the reasons for which the clinician will terminate care. It should also include permission for the clinician to contact any pharmacy to confirm the patient's medications and a statement that the patient will undergo drug screens whenever requested.

Medication List

A written list of every controlled substance prescription must be kept in the patient's chart. Many centers recommend that duplicate prescriptions be used for controlled substances and a copy placed in the chart. Alternatively, computerized prescription writing systems are readily available that keep the patient's medication record immediately accessible. Many states only allow duplicates to be issued through the state.

Chart Review

Periodic review of the chart should contain regular reviews of the patient's benefits (or lack of benefits) from opioid therapy. If the treatment goals established are not met, the clinician must document why he or she believes continued opioid therapy is indicated. The patient (and spouse, if possible) should be seen in the office regularly. Although there is no clear guideline for exactly how often the patient receiving chronic opioid therapy should be seen, many centers require an appointment every 30 days, whereas some allow more established patients to be seen every 90 days.

Investigation of Questionable Behavior

Consultation should be obtained if the clinician suspects the patient may have a substance abuse problem. Other actions taken to investigate any incidence of questionable behavior (lost or stolen medications, frequent requests to change medication) should be documented in the chart. These may include "sweeps" of area pharmacies to ensure that the patient is not obtaining other medications, counseling sessions with the patient and spouse, and drug screens.

Choice of Opioid

Despite the claims of some manufacturers, any member of the opioid group can be abused. Some tablets, such as Immediate-release morphine (MSIR®), hydromorphone (Dilaudid®), oxycodone (OxyContin®), and Meperidine (Demerol®), can be dissolved and injected by abusers. There are far more oral than parenteral abusers. Many of these persons are not part of the illicit drug trade, but instead obtain opioids from multiple clinicians, often under false pretenses. Hydrocodone (Vicodin®, Lortab®, Tussionex®), meperidine, oxycodone (OxyContin®, Percocet®), and hydromorphone are all commonly abused.

Every opioid has the potential to be abused, including those considered "agonist-antagonists," such as butorphanol, and those considered "mild," such as codeine or propoxyphene. Nevertheless, there are clearly "drugs of choice" that are preferred by persons who abuse opioids. Similarly, certain opioids have extremely high illicit values when sold on the street, whereas others have little or no value. Street values and choices of abused drugs do tend to vary somewhat at different times and in different locations, but certain trends are constant.

Every opioid has the potential to

As a rule, short-acting opioids are strongly preferred by abusers to time-release or extended-duration medications. Historically, hydrocodone is the most widely abused opioid, probably because as a schedule III medication used for both pain control and cough suppression, it is more available than other agents. Hydromorphone has been the preferred prescription opioid abused by injection for over a decade. Intravenous drug abusers strongly prefer nongeneric Dilaudid™ because it dissolves in water more readily than generic versions.

Since 1999 OxyContin® has arguably become the most commonly abused and diverted opioid, particularly in noncoastal states. Although OxyContin® is marketed as a controlled-release formula, the medication becomes immediate-release if the pill is crushed or chewed. OxyContin® abuse, which tends to be common in young adults, has been associated with a high number of accidental deaths.

Truly long-acting agents, such as KADIAN® or Duragesic®, are not preferred by abusers because they do not get a "rush" from the slow onset of these medications. However, enterprising abusers with some knowledge of "street lab" chemistry can remove the active agent.

Although there certainly are some legitimate patients who are unable to take any of the long-acting opioids, the vast majority of chronic pain patients obtain effective relief with these agents.

Opioids in Patients with a History of Substance Abuse

The two major issues concerning chronic opioid therapy in persons with a history of substance abuse come from opposite ends of the spectrum. Some clinicians mistakenly believe that a history of nonopioid substance abuse, such as alcoholism, does not place the person at risk when prescribing opioids. Others believe that

persons with a substance abuse history can never take opioid agents safely. Both points of view are incorrect.

Polysubstance abuse (or "crossover addiction") occurs commonly. From 40% to 70% of substance abusers use chemicals from more than one classification. It is not clear how often exposure to a second substance will "trigger" a relapse in a person recovering from chemical dependence, but it is clear that this can and does happen. Therefore, it must be assumed that a person recovering from alcoholism is at increased risk of developing a substance abuse problem if given opioids, although it is not clear how great this risk is. (Staines 2001)

Conversely, persons in recovery from opioid abuse can successfully undergo long-term opioid therapy for chronic pain without apparent relapse. Obviously, they are at increased risk of relapse, and most pain specialists require an informed consent to be signed before beginning opioid treatment. The rate of risk is unknown and probably varies according to several circumstances: the length of recovery, the severity of the painful condition, the person's mental health state, and the presence of an adequate recovery support group.

Most addictionologists agree that long-acting or time-release agents should be used if possible when treating a recovering person. Similarly, dosing should be around-the-clock and PRN medications should be avoided. The goal is to avoid rapid changes in mood associated with "getting high" and to instead maintain a steady state dose of opioid medication.

Summary

- During the past 20 years, data have consistently shown that about 7.5% of the U.S. adult population has a significant substance abuse problem. The most recent report of the national Institute on Drug Abuse found that there was an increase in the number of Americans (about 20.4 million) who were considered substance abusers. (SAMHSA 2006)
- The Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders defines substance abuse as a maladaptive pattern of chemical substance use that significantly interferes with a person's life.
- Substance dependence is defined as opioid use that is associated with tolerance to the substance's effect or withdrawal symptoms if the substance is discontinued. Care should be taken to differentiate physical withdrawal symptoms from substance craving. Craving is an extremely strong psychological desire to use the substance, but not a physical symptom.

- Consistent signs associated with substance abuse include changes in mental status, recent accidents or trauma, a history of poor impulse control (legal difficulties, gambling, losing jobs), and a history of poor or unpredictable responses to standard pain therapies. Patients with a past history or strong family history of substance abuse (including alcohol abuse) are far more likely to have a substance abuse problem than others are.
- Clinicians should document the patient evaluation, treatment plan, informed consent, opioid agreement, and medication list. A periodic chart review should state the benefits of the opioid therapy for the patient.

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Self-Assessment Test

Circle the best response

1). What percentage of primary care clinicians state they have received no training or education concerning substance abuse?
a. 10% c. 50%
b. 25% d. 75%

2). In the late 1990s, widespread diversion of _____ led to the prosecution of many clinicians for overprescribing.
a. Lortab®
b. Dilaudid®
c. morphine
d. OxyContin®

3). As documented over the past 20 years, what percentage of all U.S. adults has a substance abuse problem?
a. 1% c. 15%
b. 7.5% d. 25%

4). Withdrawal from opioid medications begins about _____to _____hours after the last dose of medication.
a. 4 to 6
b. 6 to 12
c. 8 to 16
d. 24 to 36

5). Peak effects of opioid withdrawal occur between _____ to_____ after the last dose of medication.
a. 24 to 36 hours
b. 36 to 72 hours
c. 4 to 6 days
d. 7 to 10 days

6). Assuming a substance abuser gets past the withdrawal phase but receives no other treatment, what are the odds that he or she will relapse within 3 months?
a. 25% or less
b. 25% - 50%
c. 50% – 75%
d. more than 90%

7). Obsessive behavior about pain medication resulting from an inadequate dose of opioid is called
a. Substance abuse
b. Addiction
c. Pseudoaddiction
d. Dependence

8). According to the State Board of Medical Examiners Guidelines, which of the following is not required documentation when a patient receives chronic opioid therapy?
a. A written evaluation
b. A psychological assessment
c. A written list of every controlled substances prescription
d. A controlled substances contract

True or False

9). It is a good idea to tell clinicians that KADIAN® has "low abuse potential."
a. True
b. False

10). A 22-year-old woman admitted to the hospital because of opioid withdrawal has a substance abuse problem.
a. True
b. False

11). If not treated, opioid withdrawal is likely to cause seizures, heart attack, or stroke.
a. True
b. False

12). As a general rule, abusers and diverters will prefer short-acting opioids rather than time-released opioids.
a. True
b. False

Answers to Self-Assessment Test

1. c	7. c
2. d	8. b
3. b	9. b (Never use the phrase "low abuse potential.")
4. c	10. b (Withdrawal does not automatically imply abuse.)
5. b	11. b
6. d	12. a

Appendix 6-1

Public Policy Statement on the Rights and Responsibilities of Healthcare Professionals in the use of Opioids for the Treatment of Pain.

A consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine.

Published by the American Pain Society, 2004. Available online at: http://www.ampainsoc.org/advocacy/rights.htm. Accessed 9-25-07.

Background

Healthcare professional (HCP) concerns regarding the potential for harm to patients, as well as possible legal, regulatory, licensing or other third party sanctions related to the prescription of opioids, contribute significantly to the mistreatment of pain. HCPs are obligated to act in the best interest of their patients. This action may include the addition of opioid medication to the treatment plan of patients whose symptoms include pain. Though many types of pain are best addressed by non-opioid interventions, opioids are often indicated as a component of effective pain treatment. It is sometimes a difficult medical judgment as to whether opioid therapy is indicated in patients complaining of pain because objective signs are not always present.

A decision whether to prescribe opioids may be particularly difficult in patients with concurrent addictive disorders, or with risk factors for addiction, such as a personal or family history of addictive disorder. For such persons, exposure to potentially rewarding substances may reinforce drug taking behavior and therefore present special risks. It is, nonetheless, a medical judgment that must be made by a HCP in the context of the provider-patient relationship based on knowledge of the patient, awareness of the patient's medical and psychiatric conditions and on observation of the patient's response to treatment. The selection of a particular opioid, or combination of opioids, and the determination of opioid dose and therapeutic schedule similarly must be based on full clinical understanding of a particular situation and cannot be judged appropriate or inappropriate independent of such knowledge. All schedule II-V opioids, including methadone, may be appropriate choices for pain control in different circumstances. It is critical that clinicians

understand the special pharmacologic characteristics of each medication in order to prescribe them safely and effectively for pain.

Despite appropriate medical practice, healthcare providers who prescribe opioids for pain may occasionally be misled by patients who wish to obtain medications for purposes other than pain treatment, such as diversion for profit, recreational use or perpetuation of an addicted state. Physicians who are willing to provide compassionate, ongoing medical care to challenging and psychosocially stressed patients, where that treatment includes the prescription of opioids, assume an additional obligation to understand the risks and management of addictive disease because they risk complications of care more often than physicians unwilling to treat this population.

Addiction to opioids may occur despite appropriate opioid therapy for pain in some susceptible individuals. Persistent failure to recognize and provide appropriate medical treatment for the disease of addiction is poor medical practice and may become grounds for practice concern. Similarly, persistent failure to use opioids effectively when they are indicated as part of the treatment of pain, including in persons with active or recovering addiction, is poor medical practice and may also become grounds for practice concern. It is important to distinguish, however, between HCPs who are knowingly complicit in diversion or other illegal prescribing activities and physicians who may inappropriately prescribe opioids due to misunderstandings regarding addiction or pain. HCPs traditionally have received little or no education on addiction or clinical pain treatment in the course of training. This omission is likely a basis for inadequate detection and management of addiction and inadequate assessment and treatment of pain.

Public Policy Statement on the Rights and Responsibilities of Healthcare Professionals in the use of Opioids for the Treatment of Pain © 2004 American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine

Recommendations

1) Healthcare professionals (HCPs) who prescribe opioids for the treatment of pain should use clear and reasonable medical judgment to establish that a pain state exists and to determine whether opioids are an indicated component of treatment. Opioids should be prescribed in a lawful and clinically sound manner. Patients

should be followed at reasonable intervals for ongoing medical management, to confirm as nearly as is reasonable that the medications are used as prescribed, that the goals of treatment are met and to revise therapy as indicated. Such initial decision making and ongoing management should be appropriately documented.

2) HCPs who are practicing medicine in good faith and who use reasonable medical judgment regarding the prescription of opioids for the treatment of pain should not be held responsible for the willful and deceptive behavior of patients who successfully obtain opioids for non-medical purposes. It is an appropriate role of the DEA, pharmacy boards and other regulatory agencies to inform physicians of the behavior of such patients when it is detected.

3) Interventions to correct the clinical care practices of HCPs who consistently fail to recognize addictive disorders, medication misuse, or medication diversion in their patients are appropriate. Interventions may include education and/or licensing or legal sanction as indicated after careful and appropriate review of records and other available information.

4) Interventions to correct the clinical care practices of HCPs who consistently fail to appropriately evaluate and treat pain in their patients are appropriate. Interventions may include education and/or licensing or legal sanction as indicated after careful and appropriate review of records and other available information.

5) For the purpose of performing regulatory, legal, quality assurance and other clinical case reviews, it should be recognized that judgment regarding a) the medical appropriateness of the prescription of opioids for pain in a specific context, b) the selection of a particular opioid drug or drugs, and c) the determination of indicated opioid dosage and interval of medication administration, can only be made properly with full and detailed understanding of a particular clinical case.

6) Regulatory, legal, quality assurance and other reviews of clinical cases involving the use of opioids for the treatment of pain should be performed, when they are indicated, by reviewers with a requisite level of understanding of pain medicine and addiction medicine.

7) Appropriate education in addiction medicine and pain medicine should be provided as part of the core curriculum at all medical and other provider training schools.

8) Legal and/or licensing actions against HCPs who are proven to be knowingly complicit in the diversion of scheduled drugs or other illegal prescribing activities are appropriate.

This document was prepared by the following committee members: Seddon Savage, MD (Chair) - APS; Edward C. Covington, MD - AAPM; Aaron M. Gilson, PhD – APS; Douglas Gourlay – ASAM; Howard A. Heit, MD - ASAM; and John B. Hunt, MD – AAPM.

Adopted by AAPM Board of Directors, March 2004
Adopted by APS Board of Directors, March 2004
Adopted by ASAM Public Policy Committee, January 2004

Appendix 6-2

A sample controlled substances agreement

The long-term use of opioids (narcotics) and benzodiazepines (tranquilizers and sleeping pills) is controversial because of uncertainty regarding their risks and benefits. Because these drugs have a risk of misuse and/or diversion, strict accountability is required on the part of the patient and clinician. The purpose of this agreement is to protect our patients' access to controlled substances, protect our ability to continue to prescribe them, and prevent the misuse and diversion of substances. There can be no exceptions to these policies, no matter how good the reasons are for wanting an exception made.

1. From this point forward, you will report receiving any controlled substances from another clinician to our office by the next business day. You understand receiving controlled substances from more than one clinician without notifying the clinicians involved is a crime (doctor shopping), and that conviction can result in a prison sentence.

2. You will fill all prescriptions for controlled substances at one pharmacy. That pharmacy and telephone number is _____.
You give our office permission to discuss your medications with pharmacists at this, or any other pharmacy, or with any other clinician that has treated you.

3. You understand that taking controlled substances will eventually result in physical dependence and stopping the medication suddenly could cause a withdrawal syndrome. You accept this risk. You further understand that should you have to leave the practice, we are not responsible for finding another clinician who will prescribe for you.

4. You understand that if you have a past history of alcohol or drug abuse, or a family history of these issues, you are more likely to develop problems with these medications. By signing this document, you state that you have notified us of any such history.

5. Controlled medications can be dangerous to others and may also be stolen for illicit use. You accept responsibility to store your medication safely and securely so that no one but yourself has access to it. A lockbox or safe is strongly recommended.

6. Lost, damaged, or destroyed medications cannot be replaced. Stolen medication may be replaced a single time after a police report is obtained. If your medication is stolen a second time, we consider this evidence that you are not capable of protecting your medication and we will not replace it.

7. You may not take extra medication, no matter how bad your pain is, without calling the office and receiving permission to do so BEFORE you take it. Medications cannot be refilled early.

8. Medications are only refilled weekdays between 9 am and 4 pm. No exceptions are made.

9. You understand that by undertaking your treatment, we do not guarantee that we can provide complete pain relief. You also understand that treatment which is initially effective may lose effectiveness over time. When this occurs, the clinician may or may not be able to change medications or dosages to restore effectiveness. Undertaking your treatment does not guarantee, nor do we assume responsibility for providing, continued access to medication.

10. You understand that random urine drug screens, are part of the requirements for continued treatment. You understand that insurance may not cover the cost of these screens. You understand that refusal to take a urine screen will

result in immediate dismissal from the practice, as will the presence of any unprescribed controlled substance in your urine.

11. If responsible legal authorities have reason to question your use of controlled substances, as might occur if they suspect drug diversion, you understand that we waive any clinician-patient confidentiality and provide immediate access to your medication records.

12. You understand that violating any terms of this agreement may result in your immediate dismissal from this practice. In such cases, we are not responsible for referring you to another clinician, nor are we responsible for providing further prescriptions. You understand that should a withdrawal syndrome occur in such circumstances, we will refer you to an appropriate facility for detoxification, and you are responsible for the cost of such treatment.

Signatures:

_____	_____
Patient	Date
_____	_____
Family Member	Date
_____	_____
Clinician	Date
_____	
Patient name printed	

SECTION TWO

Opioid Pharmacology

- Chapter 7: Pharmacology and Chemistry
- Chapter 8: Pharmacokinetics
- Chapter 9: Dosage and Administration
- Chapter 10: Safety and Adverse Experiences

CHAPTER SEVEN

Pharmacology and Chemistry

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Explain the role of the opioid receptor.
- Describe the mechanism of action of morphine and other opioids in analgesia.
- Discuss the pharmacologic effects of morphine and other opioids.
- Describe the phenomenon of tolerance to morphine.
- Describe the phenomenon of dependence to morphine.
- Explain the basic chemistry of KADIAN®.

Terminology

Acidic:	A pH less than 7.0.
Alkaline:	A pH greater than 7.0.
Anaphylaxis:	An unusual or exaggerated allergic reaction that may be life threatening.
Antagonist:	Drug that binds to a receptor site, inhibiting its action.
Baroreceptor reflex:	A reflex response to activation of a sensory nerve terminal that is stimulated by changes in pressure. These are located in the blood vessel walls.
Endogenous:	Any substance produced within the body.
Hydrophilic:	Substance that is soluble in aqueous solution (literally translates as "water loving").
Ileus:	Paralysis (usually temporary) of the bowels, which typically leads to constipation and abdominal distention. More severe ileus can cause nausea and vomiting as well.
Lipophilic:	Substance that is soluble in fatty tissue (literally translates as "lipid loving").
Miosis:	Contraction of the pupil.
Mydriasis:	Dilation of the pupil.
Narcotic:	Sleep inducing medication
Opioid:	Natural, semi-symthetic, or synthetic analgesic substance that is a mu-receaptor agonist..
Orthostatic hypotension:	Drop in blood pressure upon standing.
Pathognomonic:	Denoting a sign or symptom that is characteristic enough of a condition that it can be used to diagnose that condition.
Peptide:	A naturally occurring compound of two or more amino acids.
pH:	A measure of whether a solution is acidic or alkaline.
Pruritus:	Itching.
Psychotomimetic:	Something that causes a feeling of depersonalization or dysphoria; producing symptoms similar to psychosis.
Sphincter of Oddi:	A circular muscle located where the common bile duct passes through the small intestine that controls the flow of bile into the intestine.
Supraspinal:	Occurring at the level of the brain.
Vasodilation:	Relaxation of the smooth muscle in the blood vessels that results in an increase in the size of blood vessels.

Introduction

The pain signal is transmitted to the brain through neurons using several different chemical neurotransmitters. Opioids can effectively block the transmission of this pain signal on its way to the brain. It is possible to stimulate the descending, pain pathways in the nervous system (*see* Chapter 1). Modifying opiodss may increase or decrease pain.

Opioids, which stimulate neurons in these descending, pain-suppressing pathways, are one of the few options available for treating pain. No class of drug provides analgesia as effectively as do the opioids.

Opioid use in pain relief is favored for several reasons:

- First, opioids do not have a ceiling effect to their efficacy.
- Second, opioids have a long history of use and demonstrated efficacy.
- Third, it is widely accepted that opioids--particularly extended-release formulations--improve the quality of life of cancer patients.

This chapter reviews the mechanism of opioid analgesia and other pharmacologic effects. Particular attention is given to morphine, the "gold standard" for pain relief.

Chronic Pain Pathophysiology

The main neurotransmitter used by nociceptors (pain transmitters) synapsing with the dorsal horn of the spinal cord is glutamate. Glutamate can bind to many receptors, but the AMPA (alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid) receptor is most involved in transmitting the acute pain signal.

Chronic pain is not a prolonged version of acute pain. As pain signals are repeatedly generated, neural pathways undergo changes that make them hypersensitive to pain signals and resistant to antinociceptive (pain blocking) input. One theory explaining the transition from acute pain to chronic pain involves NMDA (*N*-methyl-D-aspartate) receptor activation. The NMDA receptors are not active unless there has been a persistent or large-scale release of glutamate (Figure 7-1). Repeated stimulation of AMPA receptors dislodges magnesium ions that act like stoppers in transmembrane sodium and calcium channels of the NMDA receptors, thereby activating the NMDA

receptors. This change marks the transition from acute pain to chronic pain. Now, more NMDA receptors are available for glutamate to bind because they have been activated (a phenomenon called windup). It therefore takes less peripheral input for pain stimulation to occur, less glutamate to transmit the signal, and more antinociceptive input to stop it.

Ketamine, dextromethorphan, and methadone all have some NMDA receptor antagonist activity and have been used to try to stop this transition from acute pain to chronic pain and to block the activity of the activated NDMA receptors. Unfortunately, drugs that target the NMDA receptor do not provide pain relief without significant side effects. For this reason, opioid receptor agonists remain the preferred treatment for chronic pain.

Endogenous Opioid Peptides

Endogenous peptides are the primary chemical messengers in the antinociceptive system of the body. Endogenous opioids bind to receptors to produce analgesia. Endogenous opioids are composed of three distinct families of peptides, all of which are pharmacologically related to morphine:

- enkephalins,
- dynorphins, and
- endorphins.

Opioid medications, such as morphine, bind to receptors and block pain modulating systems in a similar manner to these endogenous opioids.

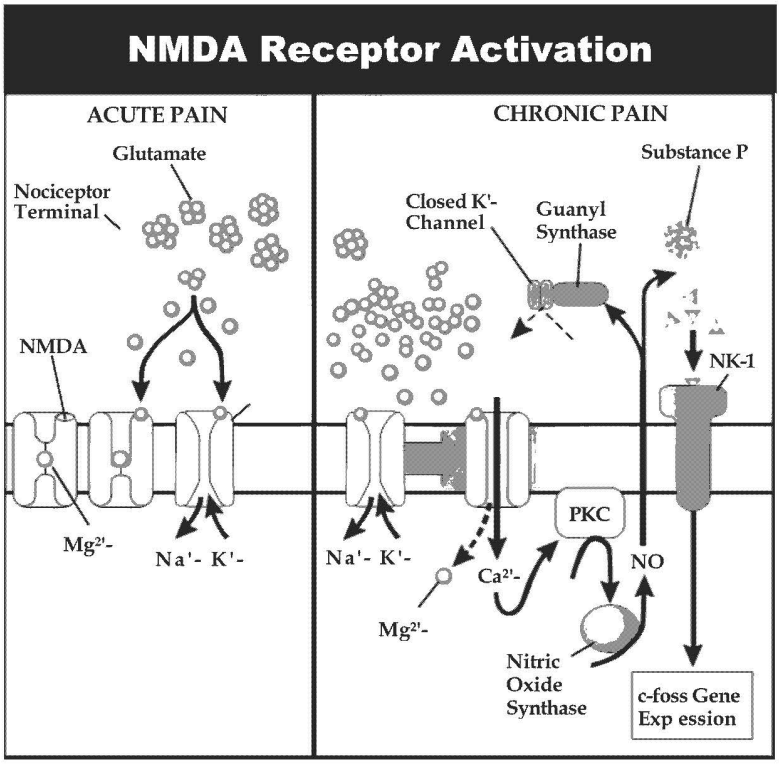


Figure 7-1

Adapted from Brookoff, 2000

Opioid Receptors

Opioids exert their effects on the body by interacting with specialized macromolecular (large molecule) components in cells called opioid receptors. Opioid receptors are located in the central nervous system (CNS), pituitary gland, the peripheral nervous system (PNS), the gastrointestinal (GI) tract, and a few other locations in the body. They are abundant in the periaqueductal gray matter of the brain and the dorsal horn of the spinal cord, two areas that are very active in pain reduction. When an opioid binds to one of these receptors as an agonist, it produces analgesia. When a drug binds to one of these receptors as an antagonist, analgesia and other effects are blocked.

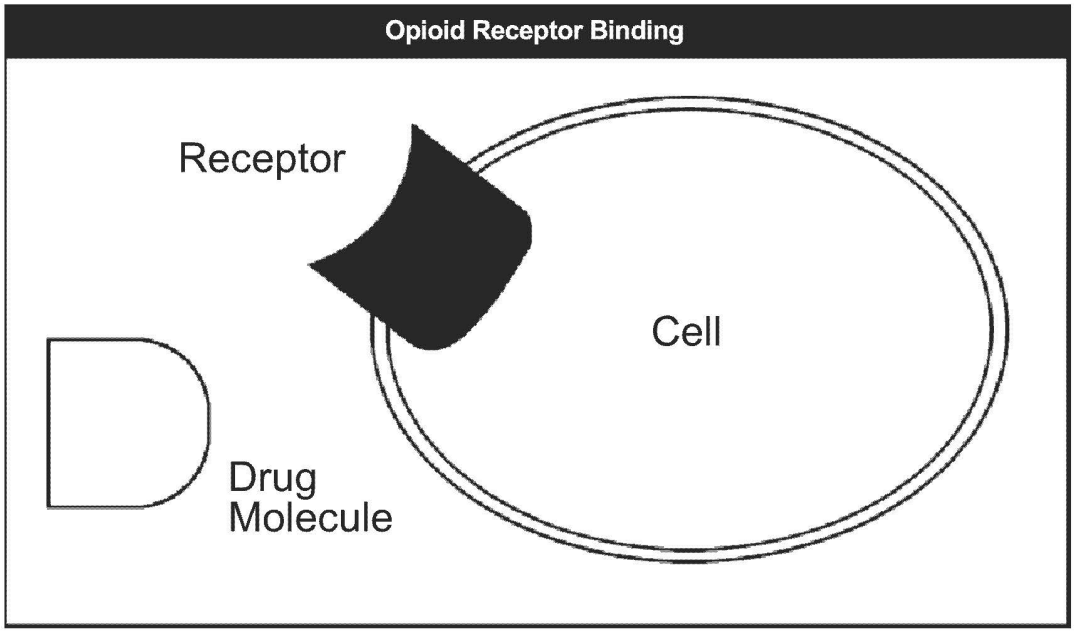
Three major types of opioid receptors are involved in analgesia:

- mu,
- kappa, and

- delta.

Many subtypes of these receptors exist. The binding of drug molecules to their specific receptors is similar to a key fitting a lock (Figure 7-2). The bond between the drug and the receptor distorts the configuration of the receptor, changing its biochemical properties and function and triggering specific responses by the cell. The body's response to the drug is a result of these changes.

Figure 7-2



Opioid Analgesics

Opioids are divided into 3 classes (Table 7-1):

Mu agonists

Most clinically useful opioid analgesics, which bind primarily to the mu (μ) receptor.

Mixed agonist-antagonists

Bind as agonists at the kappa receptor producing weak analgesia and also bind as weak antagonists at the mu receptor. The result is weak analgesia and more dysphoria and psychotomimetic effects and less intense respiratory depression than is seen with pure agonists. These drugs have very limited clinical utility.

Partial agonists

Bind as agonists at mu and kappa receptors, but have limited efficacy.

Table 7-1.

Mu agonists	Mixed agonist-antagonists	Partial agonist
Codeine Fentanyl Hydromorphone Levorphanol Meperidine Methadone Morphine Oxycodone Oxymorphone Hydrocodone	Butorphanol Dezocine Nalbuphine Pentazocine	Buprenorphine

Pharmacologic Properties

Morphine and related opioids produce their major effects on the CNS and the bowel through mu receptors. Although morphine is relatively selective for mu receptors, it can interact with the others, particularly at higher doses. The type of opioid receptor site and its location determine the effects an opioid drug produces (Table 7-2). Analgesia is a beneficial result of mu receptor binding. Side effects are unwanted results of the binding to opioid receptors.

Table 7-2

Activity of Mu, Kappa and Delta Receptors	
Opioid Receptor Site	**Activity**
Mu (μ)	Spinal and supraspinal analgesia, respiratory depression, cardiovascular effects, physical dependence, tolerance, impaired GI motility, urinary retention, pruritus, euphoria.
Kappa (κ)	Spinal and supraspinal analgesia, miosis, psychotomimetic effects (dysphoria, agitation), and sedation without pronounced respiratory depression, euphoria, or GI effects.
Delta (δ)	Spinal and supraspinal analgesia without

	respiratory compromise.

Analgesia

Analgesia is produced at mu, kappa, and delta receptors supraspinally and spinally. In the case of morphine, analgesia appears to be mediated primarily through μ (mu) receptor activation. There are two distinct subtypes of μ receptors, μ_1 and μ_2. The μ_1 receptor is responsible for morphine analgesia at the supraspinal level, whereas the μ_2 receptor mediates morphine analgesia at the level of the spinal cord. Morphine given systemically interacts with supraspinal μ_1 receptors. Both respiratory depression and constipation are thought to be mediated by μ_2 receptors.

Biliary Spasm

Opioids increase smooth muscle tone in the biliary tract, especially in the sphincter of Oddi, which regulates the flow of bile and pancreatic fluids. This can result in a decrease in biliary and pancreatic secretions and a rise in bile duct pressure. Patients may experience epigastric (upper abdominal) pain and occasionally spasm of the biliary tract, which causes pain that is similar to that experienced with a gallstone blockage of the gallbladder.

All opioids can cause constricture of the sphincter of Oddi and the biliary tract. One study showed that morphine might cause more biliary constricture than do other opioids in animals. This has not been shown to be of clinical importance in humans, however.

Cardiovascular System

Therapeutic doses of many opioids produce peripheral vasodilation, reduced peripheral resistance, and inhibition of the baroreceptor reflexes. Orthostatic hypotension and fainting can result. Morphine and other opioids provoke release of histamine, which sometimes plays a large role in hypotension.

Central Nervous System

Opioid drugs produce many CNS effects. They cause drowsiness, changes in mood, and mental clouding. Confusion, disorientation, cognitive impairment, hallucinations, and euphoria are also possible. Psychotomimetic effects are more common with kappa receptor activation.

Convulsions

High doses of morphine and related opioids produce convulsions (seizures). Most convulsions occur at doses far in excess of those required to produce analgesia.

Cough

Opioids depress the cough reflex by a direct effect on the cough reflex trigger zone in the medulla of the brain stem.

Gastrointestinal Tract

Opioid binding of mu receptors in the GI tract can delay gastric emptying, slow bowel motility, and decrease peristalsis. Opioids may also reduce secretions from the colonic mucosa. The result is slow moving, hard stool that is difficult to pass. At its worst, GI dysfunction results in ileus, fecal impaction, and obstruction.

Constipation is the most common opioid side effect and one of the few for which individuals do not develop tolerance. All patients taking "around the clock" opioid analgesics should be placed on prophylactic regimens for constipation.

Genitourinary Tract

Opioids increase smooth muscle tone in the bladder and ureters and may cause bladder spasm and the sensation of the need to void urgently. An opioid-induced increase in contraction of the bladder outlet sphincter, however, can make urination difficult. Urinary retention (inability to empty the bladder) is most common in elderly men. Tolerance to the opioid effects that lead to urinary retention develops over time.

Miosis

Morphine and most mu and kappa agonists can cause constriction of the pupil. After a toxic dose of mu agonists, miosis is marked and the resulting "pinpoint" pupils are pathognomonic; however, the miosis is replaced by mydriasis once asphyxia (inadequate oxygen supply from inadequate breathing) from respiratory depression from the toxic doses develops.

Nausea and Vomiting

Nausea and vomiting are caused by direct stimulation of the chemoreceptor trigger zone in the medulla (brainstem), sensitization of the vestibular system (needed for balance and equilibrium), and slowing of GI mobility. All clinically significant mu agonists produce some degree of nausea and vomiting.

Neuroendocrine

Morphine acts in the hypothalamus to inhibit the release of gonadotropin-releasing hormone (GnRH) and corticotrophin-releasing factor (CRF), thus decreasing levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), and endorphins. Blocking the release of these hormones from the hypothalamus leads to changes in hormones released from the endocrine glands (including the adrenal glands and gonads). In turn, this may cause decreased levels of testosterone and cortisol, disturbances in menstruation, and sexual dysfunction. Tolerance may or may not develop to the endocrine effects of opiates.

Opioid Allergy

Allergic and anaphylactic reactions are rare complications of opioid therapy. In the past 12 years, the clinical literature has carried single case reports of anaphylactic reactions to meperidine, pentazocine, morphine, and fentanyl. However, many of these reports suggested the possibility of the reactions resulting from other medications taken concurrently or from inert ingredients in the drugs formulations. None of these reports documented cross-sensitivity (an allergy to other similar agents) with other opioid analgesics. Reviews of studies involving several thousand patients receiving meperidine or morphine showed no cases of cross-sensitivity. However, if the patient has a documented "allergy" to an opioid, it may be wise to avoid drugs that are structurally similar to that opioid (Table 7-3).

Respiration

Respiratory depression is the most feared opioid-induced side effect. Opioids depress respiration by a direct effect on the brainstem respiratory centers, making the brainstem less responsive to carbon dioxide. Tolerance to the opioid effects that cause respiratory depression develops in days to weeks. The longer the patient receives opioids, the wider the margin of safety.

The agonist-antagonists were developed with the intent of decreasing the risk of respiratory depression. They have a ceiling effect (point beyond a certain dose at which further respiratory depression or analgesia is not produced), but this is usually above recommended doses.

Skin

Therapeutic doses of morphine cause dilation of cutaneous blood vessels (blood vessels in the skin). Flushing can occur on the face, neck, and upper thorax. These changes may be due in part to release of histamine and may be responsible for the sweating and some of the pruritus that occasionally follows morphine administration. Histamine release can lead to wheezing and bronchoconstriction and can trigger or worsen asthma attacks, potentially leading to status asthmaticus (a severe, life-threatening asthma attack that does not respond to usual asthmatic treatments).

These reactions are similar to an allergic reaction and can be managed with anti-histamine. However, histamine release is a pharmacologic property of the opioid and not an immune system response to an allergen (i.e., not a true allergy). The naturally occurring and semi-synthetic products are potent histamine releasers.

Table 7-3

Opioid Classification		
Opioid	Type of Product	Similar Chemical Structure
Codeine	Natural	Morphine
Fentanyl	Synthetic	Meperidine
Hydrocodone	Semi-synthetic	Morphine
Hydromorphone	Semi-synthetic	Morphine
Levorphanol	Semi-synthetic	Morphine
Meperidine	Synthetic	Meperidine
Methadone	Synthetic	Unique
Morphine	Natural	Morphine
Oxycodone	Semi-synthetic	Morphine
Oxymorphone	Semi-synthetic	Morphine
Propoxyphene	Synthetic	Morphine

Summary of the Pharmacologic Effects of Opioids

- Analgesia.
- Biliary spasm.
- Peripheral vasodilation (postural hypotension and fainting).
- CNS depression (sedation, occasionally euphoria, dysphoria).
- Convulsions.
- Suppression of the cough reflex.
- Decreased GI motility (constipation or ileus).
- Inhibition of the urine voiding reflex (urinary retention).
- Pupillary constriction (miosis).
- Stimulation of chemoreceptor trigger zone (nausea and vomiting).
- Smooth muscle contraction and spasm (constipation and reduced urine output).
- Opioid allergy
- Respiratory depression.
- Stimulation of histamine release (sweating, flushing, pruritus, red eyes, postural hypotension, wheezing or worsening of asthma symptoms).

Expected side effects of opioids are often mistaken for or mislabeled as allergies.

Addiction, Dependence, and Tolerance

Opioids often have their use limited by concerns regarding misuse, addiction, and possible diversion for nonmedical uses. An understanding of terminology is necessary for effective communication regarding tolerance, dependence, and addiction.

Addiction

Addiction is the psychological dependence on the use of substances for psychic effects and is characterized by compulsive use. Consider addiction if patients no longer have control over drug use and continue to use drugs despite harm.

Physical dependence

Physical dependence means that changes in the body's response to endogenous and exogenous opioids have developed such that a withdrawal syndrome develops after an opioid drug is stopped or quickly decreased without titration. Administration of an opioid antagonist also causes withdrawal. Warn patients to avoid abrupt discontinuation of an opioid. Many medications produce dependence. These include: opioids, sedatives, stimulants, anxiolytics, muscle relaxants, beta blockers, and antidepressants.

Pseudoaddiction

Pseudoaddiction is drug-seeking behavior that seems similar to addiction but is due to unrelieved pain. This behavior stops once the pain is relieved, often through an increase in opioid dose.

The American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine recognize the following definitions and recommend their use.

Tolerance

Tolerance is 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

Physical dependence is a state of adaptation that 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, or administration of an antagonist.

Addiction

Addiction is 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.

AAPM, APS, ASAM 2001

Pseudotolerance

Pseudotolerance is the need for an increase in dosage that is not due to tolerance, but is due to other factors, such as disease progression, new disease, increased physical activity, lack of compliance, change in medication, drug interaction, addiction, and deviant behavior.

Tolerance to Analgesic Effects

Tolerance to analgesia is the need for an increased dosage of a drug to produce the same level of analgesia. Tolerance develops to analgesia more slowly than to other opioid effects. Analgesic tolerance does not occur in every patient and is not addiction.

Tolerance to morphine is both **dose**-and **time-dependent.** Large doses of morphine given over a short period will be associated with a more rapid development of tolerance. Conversely, tolerance develops less rapidly when small doses are given. This observation is based on animal studies and its relevance to humans is unclear. In addition, great individual variation exists in the development of tolerance.

Tolerance to Side Effects

Tolerance develops to most of the adverse effects of opioids after 2 to 3 weeks of continuous administration. Tolerance to the constipating effects of opioids does not develop.

Morphine Pharmacology

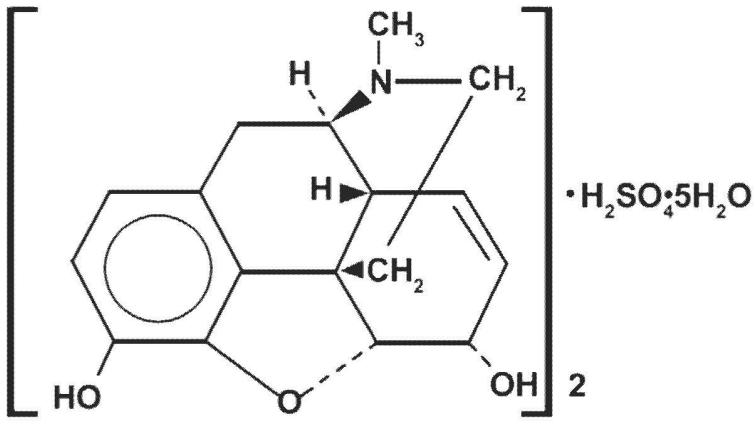
Despite the availability of several newer opioids, morphine remains the prototype opiate analgesic. As new opioid compounds are developed, their efficacy and side-effect profiles are compared with those of morphine. Morphine is a naturally occurring alkaloid derived from opium, the dried sap of the unripe fruit capsule of the poppy plant (*Papaver somniferum*). Its analgesic activity has been recognized for more than 3000 years.

Morphine is given either as the hydrochloride or sulfate salt, and these are regarded as interchangeable. The chemical structure of morphine sulfate is shown in Figure 7-3. Morphine sulfate is an odorless, white crystalline powder with a bitter taste. The bitter taste means the drug is unpalatable in liquid formulation, a drawback that can be avoided with a capsule or tablet formulation. Morphine sulfate is highly soluble in water and alcohol but is practically insoluble in chloroform and ether. Its high solubility has provided the challenge in formulating a extended-release product.

Typically, morphine is given orally (PO), intravenously (IV), subcutaneously (SC), and intramuscularly (IM). It may also be given by sublingual, rectal, epidural, and intrathecal (into the spinal fluid) routes.

Figure 7-3

Chemical Structure of Morphine Sulfate



KADIAN® PHARMACOLOGY

KADIAN® is a extended-release formulation of oral morphine sulfate presented as polymer-coated pellets in a gelatin capsule. It provides effective pain management (or similar pain control) with fewer doses of morphine than are normally required with conventional immediate-release formulations. KADIAN® capsules are formulated in five strengths containing 20, 30, 50, 60, or 100mg of morphine sulfate plus inactive ingredients.

KADIAN® Pellet Technology

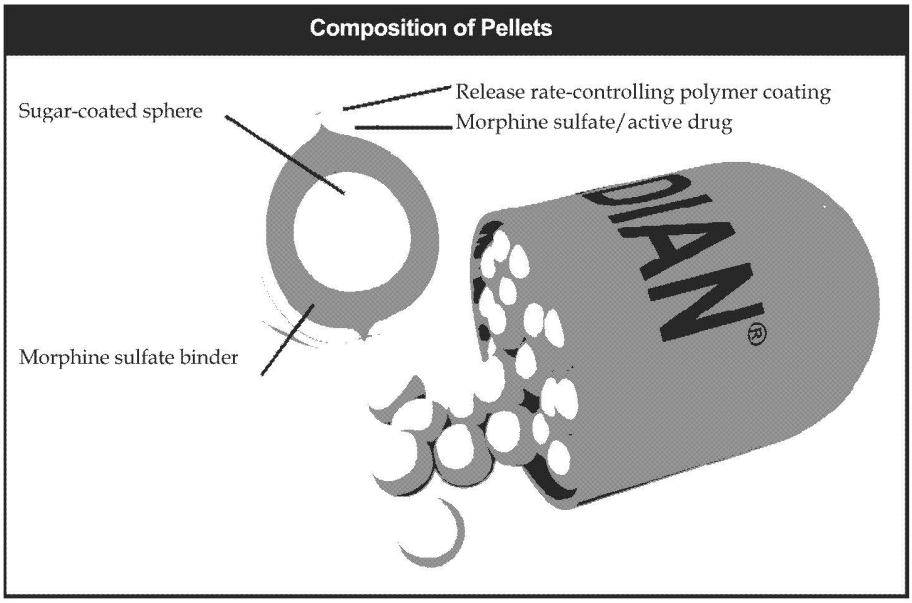
The KADIAN® capsules consist of a hard gelatin shell containing polymer-coated morphine sulfate pellets. The release of morphine from the pellets is pH dependent, with the rate of release increasing as the pH of the medium around the pellet increases.

After ingestion, the gelatin capsule dissolves in the stomach and the pellets are released. In the strongly acidic medium of the stomach, morphine release from the pellets is minimal. As the pellets pass into the more alkaline small intestine, the rate of release increases substantially. Release of morphine increases as the pellet passes through the small intestine into the large intestine, with the rate of release increasing as the pH becomes more alkaline. The pellets are designed to release morphine for up to 24 hours. This is the basis for once-a-day administration of KADIAN®.

Composition of Pellets

Each pellet has essentially four layers. The first layer is the release rate-controlling polymer coating. This coating consists of ethylcellulose, polyethylene glycol, and methacrylic acid. The second layer is the morphine sulfate or active drug. The third layer is a substance that binds the morphine to the inner core of the sphere. The core or the fourth layer is a sugar-coated sphere.

Figure 7-4: Composition of Kadian® capsule



- Ethylcellulose: a strong, insoluble component that forms the mechanical basis of the coating.
- Polyethylene Glycol: a water soluble, pH-independent component that bestows permeability at all pH levels.
- Methacrylic Acid: water soluble, pH-dependent component that bestows additional permeability at pH levels above 5.5 to 6.0.

At gastric pH, the polyethylene glycol component dissolves, forming pores through which the morphine may diffuse outward. These pores are relatively small, allowing only limited diffusion. At intestinal pH levels of 5.5 and higher, both the polyethylene glycol and the methacrylic acid dissolve. The size of the pores in the methacrylic acid is directly proportional to the pH of the surrounding fluids; the higher the pH, the larger the pore. Thus, most of the morphine release occurs through the pores in the methacrylic acid component of the polymer coating.

The ethylcellulose component of the capsule is insoluble. Therefore, remnants of the pellets may be evident as white or opaque spheres in the feces of patients treated with KADIAN®.

Summary

- Morphine has a wide range of pharmacologic actions in addition to analgesia, many of which result in unwanted side effects. The effects of morphine on the CNS include depression, stimulation, nausea and vomiting, depression of the cough reflex, and miosis. Through its direct inhibitory action on the brainstem respiratory centers, morphine also acts as a powerful respiratory depressant. Morphine also may cause orthostatic hypotension, constipation, reduced urinary output, and disturbances of menstruation and libido. Finally, morphine increases blood flow to the skin and stimulates histamine release, causing variable degrees of sweating, flushing, and pruritus and may cause wheezing or worsening of asthma symptoms.
- Patients receiving morphine for long periods often develop dose- and time-dependent tolerance to the drug's effects on the CNS. Minimal tolerance occurs to the constipating effects of morphine and patients need to continue appropriate treatment. In patients with cancer pain, tolerance to the analgesic effects of morphine is rarely the reason that dosage increases are required; rather, the patient is usually experiencing an increase in pain severity as a result of cancer or disease progression.
- Patients using opioid analgesics may continuously develop a physical dependence with or without a psychological dependence.
- KADIAN® is a unique dosage formulation that provides analgesia for up to 24 hours when dosed Q12 or Q24 hrs. It provides effective pain management with fewer doses of morphine than are normally required with conventional formulations.

Literature Cited

- Brookoff D. Chronic Pain: The Case for Opioids. Hospital Practice. 2000;69-84.

Self-Assessment Test

Circle the best response

1). Patients using opioid analgesics continuously can expect to develop - _____.
   a. Addiction
   b. Physical dependence
   c. Pseudotolerance
   d. Psychological dependence

2). Which of the following is a side effect of morphine sulfate?
   a. Hypertension
   b. Nausea
   c. Mitosis
   d. Cough

3). Histamine release is a pharmacologic property of opioids and results in all of the following except:
   a. Pruritus
   b. Sweating
   c. Flushing
   d. Allergic reactions

4). Which of the following is true regarding the composition of KADIAN® capsules?
   a. A KADIAN® pellet consists of 5 layers.
   b. The methacrylic acid of the polymer layer is permeable at all pH levels.
   c. The polymer layer is rate controlling.
   d. The size of the pores in the polyethylene glycol layer is directly proportional to the pH of the surrounding fluids.

True or False

5). Morphine and related opioids produce their major effects on the CNS and the bowel through mu receptors.
   a. True
   b. False

6). Opioid receptors are located in the CNS, pituitary gland, GI tract, and spinal cord.
   a. True
   b. False

7). Psychotomimetic effects are more common with the kappa receptor agonist activity.
   a. True
   b. False

8). The rate of release of morphine from KADIAN® increases as the pH becomes more acidic.
   a. True
   b. False

9). Analgesic tolerance is an expected result of chronic opioid therapy.
   a. True
   b. False

10). Tolerance to constipation develops in 1 to 2 weeks.
   a. True
   b. False

11). KADIAN® provides analgesia for up to 24 hours.
   a. True
   b. False

Answers to Self-Assessment Test

1. b	7. a
2. b	8. b
3. d	9. b
4. c	10. b
5. a	11. a
6. a	

CHAPTER EIGHT

Pharmacokinetics

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the types of modified-release morphine preparations.
- Describe the mechanism of morphine release in KADIAN® capsules.
- Describe the absorption of morphine from KADIAN® capsules.
- Describe the bioavailability of morphine from KADIAN® capsules.
- Describe the major findings of the single-dose KADIAN® research.
- Describe the major findings of the steady state KADIAN® research.
- Describe the pharmacokinetics of KADIAN®.
- Discuss the metabolism and excretion of KADIAN® and the clinical implications.

Terminology

AUC:	Area under the curve. Graphically, this is the area under a drug's absorption curve. It represents the amount of drug absorbed after a dose.
Bile:	A greenish-yellow bitter fluid produced in the liver and stored in the gallbladder. Bile that flows in bile ducts from the gallbladder to the intestine helps in the digestion and absorption of fat.
Bioavailability:	The degree to which a drug or other substance becomes available to the target tissue after administration.
C_{max}:	Maximum concentration in the blood of a drug after dosing.
C_{min}:	Minimum concentration in the blood of a drug after dosing.
Clearance:	A measure of the body's ability to eliminate a drug from the body.
Conjugation:	A reaction that joins a drug with another molecule to produce a form that can be eliminated by the kidney.
Delayed release:	A drug formulation that delays the release of a drug until it has passed out of the stomach and into the intestine.
Delayed gastric emptying:	Slow transit of stomach contents out and into the intestine. This can result from drug side effects or disease states.
Extended-release:	A drug formulation that releases the drug over an extended period of time.
First-pass metabolism:	Metabolism of a drug that occurs during its first passage through the liver in the circulation, right after absorption from the intestine.
Half-life ($t_{1/2}$):	Time required for an organism to eliminate one-half of a substance that has been introduced into it.
Hyperalgesia:	Abnormal sensitivity that causes normal sensations to be interpreted as pain and painful sensations to be more intense.
Linear pharmacokinetics:	Having absorption and elimination properties that lead to a proportional relation between dosing and serum drug concentrations.
Lipophilic:	lipid soluble
Metabolite:	a product of metabolism. A byproduct of a drug that has undergone chemical changes due to biochemical processes in the body.
Metabolism:	The interactions of a drug with the body's biochemical processes. It usually results in a drug's structure and properties changing. The physical and chemical processes essential for an organism to live, and also the transformation by which energy is made available for the use by the organism.
Morphine-3-glucuronide (M3G):	The predominant metabolite of morphine that has opioid antagonistic effects.
Morphine-6-glucuronide (M6G):	A metabolite of morphine that has analgesic properties.

Myoclonus:	Spasmodic skeletal muscle twitches.
Nonlinear pharmacokinetics:	Having absorption and elimination properties that lead to a nonproportional relation between dosing and serum drug concentrations. This means that responses to changes in doses are more difficult to predict.
Pharmacokinetics:	A branch of pharmacology dedicated to the determination of the fate of substances (primarily drugs) administered to a living organism (usually humans). The term is derived from the greek words "pharmacon" (meaning drug) and "kinetikos" (meaning putting in motion).
Phase I reactions:	One set of enzymatic processes in the liver that metabolize drugs. Phase I reactions include oxidation, hydrolysis, and reduction.
Phase II reactions:	One set of enzymatic processes in the liver that metabolize drugs. Phase II reactions include conjugation to form glucuronides, acetates, or sulfates.
Protein-binding:	The property of drugs that causes them to adhere to proteins in the serum.
Steady state:	Condition of dynamic equilibrium between administration and elimination of a drug.
t_{max}:	Time required to achieve maximum plasma concentration of a drug.
US Pharmacopoeia:	A legally recognized compendium of standards for drugs. It includes assays and tests for determination of strength, quality, and purity.
Volume of distribution:	A measure that describes the concentration of drug in the body tissues.

Introduction

After systemic administration, an opioid drug is absorbed into the vascular system. For the drug to produce a pharmacologic effect, it must leave the plasma, diffuse into the tissues, reach the opioid receptors, and activate them. Appropriate use of opioid analgesics requires an understanding of these pharmacologic concepts. This chapter will review the dynamics of drug absorption, distribution, metabolism, and elimination of opioids. In addition, the chapter discusses the pharmacokinetics of KADIAN®, and how these data must be integrated into clinical utilization.

General Pharmacokinetic Principles

Pharmacokinetics is the study of the absorption, distribution, metabolism, and elimination of a drug.

Absorption

Absorption describes how fast and how much of a drug leaves its site of administration (oral, parenteral, rectal). The speed and degree to which a drug is absorbed is important, although ultimately bioavailability of the drug determines to what degree a drug reaches its intended site of action.

Absorption is influenced by many factors. The larger surface area of the intestine, combined with its improved absorption properties, leads to better absorption of drugs in the intestine than the stomach. Thus, drugs that leave the stomach quickly are likely to be absorbed more quickly. Anything that delays stomach emptying may reduce or delay absorption of the drug. Drugs that are strong bases (high pH) or strong acids (low pH) do not diffuse easily into cells and therefore are absorbed poorly. Some drugs are destroyed by stomach acid and require administration in a form that has been engineered to protect it from stomach acid or it must be given by a nonoral route.

A drug that is absorbed very quickly causes a rapid rise (and then usually a rapid decline) in serum drug concentrations. A drug that is absorbed slowly leads to drug concentrations that have a lower peak; because they are absorbed over a longer time, they are present in the serum for a longer period of time. A rapid rise in serum concentrations is useful to obtain a rapid onset of action, but can lead to toxicity at the

peak concentrations and the benefits of the drug may wear off quickly. A slower rise in serum concentrations leads to a slower onset of action, but may avoid toxicity of the rapid high peak concentrations seen with faster absorption rates and provide a longer duration of action (See Figure 8-1). Strategies that take advantages of these effects are used in formulating drugs and determining dosages.

For some drugs that have slow absorption, a loading dose (a large initial dose) may be given to speed the time until a therapeutic blood concentration of the drug is reached. A maintenance dose, which is a lower dose than the loading dose, is then given to maintain the blood concentration of the drug at the desired level.

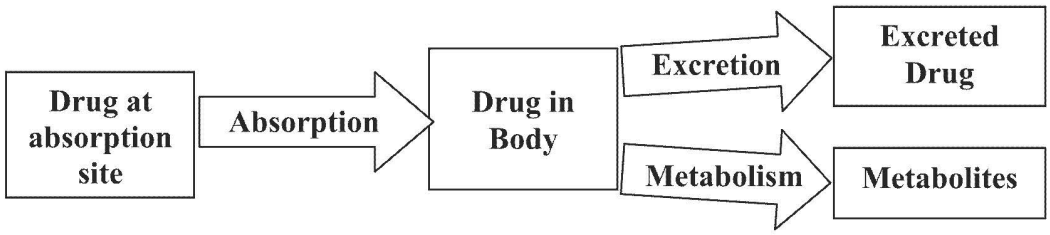
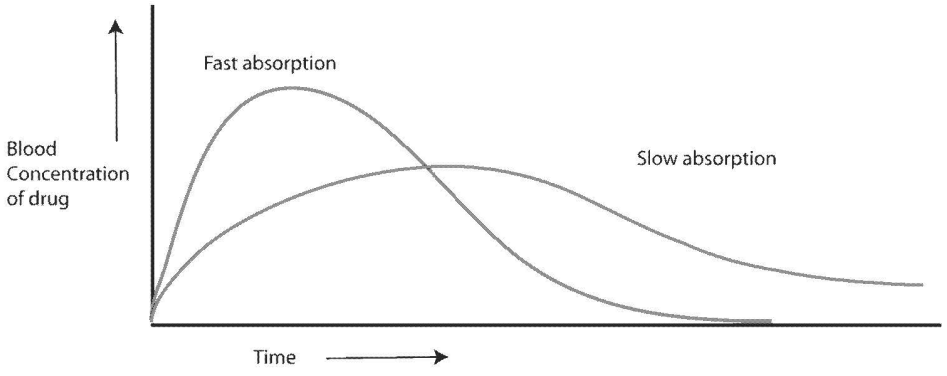


Figure 8-1: Absorption profiles



Food

Food may change the rate of absorption of many medications, usually because of the delayed gastric emptying associated with eating. This does not always mean the total

amount of drug absorbed changes; the drug may simply be absorbed more slowly. In some cases, however, the nutrients in food may actually bind medications and prevent absorption, reducing the amount of drug absorbed. For example, many drugs bind to calcium and once bound cannot be absorbed. These drugs cannot be taken with dairy products or calcium-based antacids or they will not be absorbed.

Drug Formulation

To have the desired effect, a drug must reach the site of action in an adequate quantity. There are numerous factors that affect absorption and distribution of different drugs. The properties of absorption and distribution are taken into account as the delivery form of the drug is designed so that the formulation allows the drug to be delivered to the site of action in the amount and frequency needed.

The rate of absorption of an oral drug is partly dependent upon the rate it dissolves in the gastrointestinal fluids. This factor is the basis for the so-called long-acting pharmaceutical preparations that are designed to produce a slow, uniform absorption of the drug for 8 hours or longer. Advantages of such a preparation are a reduction in the frequency of administration and maintenance of a therapeutic effect overnight. In addition, elimination of peaks in the drug concentration that occur after administration of an immediate-release dosage results in a decreased incidence or intensity of undesired effects.

The US Pharmacopoeia recognizes and defines two types of modified-release dosage forms: extended-release and delayed-release. A modified-release dosage form is a dosage form in which the rate or site of release of the active ingredients in the gastrointestinal tract has been modified.

Extended-Release

An extended-release formulation releases a drug over an extended period. This allows a reduction in dosing frequency compared with a drug presented in a conventional dosage form. Various strategies are used to control the release of a drug. For example, coatings may be placed around small amounts of drugs to produce small beads. The drug is released as the coatings dissolve. The coatings may be designed to dissolve in stomach acid (very low pH) or may be impervious to acid but dissolve in the relatively high pH of the intestine. Another example is the use of a skin patch,

which bypasses the issues of gastrointestinal absorption by taking advantage of the slow diffusion of drug into the skin layers.

Other terms used to describe these dosage formulations include *sustained-release*, *prolonged-action*, and *controlled-release*.

Delayed-Release

A delayed-release dosage form is one that delays the release of a drug until it has passed through the stomach. According to the US Pharmacopoeia, enteric-coated dosage forms are delayed-release dosage forms. Many of these drugs have coatings or packaging that is resistant to stomach acid but that is affected by the high pH of the intestine.

This manual has adopted the following classifications:

Conventional: Conventional refers to solutions or immediate-release oral dosage forms from which the total dose is immediately available.

Extended-release/controlled-release/sustained-release: In practice, these terms are used interchangeably. To separate the agents for the purposes of this manual, we will refer to KADIAN® as an extended-release formulation because it has a longer duration of action than most other oral agents. MS Contin®[1] and OxyContin®[1] are referred to as controlled-release formulations since their duration of action is somewhat shorter. However, remember that outside of this manual, these terms are used interchangeably in some cases.

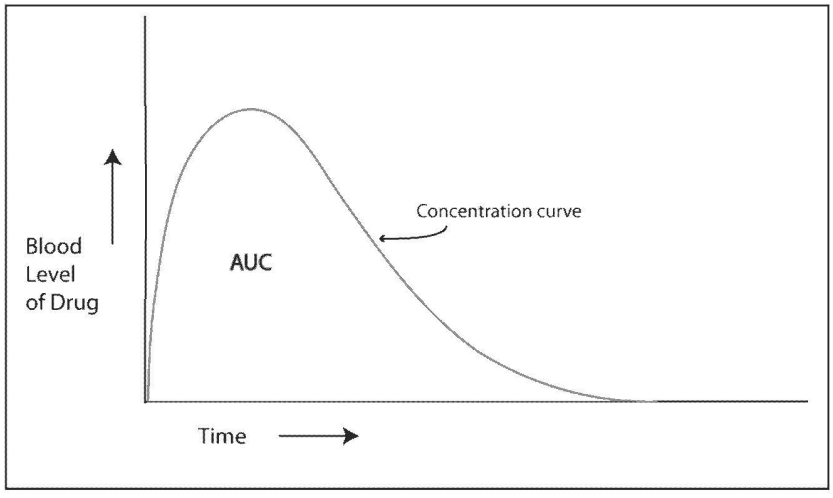
Bioavailability

Bioavailability is the extent to which a drug reaches its site of action. Factors that affect absorption of a drug affect its bioavailability. If a drug cannot be absorbed or is prevented from reaching its site of action, it is not bioavailable. For example, if a drug is destroyed by stomach acid, it is not bioavailable.

Mathematical descriptions of bioavailability are used to communicate various aspects of absorption and distribution of a drug in the body. The area under the curve (AUC), concentration, maximum concentration, minimum concentration, and time to reach concentration all are used to describe the extent to which the drug is absorbed (See Figure 8-1). The AUC is based on the absorption curve of a drug as determined under

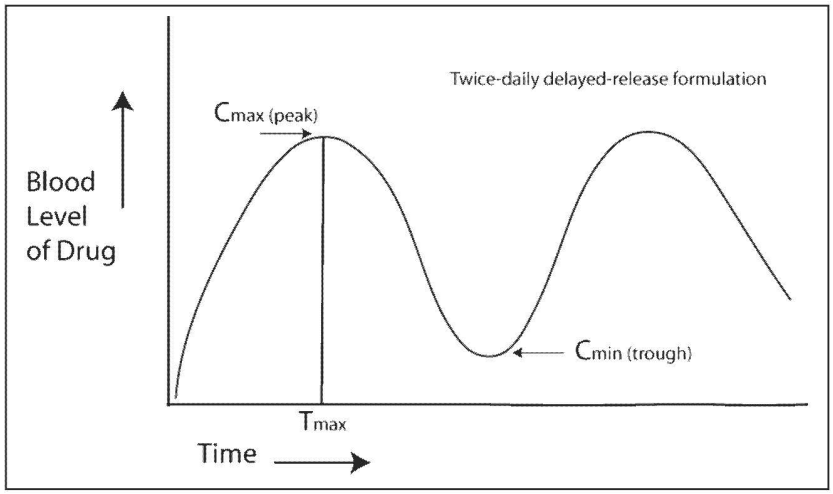
experimental conditions. In Figure 8-2, a rapid absorption curve is used to illustrate the AUC. The gray area represents the concentration of the drug in the circulation over time. In a perfect absorption state, the amount of drug represented by the entire gray area would equal the amount of the full dose given to the patient. In reality, any amount of drug that is not bioavailable (e.g., not absorbed) would not end up in the serum and would not be represented by the gray area.

Figure 8-2: Illustration of AUC



The maximum concentration (C_{max}) in the serum is the point at which the most drug is in the serum after a dose is given. That is represented by the highest point on the concentration curve. The minimum concentration (C_{min}) is the point at which the least drug is in the serum after a dose is absorbed. That is represented by the lowest point on the concentration curve. The time it takes to reach the maximum concentration (the peak) is designated as the t_{max}. (See Figure 8-3).

Figure 8-3: Biphasic blood level concentration peaks with delayed-release formulations



Factors that affect bioavailability

Several factors uniquely affect the bioavailability and the therapeutic effects of opioids. Route of administration, presence of disease states, and drug solubility are just a few of these many factors.

Route of Administration

Drugs can be delivered by different routes of administration, including intravenous, subcutaneous, intramuscular, and oral. The choice of administration route is dictated by the properties of the drug. For example, when given intravenously, a drug typically acts quickly and wears off quickly, which may or may not be desirable given the circumstances. Thus, the absorption, distribution, and elimination properties of a drug affect the decision to choose an oral or parenteral route of administration.

The oral route of administration is the most convenient and economical way to administer a drug. In addition, the drug formulation can usually be designed to control the rate of release of the drug, which, in turn, influences the absorption and serum concentrations of the drug. Not all drugs can be given orally; some drugs are destroyed by stomach acid, some have chemical properties that cause them to be poorly absorbed, others are too quickly metabolized by the first-pass effect. Nutrients and drugs absorbed from the gastrointestinal tract enter the blood at a point in the circulation where it is directed immediately through the liver. Drugs that are inactivated in the liver might therefore be rendered inactive before they even reach

the circulation. If the drug cannot be altered chemically to prevent this effect, it cannot be given orally because it will not be effective (i.e., it will not be bioavailable).

Opioids are 100% bioavailable when given intravenously because they are introduced directly into the systemic circulation. When administered orally, opioids are absorbed from the gastrointestinal tract and are transported by the portal vein to the liver, the primary site of drug metabolism. Bioavailability depends on how much of the drug is absorbed in the gastrointestinal tract and how much is inactivated as it passes through the liver. Bioavailability decreases if the liver has a great capacity to metabolize and excrete the drug. When morphine is given intravenously it has 100% bioavailability, and the recommended dose in severe pain is 10 mg. When given orally, which subjects the drug to significant liver metabolism and first-pass effect, the equivalent dose is 3 times as great
(30 mg).

Disease States

The presence of a pathologic condition also affects bioavailability. For a drug that is inactivated in the liver, bioavailability increases in patients with liver disease because the liver cannot metabolize (inactivate) and excrete the drug efficiently. For drugs that have to be metabolized to an active form before they are bioavailable, impaired liver function means that bioavailability decreases because less of the active form of the drug is available. (*See* discussion on Metabolism). In patients with kidney disease, drugs that are normally removed from the body by the kidney stay in the circulation. If doses are repeated, the drug concentrations build up, leading to increased bioavailability (and toxicity).

Drug Solubility

The lipid layer of a cell's membrane serves as a boundary that drugs must cross to reach the systemic circulation. The more lipid soluble (also called lipophilic, meaning readily dissolved into fatty tissue) the drug, the more readily it moves through membranes; thus, the faster and greater the absorption. Drugs that have strong electrical charges on them (have a high or low pH) cannot cross the lipid layer as easily as drugs with a neutral electrical charge (pH-neutral drugs). For example, fentanyl is highly lipid soluble and therefore is readily absorbed into the central nervous system (CNS). Morphine is less lipid soluble than fentanyl and therefore crosses into the CNS more slowly. Because of the same lipid solubility characteristics, fentanyl diffuses back out of the CNS quickly and morphine stays in

longer. Clinically, this means that fentanyl has a more rapid onset but wears off more quickly than morphine.

Distribution

After a drug reaches the bloodstream, it is carried throughout the body and distributes throughout the various fluids and tissues. A drug may also distribute across the placenta and into breast milk. Drug molecules will enter cells, dissolve in the plasma, bind to various proteins, and absorb into fats. Each individual drug will distribute in slightly different concentrations in various parts of the body with large amounts in certain parts of the body, and smaller amounts in other areas or tissues. Eventually, the drug reaches equilibrium, meaning it has distributed throughout the tissues.

Both rate and extent of distribution are determined by how well each tissue is perfused with blood, tissue size, binding of drug to plasma proteins and tissue components, and permeability of tissue membranes.

Volume of Distribution

The volume of distribution (V_d) is a measure that describes the concentration of drug in the body tissues (as related to the amount of drug in the plasma). The volume does not refer to an actual amount of body fluid, but rather describes the fluid volume that would be required to contain all of the drug in the body at the same concentration that is in the blood. The distribution of a drug is affected by the lipid solubility of the drug, the amount of the drug that binds to proteins in the blood (*see* discussion on Protein Binding), and how easily a drug can get into different types of tissues in the body (e.g., it is harder for drugs to diffuse into the cornea from the serum). Once enough of the drug has left the bloodstream to saturate the tissues, it is possible to determine how much of the drug was diluted in the body by calculation. Thus, the volume of distribution measures the extent of the dilution of the drug into different organs and tissues.

The volume of distribution (V_d) can be calculated by a formula:

$$V_d = \text{Amount of drug in body/concentration of drug in the plasma}$$

The V_d is useful in estimating the plasma concentration when a known drug is in the body, or conversely, in estimating the dose required to achieve a given plasma drug concentration. The amount of drug in the body can be estimated by mathematical formulas that use total body fluid volume or use a modified volume estimate if it is

known that the drug does not diffuse into some areas very readily. The calculation also depends on the rate of elimination of a drug from the tissues and the distribution half-life of the drug. The distribution half-life ($t_{1/2}$) is the time it takes for the drug to be reduced by 50%. This measure reflects the time necessary for a drug to move from blood and plasma to reach equilibrium with body tissues.

Protein Binding

Many drugs are bound to plasma proteins, primarily albumin. For most drugs, the binding is reversible and depends on the concentration of the drug in the blood, the presence of other chemicals that bind to the proteins, and the strength of the binding between the drug and the protein. Many drugs bind to proteins in the blood and these reactions are not selective. As a result, different drugs will "compete" for binding to the proteins. If a drug that is highly protein-bound is no longer able to bind to proteins (because of competition with other drugs or because an abnormally low amount of protein is available), a high amount of unbound drug will be present in the serum.

Plasma protein binding limits a drug's concentration in tissues and at its site of action because only unbound drug is pharmacologically active. Thus, if binding occurs at a higher rate than expected, the drug will be less bioavailable than expected and vice versa. Plasma protein binding also affects the body's ability to eliminate the drug. For example, a drug that normally is eliminated through the kidneys by diffusion may not be eliminated because it is bound to a large protein molecule that is too large to diffuse out through the kidney glomerular filtration system. If a patient is taking a highly protein-bound drug and then begins taking a second highly protein-bound drug, the first drug will have competition for binding sites and the blood concentrations of unbound drug (active drug) will rise, which can lead to toxicity.

Many disease states and other factors influence the concentration of proteins altering the amount of bound (inactive) drug. Protein deficiency, kidney disease that causes loss of proteins through damaged glomerular membranes, and diseases that cause excessive protein formation or degradation can all cause alterations in protein binding and therefore influence the amount of unbound (active) drug that is available.

Metabolism

When a drug passes through the liver, it is subjected to multiple processes and reactions (metabolism) that change part of the drug into different compounds. Drug metabolism usually occurs in the liver through one or both of the two types of

reactions. Phase I reactions generally make the drug molecule more water soluble so that it is prone to elimination by the kidney. Phase I reactions include oxidation, hydrolysis, and reduction. Cytochrome P450 enzymes are responsible for many Phase I reactions. The metabolic reactions usually inactivate drugs, although in some cases the metabolic changes produce active metabolites. (*See* appendix 11-2 for more information on the cytochrome P450 system.)

Phase II reactions in the liver involve conjugation to form glucuronides, acetates, or sulfates. Morphine is conjugated to an active metabolite that is even more active than morphine itself.

First-pass metabolism

Nutrients and drugs that are absorbed from the intestine enter the circulation at a point that takes them directly to the liver before going on to the general circulation. Drugs that undergo significant metabolism in the liver will then be changed before they reach the rest of the body. If a drug is partially or completely deactivated by this transport through the liver, the drug will have reduced or no efficacy. The liver metabolizes a significant portion of an orally administered opioid before it ever reaches the systemic circulation. This effect does not occur if a drug is given by injection or intravenous infusion. Thus, doses given by mouth must be much larger than doses given intravenously or by injection, because the oral doses will be partly deactivated during the transit through the liver.

Elimination

Elimination occurs by excretion and metabolism. Drugs are eliminated from the body either unchanged or as metabolites. The kidney is the primary organ for elimination of both unchanged drugs and metabolites. Drugs are also excreted in the feces, breast milk, sweat, saliva, tears, hair, and skin.

Clearance

Clearance (CL) is a measure of the body's ability to eliminate a drug from the body. This is a critical concept in the administration of long-acting drugs, because the rate of elimination affects how much total drug remains in the body before the next dose is given. If a drug is inadequately cleared or is cleared less than anticipated, the next dose of the drug may lead to toxic concentrations of drug in the blood. A steady state, in which elimination is balanced against intake to achieve a desirable blood

concentration of the drug, is the ultimate goal (*see* discussion on Steady State Concentration).

Clearance is expressed as volume cleared over time, because it represents the amount of blood cleared of the drug per unit of time.

The rate of clearance for a particular drug is usually constant, rather than dependent on the size of the dose. However, clearance rates are affected by other variables, because clearance depends on the efficiency of the kidney or liver and blood flow through the organs. Clearance changes with age, sex, disease, and body composition. If clearance is reduced, the half-life (and therefore duration of action of the drug) will be prolonged. In disease states
that increase clearance, such as dialysis, the duration of action of the drug
will be shortened.

Half-life

The terminal half-life ($t_{1/2}$) provides an estimate of how fast a drug leaves the body (rate of clearance). The terminal half-life is usually simply referred to as *half-life* ($t_{1/2}$). By definition, the half-life is the time it takes for the concentration of a drug in the body to be reduced by half (50%). The half-life is a simple way to represent a process that over the course of time may be complex. For example, elimination of a diuretic may be faster at first because urine flow is fast, but then as a patient gets relatively dehydrated and fluid flows more slowly through the kidney, the clearance slows. Thus, if you checked a rate of clearance early, it appears faster than if you check the rate of clearance later. Having a standardized point (the 50% concentration point) that is chosen to represent the rate makes it easier to compare drugs and elimination or absorption rates.

If a drug has a long half-life, it cannot be dosed as often as a drug with a short half-life. The drug with a long-half life would build up to toxic concentrations if it was dosed as frequently as a drug with a short half-life. Also, as clearance decreases, the half-life increases, because more of the drug remains in the body. In turn, if clearance is increased (by any means), the half-life decreases.

The half-life varies from one drug to another. For example, the half-life of morphine is 2 to 4 hours, whereas the half-life of levorphanol is 12 to 15 hours. It should be remembered, however, that the quoted half-life of a drug reflects an average half-life

in healthy persons studied in experimental conditions. Any given individual may have a slightly shorter or longer half-life than average.

Steady State Concentration

Steady state concentration (C_{ss}) occurs when the concentration of free drug is the same on both sides of a membrane (such as the capillary membrane that separates blood and tissue). This occurs when the rate of elimination of a drug equals the rate at which the drug enters the system. This is a dynamic process that is dependent on the sum of all the pharmacokinetic principles: absorption, metabolism, distribution, and excretion.

A steady state is desirable because it makes responses to doses predictable. If a steady state is not reached because more drug is being absorbed than eliminated (as occurs right after a dose is taken), then more drug effect can be anticipated. For example, if a patient takes a rapid-acting morphine tablet when he begins experiencing pain, he anticipates that the rapid rise in the serum concentrations will lead to less pain than he currently has, but he will also experience the other side effects of morphine. There is also no steady state as the drug wears off (more is eliminated than is absorbed), so the patient can anticipate return of pain and a decrease of side effects. An ideal situation is one in which the amount of drug taken in is balanced against the clearance of the drug such that the total level of drug in the blood stays relatively constant. In that ideal situation, the patient always has enough drug in his system to control his pain and yet never so much that it causes critical side effects. In other words, he is not constantly going through phases where the blood concentrations are rapidly increasing or decreasing, rather, the concentrations are steady.

Long-term opioid analgesic treatment is designed to maintain a steady state of opioid within the therapeutic range. The half-life is used to estimate how long it will take an opioid drug to reach steady state. This estimate can be used to decide how often to dose a drug in an attempt to reach the ideal steady state concentration. The full effects of a change in an opioid dose will not occur until the patient has taken the new dose for a time equal to 4 or 5 half lives, because that is how long it takes for state of balance between absorption and elimination to be reached.

Pharmacokinetics of Morphine

Absorption/Bioavailability

After oral administration, morphine is rapidly and completely absorbed from the gastrointestinal tract. Fifty percent of oral immediate release morphine solution reaches the systemic circulation in 30 minutes. Morphine is also readily absorbed after subcutaneous or intramuscular injection. The oral bioavailability of morphine varies considerably between individuals and because morphine undergoes considerable first-pass metabolism in the liver (see Metabolism), the bioavailable amount of drug normally ranges from about 20% to 40% of the oral dose taken. Because morphine given intravenously or by injection does not undergo first-pass metabolism, much more of a dose is bioavailable and therefore smaller total doses are given.

Distribution

Morphine is extensively distributed throughout the body. It is distributed to skeletal muscle, kidneys, liver, intestinal tract, lung, spleen, and brain. It also crosses the placenta and appears in breast milk. When compared with other opioids, morphine is relatively insoluble in lipids, which means that, in adults, only small amounts of the drug cross the blood-brain barrier (i.e., penetrate the brain and the cerebrospinal fluid that circulates around the brain and spinal cord). Morphine does not accumulate in tissues when given in normal doses, and therefore does not cause increasing toxicity with frequent dosing.

Morphine is not highly protein bound. Of the morphine that remains in the blood after first-pass metabolism in the liver (or that is given intravenously), only a relatively low proportion (30% to 35%) is reversibly bound to plasma proteins. The remainder is in a free form and hence is pharmacologically active. Certain disease states or concomitant drug therapy, which might displace morphine from its plasma protein binding sites, would not be expected to influence plasma concentrations of free morphine to any appreciable extent because much of the drug is already not protein bound.

Metabolism

Morphine is primarily metabolized by conjugation during first pass through the liver. Conjugation is a reaction that joins the morphine with another molecule into a form

that can be eliminated by the kidney. Conjugation in the liver is done by combining morphine with either D-glucuronic acid (called *glucuronidation*) or sulfuric acid.

Approximately 50% of morphine undergoes conjugation with D-glucuronic acid to morphine-3-glucuronide (M3G) and 5% to 15% forms morphine-6-glucuronide (M6G). Conjugation with sulfuric acid produces morphine-3-etheral sulfate, but this accounts for a small fraction of the metabolized morphine. Other minor metabolic pathways include the formation of normorphine and morphine-3, 6-diglucuronide (metabolized in the brain and kidneys rather than in the liver).

Role of morphine metabolites

M3G occurs in plasma at about 10 times the concentration of morphine after intravenous administration and at about 20 times the concentration of morphine after oral administration. For many years, M3G was believed to be pharmacologically inactive. However, animal studies suggest that it can penetrate the blood brain barrier and once in the CNS, can exert CNS excitatory effects and analgesic antagonistic effects (i.e., counteracts the analgesic opioid effect). In laboratory studies, M3G was shown to antagonize both the respiratory depression and the analgesic effects of M6G and morphine.

The next most abundant metabolite, M6G, is found in plasma in concentrations at least as great as those of morphine itself. The pharmacologic effects of morphine (both analgesia and side effects) are due in part to M6G. With single doses, the concentrations of M6G remain low, and morphine remains the major active analgesic agent. However, chronic oral dosing of morphine leads to accumulation of M6G to concentrations in the blood that are greater than those of morphine. Since M6G has analgesic effects, the high blood concentrations of M6G that occur with chronic morphine administration may mean that M6G contributes significant analgesic activity in patients receiving morphine for long periods of time.

Both M6G and M3G are larger molecules than morphine and therefore do not cross the blood-brain barrier as well as morphine. Certainly some of these metabolites should reach the brain where they could conceivably have an effect, but the significance of their role remains controversial. It has been suggested that both the analgesic response to morphine and the adverse effects experienced might depend on their M3G:M6G ratio. However, M3G:M6G ratios in morphine-resistant patients have been found to be similar to those in patients with well-controlled pain. Similarly, it has never been shown that metabolites influence the severity of side effects.

Laboratory evidence suggests some relation between specific metabolites and adverse side effects of morphine, which are listed in Table 8-1.

Table 8-1

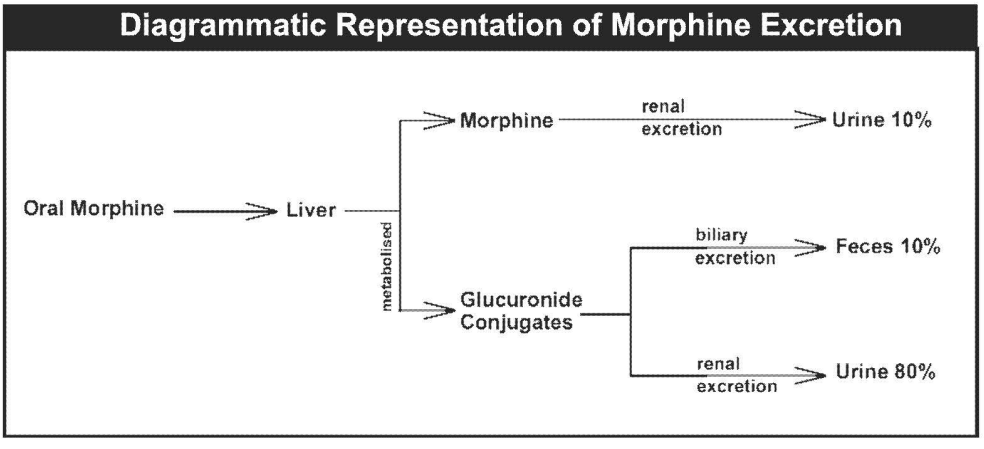
Morphine Metabolite Adverse Effects	
M6G (opioid receptor action)	M3G (nonopioid receptor action)
Drowsiness	Agitation
Nausea and vomiting	Myoclonus – seizures
Coma	Hyperalgesia
Respiratory depression	Delirium

Excretion

Elimination of the M3G and M6G metabolites by the kidneys accounts for 70% of the morphine that is eliminated from the body. Direct morphine (unchanged morphine) elimination in the urine (3%-10%), excretion of conjugates into the bile (7% to 10%) which is eliminated in the feces, and excretion via other routes (including conjugation to morphine-3-etheral sulfate and other forms) account for the remaining 30% of the morphine elimination. (See Figure 8-4).

Figure 8-4.

Diagrammatic Representation of Morphine Excretion



Effects of Hepatic and Renal Disease

Hepatic and renal disease can alter the bioavailability of a drug. In view of its extensive hepatic (liver) metabolism, the effects of morphine may be increased in patients with liver disease because the drug is not changed to forms that can

be easily eliminated. This is particularly significant in patients with advanced liver disease.

Renal impairment slows the clearance of morphine conjugates, resulting in accumulation of the active metabolite M6G (morphine6-glucuronide). Even modest levels of renal insufficiency can lead to a marked elevation of the morphine metabolites. Although most metabolites of morphine are inactive, the elevated metabolite levels may become significant in patients with renal failure resulting in a prolonged duration of action even with a single morphine dose. For these reasons, dosage reduction may be advisable in the presence of clinically significant renal impairment.

Elimination Half-Life

Morphine is rapidly eliminated from the body (the $t_{1/2}$ of morphine is 2-4 hours). Thus, oral morphine sulfate solution, which is rapidly absorbed, needs to be administered every few hours to maintain a prolonged, continuous analgesic effect. The advantage of KADIAN® in this respect is that it releases morphine for absorption over several hours, resulting in plasma morphine concentrations that are maintained for up to a 24-hour period, despite the short half-life of morphine.

Plasma Clearance

The plasma clearance of morphine (i.e., the volume of plasma cleared of the drug per unit time) after intravenous administration is 2.0 L/minute in healthy subjects and 1.2 L/minute in patients with cancer. These values, which are high, reflect the rapidity with which the body can eliminate morphine. Approximately 90% of an oral dose of morphine is excreted in the first 24 hours.

Pharmacodynamics of Morphine

The pharmacodynamics of a drug describe the relationship between the concentrations of the drug at the site(s) of action related to the magnitude of the effect(s) produced. In other words, pharmacodynamics explore what a drug does to the body.

The effects described below are common to all morphine-containing products.

Central Nervous System

The principal therapeutic actions of morphine are analgesia and sedation. The precise mechanism of analgesia is not know, however, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of the analgesic effects.

Respiratory Depression

Morphine produces respiratory depression (reduced breathing) by direction action on the respiratory centers in the brain stem. Morphine causes a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide levels in the blood. Morphine also reduces the responsiveness to electrical stimulation.

Cough Reflex

Morphine depresses the cough reflex through a direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Miosis

Morphine causes miosis (constriction of the pupils), even in total darkness. Pinpoint pupils are a sign of opioid overdose but can represent other disease processes as well (e.g. a stroke or bleeding in the pontine area of the brain).

Mydriasis

Marked mydriasis (dilation of the pupils) develops if severe hypoxia is present (as might occur with respiratory depression after an overdose).

Gastrointestinal Tract and other Smooth Muscle

Gastric, biliary, and pancreatic secretions are decreased by morphine.
Morphine causes a reduction in gastrointestinal motility due to an increase in tone in the antrum of the stomach (the muscular opening between the stomach and the duodenum). Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result
is constipation.

Biliary spasm

Morphine can cause a marked increase in biliary tree pressure as a result of spasm of the sphincter of Oddi (the junction between the bile duct and the small intestine). Bile cannot pass through the sphincter into the small intestine, causing the increased pressure. This can result in severe abdominal pain.

Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension (decreased blood pressure when standing). Vasodilation can also contribute to symptoms of itching, flushing, eye redness, and sweating.

Histamine Release

Morphine can also cause a release of histamine into the system, which in turn can contribute to hypotension. Histamine release can manifest with itching, skin redness, eye redness, and sweating.

Plasma Level-Analgesia Relationships

In any particular patient, both analgesic effects and plasma morphine concentrations are related to the morphine dose. In non-tolerant individuals, plasma morphine concentration-efficacy relationships have been demonstrated and suggest that opiate receptors occupy effector compartments, leading to a lag-time, or hysteresis, between rapid changes in plasma morphine concentrations and the effects of such changes.

The most direct and predictable concentration-effect relationships can, therefore, be expected at distribution equilibrium and/or steady-state conditions. In general, the minimum effective analgesic concentration in the plasma of non-tolerant patients ranges from approximately
5 to 20 ng/mL.

While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. The effective dose in opioid-tolerant patients may be 10 to 50 times as great (or greater) than the appropriate dose for opioid-naïve individuals. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

Pharmacokinetics Summary of Immediate-Release Morphine

- Rapid and virtually complete oral absorption
- Undergoes extensive first-pass hepatic metabolism
- Low systemic bioavailability after oral dose due to first-pass hepatic metabolism (20%-40%)
- Short elimination half-life (2-4 hours)
- Extensive tissue distribution
- Relatively low plasma protein binding
- High plasma clearance
- Rapid elimination
- One or more pharmacologically active metabolites
- Excreted predominantly in the urine
- Pharmacokinetics are altered in hepatic and renal disease

Pharmacodynamics Summary of Morphine

- Therapeutic effects include analgesia and sedation

- Can cause respiratory depression by direction action on the respiratory centers
- Depresses the cough reflex
- Causes miosis (constriction of the pupils), even in total darkness
- Mydriasis (dilation of the pupils) develops if severe hypoxia is present
- Gastric, biliary, and pancreatic secretions are decreased by morphine
- Morphine causes a reduction in gastrointestinal motility due to an increase in tone—this leads to constipation
- Causes a marked increase in biliary tree pressure, which can lead to biliary spasm.
- Causes peripheral vasodilation which may result in orthostatic hypotension
- Causes a release of histamine into the system, which in turn can contribute to hypotension and can cause itching, skin redness, eye redness, and sweating.
- The analgesic effects and plasma morphine concentrations are related to the morphine dose.
- The minimum effective analgesic concentration in the plasma of non-tolerant patients ranges from approximately 5 to 20 ng/mL.
- The effective dose in opioid-tolerant patients may be 10 to 50 times as great (or greater) than the appropriate dose for opioid-naïve individuals.

Pharmacokinetics of KADIAN®

Pharmacokinetic studies are divided into 2 general types: single dose or multiple dose. Single-dose studies typically involve healthy patients given one dose of the study medication. Multiple-dose studies may include healthy patients but are more likely to include patients using the medication for its intended purpose. Typically, the patients in multiple-dose studies have reached steady state equilibrium.

Single-Dose Pharmacokinetics

Absorption/Bioavailability

Morphine sulfate solution is used in clinical trials to represent immediate-release morphine. The area under the curve (AUC) is comparable for both KADIAN® and morphine sulfate solution, indicating that similar amounts of drug are absorbed from either preparation, so the total amount of absorbed drug is the same. However, the C_{max} (the peak serum concentration) produced by KADIAN® is lower than that

produced by morphine sulfate solution, which reflects the slower release of the drug.

The time to reach maximum concentration (t_{max}) is 8.5 hours with KADIAN® compared with 1.0 hours for morphine sulfate. KADIAN® maintains steady-state plasma morphine concentrations over 12 and 24 hours. The mean pharmacokinetic parameters of KADIAN® are provided in Table 8-2.

Table 8-2.

Mean Pharmacologic Parameters for Morphine after KADIAN® 50 mg and Morphine Sulfate Solution 25 mg (AUC and C_{max} results corrected to 50-mg dose)

Parameter	KADIAN® 50 mg	Morphine Sulfate Solution
$AUC_{0\text{-}48}$ h (ng/mL)/h	120.2 (86.3 – 167.3)	112.8 (81.1 – 157.3)
$AUC_{0\text{-}\infty}$ (ng/mL)/h	153.3 (107.2 – 219.5)	190.0 (149.5 – 241.4)
C_{max} (ng/mL)	7.3* (4.6 – 11.6)	29.6 (20.5-43.0)
t_{max} (h)	8.5 + 4.5*	1.0 + 0.3
$t > 0.75\ C_{max}$ (h)	6.7 + 6.8*	0.9 + 0.4
$t_{1/2\alpha}$ (h)	18.3 + 8.3*	24.4 +10.9
$t_{1/2\beta}$ (h)	ND	2.2 + 0.4

AUC = area under the plasma concentration curve.
C_{max} = maximum plasma drug concentration
t_{max} = time to reach maximum plasma concentration
$t > 0.75\ C_{max}$ (h) = time until plasma concentration is ≥ 75% of C_{max} (a comparative measure for extended-release formulations.)
ND = not determined
$t_{1/2\alpha}$ = half-life for the first phase of elimination
$t_{1/2\beta}$ = terminal half-life
Table is adapted from Maccarrone et al. Drug Invest 1994;7(5):262-274

Dose Proportionality

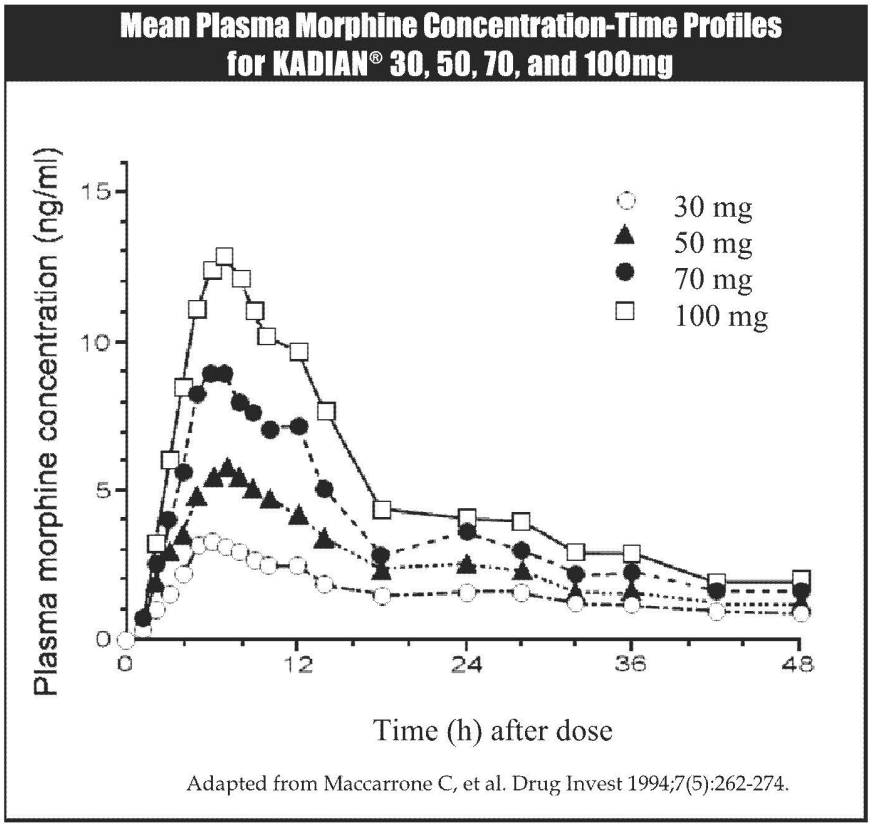
Most drugs have a proportionate relation between drug concentration in the serum and dosing. That is, the amount of drug given relates directly to the serum concentrations. In pharmacokinetic terms, this is called a linear pharmacokinetic profile. This means that serum drug concentrations change proportionally (arithmetically) with daily dosing, given time to come to steady state concentrations. For example, in a drug with

linear absorption and excretion pharmacokinetic properties, the serum concentration would double when the dose amount doubled. Nonlinear pharmacokinetic properties make it more complex to determine how the serum concentrations would change for a given change in dose. An example of nonlinear pharmacokinetics would be a drug that requires metabolism in the liver to become active, but at very high doses the liver enzyme system is saturated and can no longer increase its speed of metabolism despite increasing doses. In this case, the drug concentrations would begin to very rapidly rise when the liver enzyme system is saturated, leading to a loss of the proportional relation between the dose and the serum concentrations.

The dose of morphine often requires upward or downward adjustment during the course of therapy. Therefore, it is important that different strengths of the same formulation be dose-proportional to facilitate a safe and predictable transfer from one strength to another. The plasma morphine concentration for 4 single doses of KADIAN® (30, 50, 70, and 100mg) administered to 24 healthy volunteers in a crossover study design are shown in Figure 8-5. Both the C_{max} and the AUC increased in direct proportion to the increment in the KADIAN® dose. Thus, KADIAN® exhibited linear pharmacokinetics over the dose range tested. The t_{max} and terminal half-life did not differ across doses.

This means that if you know roughly what change in serum concentrations to expect from a 10-mg dose increase, the change will be consistent whether the 10-mg change is from 20 mg to 30 mg or from 50 mg to 60 mg. Drugs that have a linear (proportionate) relation between absorption and serum concentrations are preferable because it is easier to estimate dosage changes.

Figure 8-5

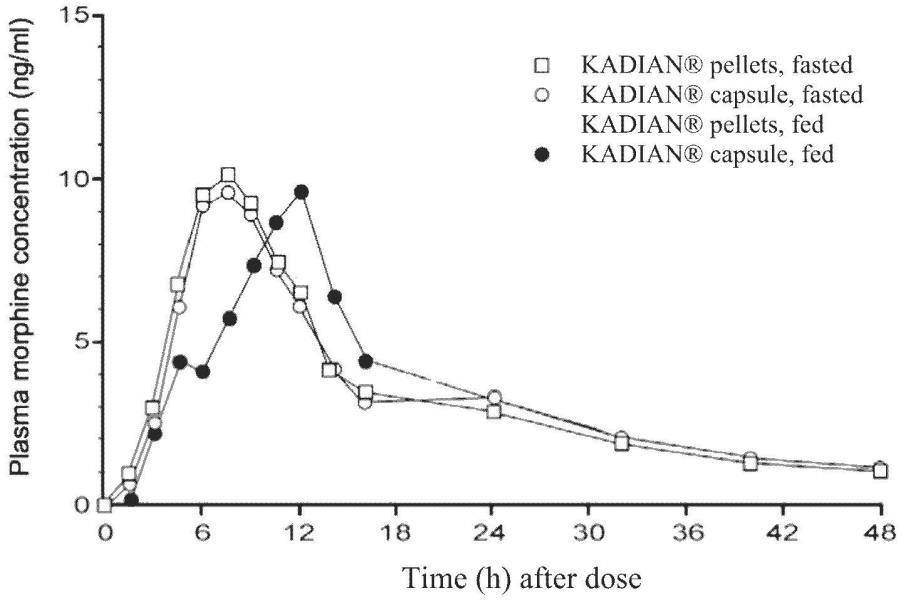


Food Effects

Consistent absorption of the active ingredient when taken with or without food is a desirable feature for any drug formulation. The extent or AUC of morphine absorption from KADIAN® capsules is not significantly affected by the presence of food. C_{max} is slightly less after a meal, but this is not considered to be significant. Food does slow the rate of absorption; t_{max} is lengthened to 10.1 hours. Thus, KADIAN® can be taken with or without food.

Figure 8-6

Mean Plasma Morphine Concentration-Time Profiles for KADIAN® 50-mg Capsules (fed and fasted) and KADIAN® Pellets (fed and fasted)



Adapted from Broomhead A, et al. *Clin Drug Invest* 1997;14(2):137-145.

Administration by Sprinkling

Another benefit of KADIAN® is that the rate of release of morphine from the pellets has not been shown to be affected when the pellets are poured onto applesauce before ingestion.

Figure 8-6 and Table 8-3 present data from a clinical study aimed at evaluating the pharmacokinetic profile and relative bioavailability of KADIAN® administered as a whole capsule or as an equivalent dose of pellets sprinkled onto a small amount of applesauce. In this study, 25 healthy male and female volunteers each received single 50-mg doses of KADIAN® capsules or pellets under both fed and fasted conditions, in a 4-period crossover study design.

Table 8-3

Mean Pharmacokinetic Parameters for Morphine after KADIAN® 50-mg Capsules (fed and fasted) and KADIAN® 50-mg Pellets				
Parameter	KADIAN® Capsules Fasted	KADIAN® Pellets Fasted	KADIAN® Capsules Fed	KADIAN® Pellets Fed (in applesauce)
$^{AUC}0$-48h (ng/ml)/hr[a]	154.5 (110.9-212.8)	154.8 (110.1-213.9)	153.3 (1 08.6-212.2)	149.0 (1 06.2-204.3)
$^{AUC}0$-∞ (ng/ml)/h[a]	182.4 (132.4-248.6)	178.5 (125.9-248.4)	175.7 (126.0-214.8)	172.1 (125.6-232.5)
*C*max (ng/ml)[a]	10.0 (6.8-4.7)	10.5 (5.7-1.77)	9.7 (6.3-14.6)	8.3[c*] (5.3-12.7)
*t*max (h)[b]	7.4+1.5[d*]7.9	+2.0[d*]11.6	+1.4	11.6 + 3.8
*t*1/2 á (h)[b]	17.0 + 5.0	16.3 + 4.4	15.1 + 3.2[f*]	15.0 + 2.9f*

a Geometric Means + 1 SD range in parentheses
b Arithmetic means + 1 SD.
c Significantly less than KADIAN® pellets fasted and KADIAN® capsule fed.
d Significantly less than KADIAN® pellets fed.
e Significantly less than KADIAN® pellets fasted.
** Statistically significant difference between treatments (p< 0.05 by ANOVA and t-test)*
Abbreviations: AUC = area under the plasma concentration time curve; C max = maximum plasma drug concentration; t max = time to reach Cmax; t1/2 = terminal half-life.
Adapted from Broomhead A, et al. Clin Drug Invest 1997;14(2)137-145.

As previously described in the section on food effects, there was a slight decrease in C_{max} and a delay in t_{max} for KADIAN® administered under fed conditions as compared with administration under fasted conditions. Importantly, the data also show that for similar conditions of food intake (fasted or fed conditions) there were no significant differences in pharmacokinetic parameters between KADIAN® capsules swallowed whole and KADIAN® pellets sprinkled on applesauce. Thus, under fasted conditions, KADIAN® capsules and KADIAN® pellets were bioequivalent and under fed conditions, KADIAN® capsules and KADIAN® pellets were bioequivalent.

Sprinkling of KADIAN® pellets onto a small amount of applesauce offers an attractive mode of administration for patients who have difficulty swallowing capsules or tablets as a result of disease progression, general debility, or the effects of radiation and chemotherapy.

The extent of absorption of morphine from KADIAN® capsules is similar to controlled-release morphine tablets and morphine sulfate solution. Gourlay (1998) reviewed the single-dose and multiple-dose pharmacokinetics of KADIAN® and other extended-release morphine formulations. Steady state pharmacokinetics and comparisons with other controlled-release products are discussed in Chapter 11.

Pharmacokinetics Summary of KADIAN®

- The AUC is comparable for both KADIAN® and morphine sulfate solution, indicating that similar amounts of drug are absorbed from either preparation.
- The C_{max} (the peak serum level) produced by KADIAN® is lower than that produced by morphine sulfate solution, reflecting the slower release of the drug. This is a characteristic of an extended release formulation and may result in fewer side effects.
- The slow rate of drug release in the gastrointestinal tract leads to a slow rate of absorption.
- The rate of absorption is slowed marginally by food but this is not clinically relevant, because bioavailability is not significantly affected.
- KADIAN® provides adequate plasma morphine concentrations, which permits once daily dosing.
- The dose-serum concentration relationship is linear, making it easier to predict changes in serum concentrations when doses are changed.
- KADIAN® absorption is the same whether the dose is taken as a whole capsule or sprinkled on applesauce.
- The unique pharmacokinetic profile of KADIAN® indicates that it has extended-release properties that provide the option of 24-hour pain control with a single daily dose. However, a patient's response to morphine is highly individualized and there is no demonstrated correlation between blood plasma concentrations and the degree of pain relief that each patient will experience.

Summary

- Morphine is extensively distributed throughout the body, and does not accumulate in tissues when given in normal doses. Only a relatively low proportion (30%-35%) of morphine present in the bloodstream is bound to plasma proteins. Thus, alterations in the degree of protein binding of morphine would not be expected to

influence plasma concentrations of free (pharmacologically active) morphine to any appreciable extent.

- Morphine is rapidly eliminated from the body and has a short plasma elimination half-life (2 to 4 hours). Thus, oral morphine sulfate solution, which is rapidly absorbed, needs to be administered every 4 hours in an attempt to maintain continuous analgesia. The extended-release formulation of KADIAN® is advantageous in that it allows plasma morphine concentrations to be maintained for up to a 24-hour dosing intervals.
- The major metabolic pathway of morphine involves glucuronidation, which occurs predominantly in the liver. Thus, the effects of morphine may be increased in patients with hepatic disease. Because morphine is excreted primarily via the kidneys, renal impairment slows the clearance of morphine conjugates, resulting in accumulation of the active metabolite morphine-6-glucuronide (M6G). For this reason, dosage reduction may be advisable in the presence of clinically significant hepatic or renal impairment.
- KADIAN® consists of polymer-coated pellets of morphine. The less acidic environment of the small intestine leads to gradual pH-dependent release of morphine from the pellets over several hours, maintaining plasma morphine concentrations for up to a 24-hour period. Thus, although the extent of absorption of morphine from KADIAN® capsules is similar to that of morphine sulfate solution or controlled-release morphine tablets, the rate of absorption of morphine from KADIAN® capsules is significantly slower.

Literature Cited

Maccarrone et al. Drug Invest 1994;7(5):262-274

Broomhead A, et al. Clin Drug Invest 1997;14(2):137-145.

Self-Assessment Test

Circle the best response

1). An extended-release formulation of a drug allows the -
_____.
a. dosing interval to be extended
b. Half-life to increase
c. AUC to decrease
d. Absorption rate to increase

2). The lower bioavailability of orally administered morphine compared with parenterally administered morphine is largely accounted for by a
_____.
a. Slower rate of absorption of oral morphine.
b. Lower C_{max} obtained with oral morphine
c. Extensive first-pass metabolism of oral morphine
d. High rate of clearance of oral morphine

3). The time to peak plasma morphine concentrations after administration of oral morphine sulfate solution is approximately _____hours.
a. 1 c. 3
b. 2 d. 4

4). The time to peak plasma concentrations after KADIAN® administration is approximately _____hours.
a. 2 c. 6
b. 4 d. 8

5). Glucuronidation, the major metabolic pathway of morphine, occurs primarily in the _____.
a. Kidneys c. Brain
b. Liver d. Tissues

6). Which statement is true regarding the protein binding of morphine sulfate?
a. Morphine is highly protein bound.
b. The plasma concentration of morphine is not appreciably affected by alterations in plasma protein binding.
c. Only morphine sulfate bound to proteins is pharmacologically active.
d. Other drugs that are highly protein bound would influence drug concentrations or morphine sulfate if given concomitantly.

7). Which statement is true regarding the morphine metabolites M6G and M3G?
a. M3G is pharmacologically inactive.
b. More M6G is produced than M3G.
c. The pharmacologic effects of morphine are due primarily to M6G.
d. More M6G is produced after administration of KADIAN® than after immediate-release morphine administration.

8). The rapid elimination of morphine from the body is reflected by its_____.
a. Long half-life.
b. High rate of plasma clearance.
c. Slow rate of absorption.
d. Significant metabolite production.

True or False

9). Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion of pharmaceutical agents.
a. True
b. False

10). The extent of morphine absorption from KADIAN® capsules is decreased by the presence of food.
a. True
b. False

11). The oral bioavailability of morphine normally ranges from 10% to 20%.
a. True
b. False

12). KADIAN® shows nonlinear pharmacokinetics over a dose range of 30 to 100 mg.
a. True
b. False

13). Steady state plasma morphine concentrations are achieved within 12 to 24 hours of starting KADIAN® therapy.
a. True
b. False

14). The kidneys are the primary route of excretion of morphine.
a. True
b. False

Answers to Self-Assessment Test

1. a	8. b
2. c	9. a
3. a	10. b
4. d	11. b
5. b	12. b
6. b	13. b
7. c	14. a

CHAPTER NINE

Dosage and Administration

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the factors to be considered in selecting the initial dose of KADIAN®.
- Describe the key factors in switching a patient from another opioid to KADIAN®.
- Describe the potential adverse interactions of KADIAN® with other medications.
- Describe the key information to be provided to patients taking KADIAN®.

Terminology

Bioequivalent drugs:	Two drugs that are similar in absorption and physiologic activity.
Breakthrough pain:	Pain that is not fully controlled with the current pain control regimen. It may be episodic.
Dosing interval:	The time between administration of doses.
Dose titration:	Adjustment of a dose to achieve the best therapeutic response with a minimum of undesirable side effects.
Equianalgesic dosing:	A dose of an analgesic drug that is equivalent in strength to a dose of another analgesic drug.
Extent of absorption:	The degree to which a dose of medication is taken up into the system from the site of administration.
French:	A measurement scale used for denoting the external diameter of catheters, sounds, and other tubular instruments. The scale is expressed in units, and each unit equals about 0.33mm. Thus, a 16-French catheter has a 5.3-mm external diameter (16 X 0.33mm).
Gastrostomy:	The creation of an opening in the stomach through which a tube is placed to allow administration of fluids, food, and medications in individuals who cannot swallow.
Gastrostomy tube:	A tube inserted through a gastrostomy opening into the stomach of a patient used for feeding. It is also known as a "G-tube" or a "feeding tube." There is a small balloon on the tube that is inflated within the stomach to prevent the tube from falling out and a closed port on the end of the external section of the tube that can be opened to allow fluids and medications to be administered. Water and other fluids can be flushed through the tube from the opening of the port to clear obstruction or to make sure all the material introduced has fully passed through into the stomach. (Note: not a NG tube)
Incident or episodic pain:	Pain that occurs in addition to a patient's usual pain. An example would be chronic pain that is intensified by extra physical activity.
Nasogastric tube:	A tube of soft rubber or plastic that is inserted through a nostril into the stomach. This tube is used for various medication problems, including decompressing/draining the stomach of gas or digestive fluids if it becomes distended due to obstruction. Nasogastric tubes are of a relatively small diameter to maintain patient comfort, therefore are prone to blockage if material (e.g. medications or food) are administered through them. (Note: not a NG tube)
Parenteral:	Administration of a drug by means other than absorption through the intestine. These methods include intravenous, intramuscular, or subcutaneous delivery of a drug.
Trough:	The lowest level of drug concentration in the blood.

Introduction

KADIAN® is a extended-release formulation of morphine sulfate that is composed of polymer-coated pellets of drug presented in capsule form. Eight color-coded dose strengths are available: 10 mg (light blue), 20 mg (yellow), 30 mg (blue violet), 50 mg (blue), 60 mg (pink), 80 mg (light orange), 100 mg (green), and 200 mg (light brown). These permit flexible dose titration. This chapter will review recommendations for administration and dosing of KADIAN®.

Administration

KADIAN® has three modes of administration that permit dosing flexibility. KADIAN® can be given as a whole capsule, by sprinkling the contents of the capsule on applesauce , or through a gastrostomy tube, 16 French or larger.

The safety of KADIAN® has not been directly investigated in patients under the age of 18 years.

Whole Capsule Administration

KADIAN® capsules should be swallowed whole. The capsules or pellets should not be chewed, crushed, or dissolved, however, as this could lead to the rapid release and absorption of a potentially toxic dose of morphine.

Sprinkle Administration

In a study of healthy volunteers, KADIAN® pellets sprinkled over applesauce were found to be bioequivalent to KADIAN® capsules swallowed whole with applesauce under fasting conditions. (Add reference: Kerr and Tester) Other foods have been tested but are not approved by the FDA. Patients who have difficulty swallowing whole capsules or tablets may benefit from this alternative method of administration.

Directions for sprinkle administration

1. Open capsule.
2. Sprinkle the entire contents of the capsule (i.e., all pellets) into a small amount of applesauce. Applesauce should be room temperature or cooler.

3. Use immediately.
4. The contents of the capsule should not be chewed or crushed, because this increases the risk of a toxic or fatal overdose.
5. Rinse mouth to ensure that all pellets have been swallowed.
6. Patients should consume the entire portion and should not divide the applesauce into separate doses.

Gastrostomy Tube (G-tube) Administration:

The pellets in KADIAN® capsules are small enough to pass through a 16-French (or larger) gastrostomy tube and may be administered in this manner to patients with a gastrostomy tube in place. Follow these procedures and principles when using KADIAN® by G-tube administration:

1. Fit 16-French or larger G-tube with a funnel at the port end of the G-tube. Flush the G-tube with water to ensure that it is wet prior to administration.
2. Open capsule and sprinkle the entire contents (i.e., all pellets) into 10mL of water in a beaker or other appropriate container.
3. Use a swirling motion to pour the pellet-water mixture through the funnel and into the G-tube.
4. Rinse the beaker or container with an additional 10mL of water and pour this through the G-tube.
5. Repeat rinsing until no pellets remain in the beaker.

The administration of KADIAN® pellets through a nasogastric tube should not be attempted.

Dosage

The extended-release nature of KADIAN® allows it to be given on either a once-a-day (Q24h, every 24 hours) or twice-a-day (Q12h, every 12 hours) schedule. To avoid accumulation of morphine, the dosing interval of KADIAN® should not be more than every 12 hours. KADIAN® produces analgesia similar to that produced by immediate-release and controlled-release formulations for the same total daily dose of morphine.

Patients who do not have a proven tolerance to opioids should be treated to clinical response (i.e., the pain control goal for the patient has been reached) using an immediate-release morphine formulation and should then be converted to an extended-release product. However, if KADIAN® is chosen as the initial opioid, the patient should be started on the 20-mg strength dosage. The dose may be increased by 20 mg every other day. Dosage adjustment is needed until the patient has achieved the best balance between baseline analgesia and opioid side effects such as confusion, sedation, nausea and vomiting, and constipation.

In opioid-tolerant patients, KADIAN® should be started by administering one-half of the estimated total daily oral morphine dose every 12 hours or 24 hours. The dose should be titrated no more frequently than every other day to allow the patient to stabilize on the new dose before increasing the dose. **The 100-mg and 200-mg capsules are only for use in patients who are known to be opioid-tolerant.**

Considerations in the Adjustment of Dosing Regimens

Adjustments in the dosage regimen of KADIAN® can be made to minimize side effects in patients having trouble tolerating KADIAN® or other opioids. Adjustments can be done by decreasing the strength of the dose or decreasing the frequency of dosing.

- For example, if the patient is started on KADIAN® every 24 hours and excessive opioid side effects are observed, the next dose should be reduced in strength. If dose reduction leads to inadequate analgesia, consider keeping the dose at the lower total dose, but increasing the dosing interval to every 12 hours. This may permit adequate plasma drug levels to maintain pain control without the higher drug levels associated with side effects. Inadequate analgesia may include end of dose pain, breakthrough pain, incident pain, or simply inadequate baseline pain relief. If inadequate analgesia or pain occurs on a 12-hour dosing regimen, a supplemental dose of a short-acting analgesic may be given as an alternative to the higher doses of long-acting opioids. If breakthrough pain continues despite these attempts to minimize side effects, the dose of KADIAN® may be increased cautiously. About half of patients with cancer-related pain will require dose escalation. (Zech 1995) In a study of patients with non-cancer chronic pain, 44% required dose escalation by 3 months, 23% in the second three month follow up period, and then for 10% in each follow-up period thereafter. (Portenoy 2007)

Some patients experience the majority of side effects only at the time of peak plasma concentration. For these patients, an alternative is to give the dose in the late

afternoon. The peak plasma concentration will then occur during the sleep cycle when the patient will be less aware of side effects.

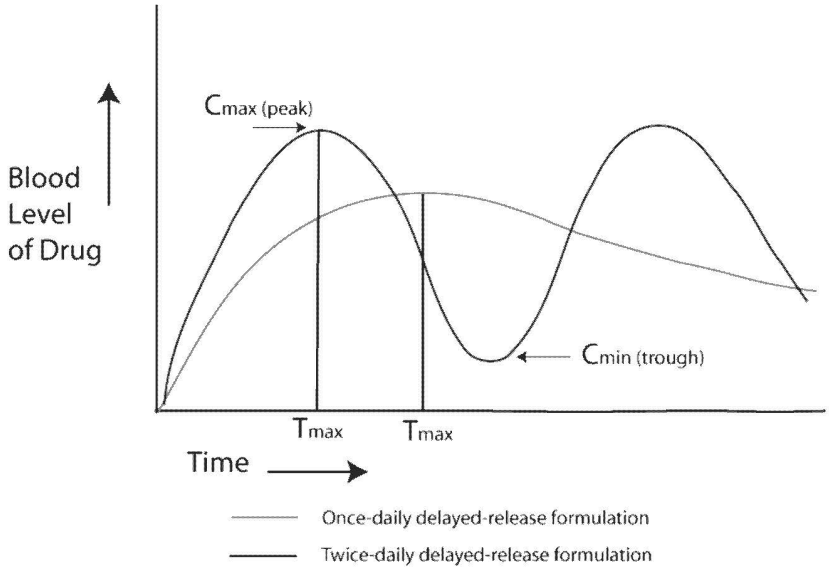
Bioequivalence

KADIAN® capsules have the same extent of absorption (also referred to as "area under the curve" or AUC; see Chapter 8 on pharmacokinetics for full description) as immediate-release and controlled-release oral formulations of morphine sulfate. This means that the total amount of morphine absorbed is the same for an equivalent morphine dose, whether given as an extended-release or immediate-release form.

KADIAN® capsules have the same extent of absorption as immediate-release and controlled-release oral formulations of morphine sulfate. The total amount of morphine absorbed is the same, but the time to peak blood levels and the maximum concentrations in the blood are lower with the extended release formulation.

However, key pharmacokinetic parameters of immediate-release formulations and some extended-release formulations differ from those of KADIAN®. The time to peak blood levels (T_{max}) is prolonged and the maximum serum concentration level (C_{max}) is lower with KADIAN®. Thus, the immediate-release and some extended-release products are not bioequivalent to KADIAN®. Drug products are bioequivalent when the rates and extent of bioavailability of the active ingredient in the products are not significantly different under suitable test conditions.

Figure 9-1: Differences in Peak and Trough Concentrations and T_{max} between once-daily and twice-daily delayed-release preparations



Conversion from KADIAN® to the same total daily dose of other controlled-release morphine preparations may lead to either excessive sedation at peak serum concentrations or inadequate analgesia at trough serum concentrations. This is because the T_{max} may occur more rapidly and the C_{max} may be higher with the other preparation than with KADIAN®. These rapid and higher peak levels may be associated with increased side effects; therefore, close observation and appropriate dosage adjustments are recommended in this situation.

Selection of a KADIAN® Starting Dose

It is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior opioid analgesic treatment experience. In the selection of the initial dose of KADIAN®, attention should be given to

- the total daily dose, potency, and kind of opioid the patient has been taking previously;
- the reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed;
- the patient's degree of opioid tolerance;
- the general condition and medical status of the patient;
- concurrent medication(s); and
- the type and severity of the patient's pain.

Conversion from other oral morphine to KADIAN®

Patients taking other oral morphine formulations may be converted to KADIAN® by totaling the daily dose of morphine and giving one-half of the total as daily dose KADIAN® capsules every 12 hours. The first dose of KADIAN® may be given with the last dose of conventional oral morphine because of the long delay until the peak effect after administration of KADIAN®. For example, if a patient had been previously taking a total of 60 mg of immediate-release morphine each day, the initial starting dose of KADIAN® could be 30 mg twice daily.

Equianalgesic Tables

Patients who have never been treated with opioids should be started on the low, recommended starting doses because these patients lack tolerance to opioids. However, patients who are already receiving opioids are likely to have developed tolerance and may experience insufficient pain relief and possibly withdrawal if adequate doses are not administered. Because opioids have different formulations and potencies, it is important to know what strengths of a new opioid drug are equal to the strength of the formulation that the patient is currently being treated with. For example, if a patient is taking 200mg of codeine a day, they might be started at the equivalent dose of morphine, 60mg, given as 30mg twice daily.

Multiple tables of oral and parenteral opioid equivalents are available for use to guide these conversions. These tables are called equianalgesic-dosing tables. Although the equianalgesic doses are equal in theory, in practice, there is variable cross-tolerance to opioids among individual patients. In addition, the ratios obtained from these tables are only approximate; therefore use caution when converting a patient from one opioid or one dosage form to another. It may be advisable to initiate the dose of the converted opioid at 50% of the first opioid to avoid excessive side effects unless a patient is in severe pain.

There are several methods to help you convert from one opioid drug or dosage form to another. Because there are several ways to calculate an equianalgesic dose, the choice of method is primarily one of individual preference.

Ratios

Using the equianalgesic chart in Table 9-1 as an example, note that the chart provides a list of analgesics at doses, both oral and parenteral, that are approximately equal to each other in the ability to provide pain relief. In other words, all the doses are theoretically interchangeable. All the opioid doses listed in the equianalgesic chart are appropriate starting doses given every 4 hours for adults with severe pain.

Example: Oral Morphine to IV Morphine

- Look at Table 9-1 and find the oral dose listed for morphine (30 mg) and the parenteral dose (10 mg).
- This gives a 30:10 or a 3:1 ratio for oral to parenteral morphine.
- This means that it takes approximately 3 times more morphine orally than parenterally (e.g., IV) to produce the same analgesic effect.
- One can simply divide any oral morphine dose by 3 to determine the approximate equianalgesic parenteral morphine dose.
- For safety reasons, this dose is often halved for initial dosing, because it may be difficult to predict side effects. The dose is increased if the patient tolerated the initial dose and needs additional pain relief.

Table 9-1

Equianalgesic Table Adapted from Goodman and Gilman, 9th Edition		
Drug	Parenteral (mg)	Oral (mg)
Morphine	10	30 – 60**
Hydromorphone	1.3	7.5
Oxymorphone	1	5 (rectal)
Oxycodone	-	5-10*
Codeine	130	200
Hydrocodone	-	5-10*
Propoxyphene	-	65*
Meperidine	75	300
Levorphanol	2	4
Methadone	10	20
Fentanyl	0.1 µg	-
Nalbuphine	10	-
Butorphanol	2	-

*The dose of propoxyphene is not necessarily equivalent to 10 mg of subcutaneous morphine.

Example: Conversion from IV morphine to KADIAN®

- When converting IV morphine to oral morphine, use the same equianalgesic dose described above. In this instance, the ratio is 1:3.
- Simply multiply any IV morphine dose by 3 to determine the approximate equianalgesic oral morphine dose.
- If you want to take 20 mg IV total daily dose of morphine and convert it to KADIAN®, you would multiply 20 mg IV morphine by 3 to get 60 mg oral KADIAN® (60 mg once a day OR 30 mg twice a day).
- For safety reasons, KADIAN® may be started at a lower dose.

Proportions

Another method of calculating equianalgesic doses (EAD) is to set up simple math proportions using ratios. Use the following equation to calculate equianalgesic doses. Do a separate calculation for each old drug and route.

$$X = \text{Old dose} \times \frac{\text{New drug EAD}}{\text{Old drug EAD}}$$

Where X = Total daily dose of new drug

New drug EAD = Equianalgesic dose from chart of new drug and route

Old dose = Total daily dose of old drug

Old drug EAD = Equianalgesic dose from chart of old drug and route

Example: Conversion of KADIAN® to IV morphine

- Use the proportion equation to estimate the required parenteral morphine dose for a patient taking 60 mg of KADIAN®.
- In this example, the "new drug" will be IV morphine and the "old drug" is KADIAN®.
- Look at Table 9-2 to find equianalgesic doses for morphine IV ("New drug EAD") and oral morphine ("Old dose").

$$X = \quad 60\ \text{mg} \quad \times \quad \frac{10\ \text{mg}}{30\ \text{mg}} \quad = 20\ \text{mg}$$

- After you insert the numbers into the equation, you find that $X = 20$ mg IV morphine daily.
- Consider decreasing the total daily dose by 50% for safety (10 mg).
- The dose is then divided by the number of times a day the dose will be given. The dose interval is based on duration of action of the drug.
- IV morphine is given approximately every 4 hours, so 3 mg of IV morphine given every 4 hours would give the total of 10 mg (50% of the total calculated equivalent dose) given over 24 hours.

- This approach is likely to require a dosage increase in the first 24 hours for many patients (because it was started at 50% of the equivalent dose of the old drug), but is recommended because it is less likely to cause overdose or undesirable side effects than going directly to the calculated equivalent dose without titration.

Use of KADIAN® as the First Opioid Analgesic

There has been no evaluation of KADIAN® as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate the doses to achieve adequate analgesia when using extended-release morphine, it is ordinarily advisable to begin treatment with an immediate-release morphine formulation.

Opioid analgesic agents may not effectively relieve all types of pain. For example, neuropathic pain and headaches often require treatment with other types of medications containing analgesic properties. This does not mean that patients suffering from these types of pain should not be given an adequate trial of opioid analgesics. However, such patients may need to be promptly evaluated for other types of pain therapy.

Table 9-2

Equianalgesic Table Adapted from APS		
Drug	Parenteral (mg)	PO (mg)
Morphine	10	30

Hydromorphone	1.5	7.5
Oxymorphone	1	10 (rectal)
Oxycodone	-	20
Meperidine	75	300
Levorphanol	2(acute) 1 (chronic)	4(acute) 1 (chronic)
Methadone	10(acute) 2-4 (chronic)	20(acute) 2-4 (chronic)
Fentanyl	0.1	-

Individualization of Dosage

The use of opioid analgesics in the management of chronic malignant and chronic benign pain is described in materials published by the World Health Organization (WHO), the Agency for Health Care Research and Quality, and the American Pain Society, which are available from Alpharma Pharmaceuticals LLC upon request. Treatment should be individualized by using appropriate pain management principals.

KADIAN® is a third-step drug that is most useful when the patient requires a constant level of opioid analgesia as a "foundation" or "baseline." When a patient has reached the point where comfort cannot be provided with a combination of nonopioid medications (NSAIDs and acetaminophen) and intermittent use of moderate or strong opioids, the patient's total opioid therapy should be converted into a 24-hour oral opioid equivalent. The addition of KADIAN® is done to provide a constant level of analgesia, and the level of analgesia can then be supplemented by the use of other medications (e.g., NSAIDs) as needed.

If breakthrough or incident pain occurs, the dose may be supplemented with a small dose (less than 20% of the total daily dose) of an immediate-release opioid analgesic. Patients who are excessively sedated after a once-a-day dose or who regularly experience inadequate analgesia before the next dose should be switched to Q 12 hr. dosing. If two or more breakthrough medications are needed, titration of the baseline or long-acting opioid medication should be done.

Pure mu-agonist opioids do not have a maximum dose. Doses are titrated to pain relief, and so no ceiling can be

Pure mu-agonist opioids do not have a maximum dose; doses are titrated to pain relief.

given as to the recommended maximal dose. The total dose of KADIAN® should be advanced until the desired therapeutic endpoint is reached or clinically significant opioid-related adverse reactions occur.

Information for Patients

Patients receiving KADIAN® should be given the following instructions by the medical practitioner:

1. Patients should be advised that KADIAN® contains morphine and should be taken only as directed.
2. Patients should be advised that KADIAN® capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternately, KADIAN® capsules may be opened and the entire contents sprinkled on a small amount of apple sauce immediately prior to ingestion. KADIAN® capsules or the contents of the capsules must not be chewed or crushed due to a risk of fatal overdose.
3. Patients should be advised that KADIAN® 100 mg and 200 mg Capsules are for use only in opioid-tolerant patients. Special care must be taken to avoid accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, as such unsupervised use may have severe, even fatal, consequences.
4. Patients should be advised that the dose of KADIAN® should not be adjusted without consulting the prescribing health care provider.
5. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
6. Patients should be advised that KADIAN® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on KADIAN® or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected.
7. Patients should be advised that KADIAN® should not be taken with alcohol or other CNS depressants (sleeping medication, tranquilizers) except by the orders of the prescribing healthcare provider because dangerous additive effects may occur resulting in serious injury or death.

8. Women of childbearing potential who become or are planning to become pregnant, should consult their prescribing healthcare provider prior to initiating or continuing therapy with KADIAN®.
9. Patients should be advised that if they have been receiving treatment with KADIAN® for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the KADIAN® dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their prescribing healthcare provider should provide a dose schedule to accomplish a gradual discontinuation of the medication.
10. Patients should be advised that KADIAN® is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
11. Patients should be advised that severe constipation could occur as a result of taking KADIAN® and appropriate laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy.
12. Patients should be instructed to keep KADIAN® in a secure place out of the reach of children. When KADIAN® is no longer needed, the unused capsules should be destroyed by flushing down the toilet.

FDA Safety Warnings for KADIAN®

The following are included in black box warnings from the FDA regarding KADIAN®:

- KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
- KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.
- KADIAN® capsules are **NOT** for use as a **PRN** analgesic.
- KADIAN® 100-mg and 200-mg capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already

tolerant to high doses of opioids. KADIAN®.capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The pellets in the capsules are not to be chewed, crushed, or dissolved due to the risk of rapid release and the absorption of a potentially fatal dose of morphine.

Additional warnings included in the prescribing information are as follows:

- KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Summary

- KADIAN® is available in color-coded 10 mg (light blue) 20-mg (yellow), 30-mg (blue violet), 50-mg (blue), 60-mg (pink), 80-mg (light orange), 100-mg (green), and 200-mg (brown) capsules. KADIAN® capsules are administered orally once or twice daily (Q12 or Q24 hours). KADIAN® capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternatively, KADIAN® capsules may be opened and the entire contents sprinkled on a small amount of applesauce immediately before ingestion, or the pellets can be mixed with a small amount of water and administered through a 16-French (or larger) gastrostomy tube. The administration of KADIAN® pellets through a nasogastric tube should not be attempted.
- KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.
- The pellets in KADIAN® should not be chewed, crushed, or dissolved because of a risk of overdose.
- Selection of the initial KADIAN® dosage should take into account the total daily dose, potency and characteristics of previously administered opioid analgesics, the reliability of the relative potency estimate used to calculate the total dose of morphine required, the patient's degree of opioid tolerance, the patient's general medical condition, other medications that the patient is concurrently taking, and the type and severity of the patient's pain.
- Patients already taking other oral morphine formulations can be converted to KADIAN® therapy by administering the patient's current total daily morphine dose of KADIAN® every 24 hours or one-half of the patient's current total daily morphine dose of KADIAN® every 12 hours, with subsequent dosage

adjustments as necessary.

- Patients already taking parenteral morphine or other parenteral or oral opioids should be converted with caution to KADIAN® because of individual patient variations and uncertainties regarding relative estimates of opioid potency and cross-tolerance. Only approximate guides as to the relative potencies of opioids are available. Researchers suggest that, for morphine, an oral dose 3 times greater than the parenterally administered dose is equipotent, but specific recommendations cannot be made for conversion from other parenteral or oral opioids to oral morphine. In these circumstances, the initial KADIAN® dosage regimen chosen should be conservative and 24-hour morphine requirements should, if anything, err on the side of underestimation.

Literature Cited

- Portenoy et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clin J Pain. 2007;23:287-299.
- Zech et al. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain. 1995;63:65-76.

Self-Assessment Test

Circle the best response

1). Which of the following is not a KADIAN® capsule strength?
   a. 20mg
   b. 50mg
   c. 80mg
   d. 150mg

2). Which of the following is true regarding KADIAN® administration?
   a. Administer orally every 12 or 24 hours.
   b. Administer with meals.
   c. Mix with applesauce and place in a 16-French or larger G-tube.
   d. Sprinkle contents into applesauce up to 48 hours before ingestion.

3). Which of the following is true regarding the bioequivalence of KADIAN®?
   a. KADIAN® is bioequivalent to other long-acting morphine products.
   b. The area under the curve (AUC) of KADIAN® is similar to that of other controlled-release morphine products.
   c. The C_{max} achieved with KADIAN® is greater than the C_{max} achieved by other controlled-release morphine products.
   d. The slow release of morphine sulfate from KADIAN® reduces the area under the curve (AUC).

4). In patients who have not previously received opioids, the initial KADIAN® dose is:
   a. 20 mg every 24 hours
   b. 30 mg every 24 hours
   c. 20 mg twice daily
   d. 30 mg twice daily

5). When converting from parenteral morphine to oral morphine, the literature suggests giving an oral dose _____times greater than the parenterally administered dose.
   a. 3 to 6
   b. 5 to 10
   c. 10 to 20
   d. at least 100

True or False

6). When converting patients from other oral morphine preparations to KADIAN®, the initial once-daily KADIAN® dose would be equivalent to the patient's current total daily morphine dose every 24 hours.
   a. True
   b. False

7). Excessive opioid side effects soon after conversion to KADIAN® should be treated by discontinuing KADIAN®.
   a. True
   b. False

8). Any breakthrough or incident pain may be treated with a short-acting opioid analgesic.
   a. True
   b. False

9). A patient's KADIAN® dose can be increased every 24 hours.
   a. True
   b. False

10). KADIAN® impairs the central nervous system and motor skills less than do other opioids.
   a. True
   b. False

Answers to Self-Assessment Test

1. d	6. a
2. a	7. b
3. b	8. a
4. a	9. b
5. a	10. b

CHAPTER TEN

Safety and Adverse Experiences

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Discuss the common adverse effects of KADIAN® and other opioids.
- Describe the potential serious adverse effects of KADIAN® and other opioids.
- Discuss the abstinence syndrome that can occur when chronic opioids are discontinued.
- Discuss the clinical manifestations of opioid overdose.
- Understand the use of opioids in pregnancy, labor and delivery, and breastfeeding.
- Identify the contraindications and precautions to the use of KADIAN®.
- Discuss potential drug interactions involving KADIAN®.

Terminology

Addison's disease:	A deficiency of the adrenal cortex and therefore the hormones produced in this area.
Amblyopia:	Weakness in vision in one eye that can cause it to relax and drift relative to the other (also called *lazy eye*).
Amenorrhea:	Lack of menstrual periods.
Ames test:	A test for potential carcinogenic properties of a drug. It uses the rate of genetic mutations caused in a strain of the bacterium *Salmonella*.
Amylase:	An enzyme that occurs in saliva and pancreatic juice and aids the digestion of starch. Amylase will also hydrolyze glycogen to yield glucose and other sugars.
Anaphylaxis:	A severe, life-threatening allergic reaction.
Antiemetic:	A drug that prevents nausea.
Arthralgia:	Joint aching.
Ataxia:	A lack of coordinated muscular movements that can result from neurologic disorders.
Atelectasis:	Collapse of the alveoli (tiny air sacs) in the lungs.
Axial skeletal fusion:	Calcification of the spinal column that leads to calcified connections between the bones, leading to a loss of motion.
Black box warnings:	Warnings required by the FDA for a product. They are called "Black Box" because they are required to be placed in a black box in a prominent position in the pharmaceutical information for a given drug ("package insert").
Biliary colic:	Abdominal pain that results from obstruction of the biliary tree (bile ducts or gallbladder).
Bradycardia:	Low heart rate.
Carcinogenic:	Any substances producing cancer.
Cimetidine:	A drug that reduces the production of stomach acid (also called Tagamet®).
Cordotomy:	A surgical procedure involving the division of the spinothalmic tract. The spinothalmic tract contains the nerve fibers responsible for transmitting the sensation of pain up the spinal cord.
Cytochrome (CYP) P450 isoenzymes: Liver enzymes that metabolize drugs.	
Decubitus ulcer:	An ulceration of the skin caused by pressure over a bony prominence.
Delirium tremens:	An alcohol withdrawal syndrome that results in confusion and hallucinations (DTs).
Detrusor muscle:	The muscle in the bladder that contracts to initiate urination.

Diaphoresis:	Sweating.
Edema:	Excessive accumulation of fluid in a tissue.
Embryocidal:	Causes death of an embryo in pregnant women.
Encephalopathy:	A disease or process causing abnormalities in the tissue of the brain.
Flaccidity:	A decrease in muscle tone.
Gastric stasis:	A relaxation of the stomach that causes it to not digest or propel its contents into the small intestine.
Hypercapnia:	The presence in the blood of an unusually high concentration of carbon dioxide.
Hyperpyrexia:	Increased body temperature (fever).
Hyperreflexia:	Excessively increased reflexes.
Hypotension:	Low blood pressure.
Hypothyroidism:	Low levels of thyroid hormones.
Hypoxia:	A deficiency of oxygen in a tissue.
***In vitro**:*	Within a test tube.
***In vivo**:*	Within the living body.
Inappropriate ADH secretion:	A syndrome in which antidiuretic hormone (ADH) is secreted abnormally.
Intraperitoneal:	Within the membrane of the abdominal cavity.
Kyphoscoliosis:	Abnormal curvature of the spine both forward and sideways.
Lethargy:	Extreme drowsiness from which it is difficult to rouse an individual.
Leukocytes:	White blood cells.
Malaise:	A generalized uncomfortable feeling that may be accompanied by physical discomfort.
Metastases:	The distant spread of a malignant tumor from its site of origin.
Miosis:	Contraction of the pupils.
Monoamine oxidase inhibitor:	A type of drug used to treat depression.
Mouse micronucleus test:	This is a commonly used test that determines whether a compound is able to cause chromosome aberrations in mice. It is used to predict genotoxicity (teratogenicity) of a new drug.
Mutagenic:	An agent that increases the rate of mutation.
Myalgia:	Pain in the muscles.
Myoclonic jerks:	Mild to moderate muscle contractions.
Myxedema:	A dry, firm, waxy swelling of the skin and subcutaneous tissues found in patients with underactive thyroid glands.
Noncardiogenic pulmonary edema:	A build-up of fluid in the lungs that is not caused by heart failure.

Nystagmus:	An abnormal sideways or up-and-down movement of the eyes that is associated with neurologic abnormalities or disease of the vestibular apparatus of the ear.
Pallor:	Paleness.
Pancuronium:	A drug used in anesthesia that paralyzes skeletal muscle.
Paralytic ileus:	Loss of motility of the small intestine.
Prostatic hypertrophy:	Enlargement of the prostate gland.
Q24h/Q12h:	Shorthand for every 24 hours and every 12 hours. *Q* is an abbreviations for *every* from the Latin *quaque*.
Rhinitis:	Inflammation of the mucous membranes of the nose.
Stomach atony disorder:	A condition caused by a loss of muscle tone in the stomach. It can lead to pain, nausea and vomiting, and distension.
Syncope:	Fainting.
T-cells:	White blood cells primarily responsible for cell-mediated immunity.
Teratogen:	An agent that induces the formation of abnormalities of the fetus.
Toxic psychosis:	Alterations of mental state caused by drug toxicity.
Urethral stricture:	Narrowing of the passage through which urine is voided.
Vasopressors:	Drugs that stimulate the contraction of blood vessels and therefore bring about an increase in blood pressure.
Vertigo:	Dizziness, specifically the type that causes a spinning sensation.

Introduction

The benefit of opioid therapy is generally very favorable when treatment is optimized. However, these medications do have potentially significant adverse effects. In addition, there are specific patient populations who should avoid or exercise caution when using KADIAN® and other opioids. Patients taking medications that cause sedation or central nervous system depression, phenothiazines, general anesthetics, or vasodilatory or other drugs that lower blood pressure should also be aware of the potential for serious adverse events when such medications are used concomitantly with opioids. This chapter will review the clinical presentations of these safety issues.

Opioid Adverse Reactions

The adverse effects of morphine, and therefore KADIAN®, are essentially the same as those observed with other opioid analgesics. Serious adverse reactions that may be associated with KADIAN® include:

- respiratory depression,
- respiratory arrest,
- circulatory depression,
- cardiac arrest,
- hypotension, and
- shock.

The less severe adverse effects include

- drowsiness,
- dizziness,
- constipation, and
- nausea and vomiting.

Adverse reactions are more likely to occur in opioid-naïve patients or with dosage increases in opioid-tolerant patients. In addition, the risk of an adverse effect increases as the dose of the opioid increases. Fortunately, most adverse effects are temporary. They will cease or decrease as opioid therapy is continued and some

degree of tolerance develops. Adverse effects should be expected and managed as a part of opioid analgesia.

Management of Constipation

Virtually all patients suffer from constipation while taking opioids chronically. Tolerance does not usually develop to this side effect. Thus, it requires an aggressive preventive approach, regular assessment, and aggressive management if symptoms are detected. Exercise, adequate fluid intake, eating bulk-containing foods, and taking natural colon stimulants such as prune juice will help to prevent constipation. The most common approach is to use a laxative regularly. Treatment continues as long as the patient takes opioids.

Management of Nausea and Vomiting

Nausea and vomiting are common after single doses of opioids or as an early undesirable effect of chronic opioid therapy. Vomiting accompanies nausea more often when constipation is not well controlled. Prophylactic treatment of nausea is not recommended because tolerance usually develops after several days. However, it may be necessary to use a scheduled antiemetic for the first week of therapy. A reduction in the dose by 10%-25% may also help reduce nausea. Persistent nausea and vomiting may be due to gastric stasis. Gastric stasis can be treated with metoclopramide, a drug that increases gut motility.

Management of Sedation

Most patients experience drowsiness at the onset of therapy or with a dose change. Tolerance to sedation usually develops over several days. If significantly sedated, patients should be discouraged from driving and operating mechanical equipment. Excessive or persistent sedation should be investigated. Factors that contribute to persistent sedation include the following: intolerance to the dose used, concurrent sedative medications, the presence of hepatic or renal insufficiency, hypoxia or hypercapnia due to exacerbated respiratory failure, disease severity, and the patient's general condition. If sedation continues, it can be managed with central nervous system stimulants such as methylphenidate, dexamphetamine, or modafinil.

Management of Myoclonus

Patients taking high doses of opioids often experience myoclonic jerks. If it disrupts sleep or causes an exacerbation of pain (e.g., bone metastases) changing to

another opioid may help. Mild myoclonus is common and resolves as tolerance develops. It can be treated with low doses of diazepam or clonazepam and other benzodiazepines.

Management of Skin Reactions

The itching, flushing, and rash that can occur because of the release of histamine will typically resolve in less than 2 weeks. Patient symptoms can be treated with antihistamines.

KADIAN® Clinical Safety

Clinical trials are often the best means of determining adverse event rates. KADIAN® has been evaluated in several clinical trials that have shown that its adverse events are similar to those of other opioids. These data were collected from several clinical studies of volunteers or patients who received KADIAN® in single doses or in repeated doses for periods of up 7 to 14 days. Brief descriptions of the adverse event data from each of the repeated-dose studies (i.e., studies simulating typical clinical conditions) are presented below:

Broomhead A, et al. *J Pain Symptom Manage* 1997;14(2):63-73.

This parallel-group clinical study evaluated adverse event data collected over a 7-day treatment period for 61 patients receiving KADIAN® q24h, 52 patients receiving KADIAN® q12h, and 56 patients receiving MS Contin® q12h for treatment of moderate to severe cancer-related pain.

Central nervous system adverse events judged to be related to treatment had the highest frequency of adverse events: 11.5% in the KADIAN® q24h group, 13.5% in the KADIAN® q12h group, and 1.8% in the MS Contin® group. Despite the administration of high doses of morphine once daily in the morning in the KADIAN® q24h group, there was no significant difference among treatment groups for "nervous system" or other categories of adverse events. The incidence of emergent adverse events was acceptable for all three treatment groups given the patient population and the known side effects of morphine.

Floter T, et al. *Clin Drug Invest* 1997;14(3):183-191.

This parallel-group clinical study evaluated adverse event data collected over a 14-day treatment period for 104 patients receiving KADIAN® q12h and 74 patients receiving MS Contin® q12h for treatment of moderate to severe malignant or nonmalignant pain. Typical morphine-related adverse events were reported with a comparable incidence in both treatment groups: 24% for patients receiving KADIAN® q12h and 26% for patients receiving MS Contin® q12h.

Gourlay GK, et al. *Pain* 1997;69:295-302.

This two-period crossover study evaluated adverse events during 7-day treatment periods for 24 patients receiving KADIAN® q24h and MS Contin® q12h for treatment of severe cancer pain.

Both KADIAN® and MS Contin® q12h were associated with a low incidence of side effects. There were no significant differences between treatment groups in the incidence of nausea and vomiting, constipation, sedation, or appetite suppression. The only significant difference was observed on day 5 of treatment, when the incidence of confusion was higher in the KADIAN® q24h group. This difference, however, was considered a chance event because the assessments for confusion on the other assessment days were not significantly different.

Kerr RO, Tester WJ. *Clin Drug Invest 2000;19(1):25-32.*

None of the comparisons of tolerability between KADIAN® q24h and MS Contin® q12h had statistically significant differences. Most adverse events were those expected to occur with morphine, and the frequency and severity of morphine-related adverse events (nausea and vomiting, constipation, sedation, confusion, and appetite) for the KADIAN® treatment period were comparable with those for the MS Contin® treatment period. The percentage of patients who dropped out of the study because of adverse events (8% for KADIAN® and 5% for MS Contin®) and the percentage of patients experiencing serious adverse events (8% for KADIAN® and 9% for MS Contin®) were comparable during the KADIAN® and MS Contin® treatment periods.

Adverse Events – Single Dose and Repeated Dose

In controlled clinical trials in patients with cancer pain, the most frequently reported adverse events thought to be related to KADIAN® were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%), and anxiety (6%). Other less common side effects expected from morphine or seen in less than 3% of patients in the clinical trials are listed below.

- **Body as a Whole:** asthenia (muscular weakness), accidental injury, fever, pain, chest pain, headache, diaphoresis, chills, flu-like syndrome, back pain, malaise, withdrawal syndrome
- **Cardiovascular:** tachycardia, atrial fibrillation, hypotension, hypertension, pallor, facial flushing, palpitations, bradycardia, syncope
- **Central Nervous System:** confusion, dry mouth, anxiety, abnormal thinking, abnormal dreams, lethargy, depression, tremor, loss of concentration, insomnia, amnesia, paresthesia (abnormal sensation), agitation, vertigo, foot drop, ataxia (altered gait), hypesthesia (decreased sensation of touch), slurred speech, hallucinations, vasodilation, euphoria, apathy, seizure, myoclonus
- **Gastrointestinal**: vomiting, anorexia, dysphagia (difficulty swallowing), dyspepsia (heartburn), diarrhea, abdominal pain, stomach atony disorder, gastroesophageal reflux, delayed gastric emptying, biliary colic
- **Endocrine:** hyponatremia (low blood sodium) due to inappropriate ADH secretion, gynecomastia (breast development in males)
- **Hemic & Lymphatic:** anemia, leukopenia (low white blood count), thrombocytopenia (low platelet count)
- **Metabolic & Nutritional:** peripheral edema, hyponatremia (low sodium levels), edema
- **Musculoskeletal:** back pain, bone pain, arthralgia
- **Respiratory:** hiccup, rhinitis (runny nose), atelectasis, asthma, hypoxia, dyspnea (shortness of breath), respiratory insufficiency, voice alteration, depressed cough reflex, noncardiogenic pulmonary edema.
- **Skin and Appendages:** rash, decubitus ulcer, pruritus (itching), skin flush
- **Special Senses:** amblyopia, conjunctivitis, miosis, blurred vision, nystagmus, diplopia (double vision)
- **Urogenital:** urinary abnormality, amenorrhea, urinary retention, urinary hesitancy, reduced libido, reduced potency, prolonged labor

Most adverse events were mild or moderate in intensity. Overall, severe events were reported by 9% of patients receiving KADIAN®, 9% of patients receiving MS Contin®, and 15% of patients receiving immediate-release morphine. Sixteen patients discontinued clinical trials because of serious adverse events. In all except 5 of these patients (3 receiving KADIAN® and 2 receiving immediate-release morphine), the events were considered unrelated to the study medication. A total of 47 deaths occurred during the clinical trials of KADIAN®. All were attributable to disease progression, not to the medication.

Dependence and Withdrawal

Physical dependence develops to morphine with chronic use. Thus, the patient may experience the withdrawal/abstinence syndrome if morphine is abruptly discontinued. This is usually mild and is characterized by rhinitis, myalgia (muscle aches), abdominal cramping, and occasional diarrhea. Most observable symptoms disappear in 5-14 days without treatment. However, there may be a phase during chronic abstinence that lasts for 2-6 months characterized by insomnia, irritability, and muscle aches.

Overdose

Acute overdose with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, miosis, and sometimes pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis (dilation) rather than miosis (constriction) may be seen due to severe hypoxia in overdose situations.

Primary attention is given to the reestablishment of an unobstructed airway and institution of assisted or controlled ventilation. Gastric contents may need to be emptied to remove unabsorbed drug when a extended-release formulation such as KADIAN® has been taken. Activated charcoal is given to help bind the drug and prevent it from being absorbed. The airway should be open before attempting treatment by gastric emptying or activated charcoal. Opioid antagonists may be given to block opioid receptors and prevent adverse effects of the drug. Supportive measures (including oxygen and vasopressors) are used in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Respiratory Depression

Fear of respiratory depression prevents adequate opioid use. As long as there is pain, there is little likelihood that respiratory depression will occur. Close monitoring for respiratory depression is needed in opioid-naïve patients or when another pain intervention, such as an anesthetic block, takes away the pain stimulus.

If a patient arouses easily, he or she is unlikely to have respiratory depression. Treatment is considered when a patient has a persistent respiratory rate of <8 per minute (for 30 minutes or longer despite stimulation) or oxygen saturation < 90%. Patients may be encouraged to breathe by stimulating the painful area or by coaching the patient to breathe. Naloxone, an opioid antagonist, may be given to reverse the effects of the opioid and thus reverse the respiratory depression.

Antagonists

The pure opioid antagonists, naloxone, naltrexone, or nalmefene, are antidotes to the respiratory depression that results from opioid overdose. They work by blocking activity at the mu receptor. Use of an opioid antagonist is reserved for cases where such treatment is clearly needed. Opioid antagonists may have a shorter duration of action than some of the long-acting products such as KADIAN®. Thus, additional doses of the antagonist may be needed. KADIAN® will continue to release and add to the morphine load for up to 24 hours after administration, and the management of an overdose should be monitored accordingly.

Opioid-tolerant Individuals

Opioid antagonist agents should be administered cautiously to persons who are known or suspected to be physically dependent on KADIAN® or other opioids. Antagonist administration may cause a complete reversal of opioid effects and precipitate an acute withdrawal syndrome. Careful titration of opioid antagonists is necessary to treat serious respiratory depression in the opioid-dependent patient.

Contraindications for the Use of KADIAN®

KADIAN® is contraindicated (i.e., not to be used) in

- Patients with known hypersensitivity to morphine, morphine salts, or any of the capsule components of KADIAN® because of the risk of anaphylaxis.
- Patients with acute or severe bronchial asthma and those with respiratory depression. In these patients, KADIAN® would further compromise respiratory function through its depressant effects on respiration.
- Patients with obstruction of the gastrointestinal tract, especially a condition of the intestine known as paralytic ileus. The concern is that obstructions to the flow of material along the gastrointestinal tract could lead to retention of the drug in the stomach for an extended period, with subsequent release of a bolus morphine dose into the small intestine.

Precautions for the Use of KADIAN®

KADIAN® is intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. As with any potent opioid, it is critical to adjust the dosage regimen of KADIAN® according to the needs of each individual patient, bearing in mind any prior analgesic treatment.

Although it is not possible to mention every consideration that is important to the selection of the initial dose of KADIAN®, attention should be drawn to the following:

- The total daily dose, potency, kind, and characteristics (e.g., pure agonists or mixed agonists/antagonists) of previously administered opioid analgesics.
- The reliability of the equianalgesic dose equivalents used to calculate the total dose of morphine required.
- The patient's degree of opioid tolerance.
- The general condition and medical status of the patient.
- Other medications that the patient is concurrently taking.
- The type and severity of the patient's pain.

Cordotomy

Surgical treatment of pain may enhance the adverse effects of morphine on the respiratory system. Postoperative respiratory depression has occurred in a few isolated cases in patients treated with controlled-release morphine preparations before cordotomy. Patients who are scheduled for this or some other surgical procedure to interrupt pain transmission pathways should not receive KADIAN® within 24 hours of the procedure and pain should be managed with parenteral short-acting opioids. In addition, the post-procedure analgesics should be individualized through titration to avoid adverse effects.

Pancreatic/Biliary Tract disease

KADIAN® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including pancreatitis. Opioids may cause increases in the serum amylase level.

Special Risk Groups

KADIAN® should be administered with caution, and in reduced dosages, to

- Patients who are elderly or debilitated and those with Addison's disease, myxedema, and hypothyroidism. These conditions increase the likelihood of morphine-induced respiratory depression.
- Patients with severe renal or hepatic impairment in whom the metabolism or excretion of morphine would be reduced, thus exacerbating any potential adverse effects.
- Patients with prostatic hypertrophy or urethral stricture. Morphine causes increased tone in the detrusor muscle of the urinary bladder, resulting in urinary urgency. At the same time, morphine also increases tone in the sphincter of the bladder, thus causing difficulty in urination. These effects exacerbate symptoms that are already present in prostatic hypertrophy and urethral stricture.
- Patients with central nervous system depression, toxic psychosis, acute alcoholism, or delirium tremens. These conditions are all exacerbated by morphine's effect on the central nervous system.
- Patients with severe kyphoscoliosis in which deformities of the spine reduce lung capacity.
- Patients undergoing biliary surgery and patients with acute pancreatitis secondary to biliary tract disease. Morphine potentially increases the tone of the sphincter of Oddi and may worsen biliary obstruction.

Driving and Operating Machinery

Morphine may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of morphine with other central nervous system depressants, including other opioids, phenothiazines, sedatives or hypnotics, and alcohol.

Carcinogenicity, Mutagenicity, and Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of morphine have not been conducted. There are no reports of carcinogenic effects in humans. *In vitro* (test tube) studies reported that morphine did not cause mutations in the Ames test with *Salmonella.* However, it induces chromosomal changes in human leukocytes and lethal mutations in *Drosophila. In vitro,* morphine was mutagenic in human T-cells, increasing the DNA fragmentation. *In vitro,* morphine was mutagenic in the mouse micronucleus test and induced chromosomal changes in spermatids and murine lymphocytes.

Chronic opioid abusers (e.g., heroin abusers) and their offspring display higher rates of chromosomal damage. However, the rates of chromosomal abnormalities were similar in unexposed individuals and in heroin users enrolled in long-term opioid-maintenance programs.

Pregnancy

Teratogenic Effects (Pregnancy Category C)

Morphine is classified by the FDA as a Category C drug in pregnancy (Table 10-1). Teratogenic effects of morphine have been reported in the animal literature. High parental doses during the second trimester were teratogenic in neurologic, soft, and skeletal tissue. The abnormalities included encephalopathy and axial skeletal fusions. These doses were often toxic to the mother and were 0.3- to 3-fold the maximum recommended human dose (MRHD) on a mg/m^2 basis. Morphine-induced maternal hypoxia and malnutrition may have contributed to the teratogenic

effects. Treatment of male rats with approximately 3-fold the MRHD for 10 days before mating decreased litter size and viability.

Nonteratogenic effects

Morphine given subcutaneously at toxic maternal doses to rats during the third trimester at approximately 0.15-fold the MRHD caused reversible reductions in brain and spinal cord volume, testes size and body weight in the offspring, and decreased fertility in female offspring. The offspring of rats and hamsters treated orally or intraperitoneally throughout pregnancy with 0.04- to 0.3-fold the MRHD of morphine show delayed growth, motor, and sexual maturation and decreased male fertility. Chronic morphine exposure of fetal animals' results in mild withdrawal, altered reflex and motor skill development, and alters responsiveness to morphine that persisted into adulthood.

There are no well-controlled studies of chronic in utero exposure to morphine sulfate in humans. However, uncontrolled retrospective studies of human neonates chronically exposed to other opioids in utero have shown reduced brain volume that normalizes over the first month of life. Infants born to opioid-abusing mothers are more often small for gestational age, have a decreased ventilatory response to CO_2 and an increased risk of sudden infant death syndrome. Morphine should only be used during pregnancy if the need for strong opioid analgesia justifies the potential risk to the fetus.

Table 10-1

FDA Pregnancy Risk Factor Classifications	
Category A	Controlled trials in women fail to demonstrate a risk to the fetus in the 1st trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote.
Category B	Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled trials in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in their 1st trimester (and there is no evidence of risk in later trimesters).
Category C	Either studies in animals have demonstrated adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies

	in women and animals are not available. Drugs should be given only if the potential benefit justifies the risk to the fetus.
Category D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk, for example, if the drug is needed in a life-threatening situation or for a serious disease for which safe drugs cannot be used or are ineffective.
Category X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both and the risk of use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Labor and Delivery

KADIAN® is not recommended for use in women during and immediately prior to labor where short-acting and analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation that tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.

Neonatal Withdrawal Syndrome

If a mother uses opioids during pregnancy, the fetus is also exposed. After birth, the newborn may experience neonatal withdrawal syndrome (NWS). Symptoms of NWS include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The onset, duration and severity of the disorder differ based on such factors as the drug used, time and amount of mother's last dose, and rate of elimination of the drug from the newborn. Approaches to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paregoric or phenobarbital.

Nursing Mothers

Low levels of morphine sulfate have been detected in human milk. Withdrawal symptoms can occur in breastfeeding infants when the mother discontinues morphine sulfate. Because of the potential for adverse reactions to nursing infants from KADIAN®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

There are studies from literature reporting the safe and effective use of both immediate-and extended-release oral morphine preparations for analgesia in children when dosed on a per kilogram basis. However, the safety of KADIAN®, both the entire capsule and the pellets sprinkled on applesauce, has not been directly investigated in patients below the age of 18 years. Moreover, administration of pellets by means of gastrostomy tube (G-tube) has not been investigated in pediatric patients. The range of doses available is not suitable for the treatment of very small children or those who are not old enough to take capsules safely. The applesauce sprinkling method is not an appropriate alternative for these patients.

Drug Interactions

Increasingly, it is recognized that clinically significant drug interactions can occur with opioids that result in additive side effects, or an increase or decrease in intended therapeutic effects of one or both medications. Drug-drug interactions are generally divided into two broad categories: pharmacodynamic and pharmacokinetic.

Pharmacodynamic interactions occur when there is an alteration in the pharmacologic activity of a drug resulting in antagonist, additive, or synergistic effects. These interactions generally do not involve changes in the actual plasma or tissue concentration of either drug involved. These interactions are common with opioid analgesics.

Pharmacokinetic interactions are those drug interactions that alter either the absorption, distribution, metabolism, or elimination of one or more administered drugs. Changes in these parameters are often the result of one or more cytochrome (CYP) P450 isoenzymes involved in oxidative metabolism.

Pharmacodynamic Interactions

Medications that can interact with opioid analgesics include agents with similar pharmacologic effects. Agents such as ethanol and benzodiazepines that cause central nervous system and respiratory depression should be used cautiously in the patient receiving opioids. Another common type of opioid pharmacodynamic interaction is the excitatory response or serotonin syndrome that may occur when opioids are used in combination with monamine oxidase inhibitors. Mental status change, hyperpyrexia, hyperreflexia, myoclonus, ataxia, diaphoresis, diarrhea, coma, and death characterize serotonin syndrome.

Pharmacokinetic Interactions

Absorption Interactions

Many types of absorption interactions result in changes in the amount of the drug absorbed or the rate at which a drug is absorbed. A decrease in the rate of absorption may result in failure of a drug to reach a therapeutic concentration even if the total amount of drug absorbed is unchanged. Any drug that slows gastric motility, such as anticholinergics or opiates, can slow the absorption rate. In other words, opioids can slow the absorption rate of other opioids.

Changes in the amount of drug absorbed may also be due to changes in gastrointestinal pH. Many medications require a specific gastrointestinal pH to be absorbed. Antacids, H_2-receptor antagonists, and proton pump inhibitors all increase the pH of the stomach. If a drug that requires an acidic pH is given with one of these medications, its absorption will be reduced.

Distribution Interactions

Protein-binding displacement interactions are common distribution interactions. Once absorbed, drugs are distributed by the blood as both free drug and protein-bound drug. Only the free or unbound fraction of the drug is active. Any changes in the percentage bound can lead to a change in a drug's availability to receptor sites and its metabolism and excretion. When two or more highly protein-bound drugs are administered together, the two drugs may compete for the same binding site. This is competitive binding. As a result, one may increase the free fraction of the other, causing more active drug. Drug interactions of this class are complex but probably overstated. Drugs most likely to result in clinically important

interactions are greater than 90% protein-bound.

Metabolism Interactions

Metabolism is the process of breaking down drugs to metabolites both active and inactive so that they can be eliminated. Hepatic cells metabolize many drugs by an enzyme system called the cytochrome P450 system (CYP). Certain drugs are known to induce this enzyme system, which causes a drug to be cleared from the body more quickly. Other drugs may interact as enzyme inhibitors, increasing the length of time a drug remains in the body. The CYP system is broken down into individual enzymes called isoenzymes. Examples of isoenzymes include 3A4, 2C19, and 2D6. The 3A4 isoenzyme is responsible for most drug metabolism. However, CYP plays a potentially significant clinical role in opioid analgesic use.

For example, oxycodone is a substrate of CYP 2D6, meaning it requires this enzyme to be broken down and activated. Paroxetine, an antidepressant commonly used in pain management, is a potent inhibitor of 2D6. Thus, paroxetine can potentially inhibit CYP 2D6 and prevent the breakdown of oxycodone to its active metabolite. As a result, analgesic efficacy may be lost. Hydrocodone, codeine, oxycodone, and tramadol all require CYP 2D6 for activation. Table 10-2 lists examples of drugs that utilize the CYP 2D6 isoenzyme. Many cytochrome P450 interactions are theoretical and the clinical significance of such potential interactions is unknown.

Table 10-2

CYP 2D6 Enzyme Activity		
Substrates	**Inhibitors**	**Inducers**
Oxycodone Tramadol Hydrocodone Codeine Meperidine Propoxyphene Methadone	Celecoxib Cimetidine Citalopram Sertraline Paroxetine Fluoxetine Propoxyphene Methadone	Carbamezapine Ethanol Phenobarbital Phenytoin Rifampin

KADIAN® Drug Interactions

Screening for drug interactions plays an important role in maximizing a patient's pain regiment while maintaining a level of safety. KADIAN® has few documented drug interactions. It is not highly protein bound. It is not metabolized by the cytochrome P450 enzyme system in the liver. Thus, interactions due to inhibition or induction of the enzymes do not occur. Below is a list of identified drugs that may have clinically significant interactions when given with KADIAN®.

Pharmacodynamic Interactions

Central Nervous System Depressants

KADIAN® should be used with great caution and in reduced dosages in patients receiving other medications which have depressant effects on the central nervous system. In such circumstances, there is increased risk of respiratory depression, hypotension, profound sedation, and coma. Examples of drugs that depress the central nervous system are sedatives, hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Consider a reduction in the dose by at least 50% of one or both medications.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (used as antidepressants) intensify the effects of morphine and other opioid drugs. The patient may become anxious and confused, and may experience significant depression of respiration with resultant coma. Monoamine oxidase inhibitors (MAOIs) are slowly eliminated from the body, which means any unwanted drug effects will persist. For these reasons KADIAN® should not be given to patients receiving MAOIs, or those treated with these drugs within the previous 14 days. Fortunately, MAOIs are rarely used today.

Diuretics

Morphine reduces the efficacy of diuretic drugs (which increase urine output) by stimulating the release of antidiuretic hormone. In patients receiving KADIAN® and diuretics, either an increase in diuretic dosage or an alternative therapy should be considered.

Mixed Agonist/Antagonist Opioid Analgesics

In theory, mixed agonist/antagonist opioid analgesics (such as pentazocine) should not be administered to patients treated with KADIAN® (or other pure opioid agonists), because these may reduce the analgesic effects of the pure opioid agonist or precipitate withdrawal symptoms.

Muscle Relaxants

KADIAN® may enhance the neuromuscular blocking effects of skeletal muscle relaxants, e.g., pancuronium, and thus produce an increase in respiratory depression. Downward adjustment of the dosage of skeletal muscle relaxant is advisable in such patients.

Pharmacokinetic Interactions

Gastrointestinal Agents

Absorption is not influenced by changes in stomach pH because absorption occurs in the intestines. H_2-receptor antagonists, proton pump inhibitors, and antacids lower the pH of the gut and theoretically could interfere with the release of morphine from KADIAN®, because this is a pH-dependent release. Clinical experience to date with KADIAN® provides no indication that concomitant administration of gastrointestinal agents affects the magnitude or duration of analgesia provided by KADIAN®. This may reflect the limited ability of such agents to raise the pH to a level needed for significant morphine release from the pellets as well as the limited amount of time the pellets typically spend in the stomach. No specific clinical trials evaluating the efficacy of KADIAN® in patients concurrently receiving antacids or gastric acid secretion inhibitors have been conducted.

Cimetidine

There has been one report of confusion and severe respiratory depression when a patient undergoing hemodialysis was administered morphine and cimetidine (an H2-receptor antagonist drug used to treat stomach ulcers). Caution is required when KADIAN® and cimetidine are co-administered in patients receiving hemodialysis.

FDA Safety Warnings for KADIAN®

The following are included in the black box warnings from the FDA regarding KADIAN®:

- KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
- KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.
- KADIAN® capsules are NOT for use as a PRN analgesic.
- KADIAN® 100-mg and 200-mg capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. KADIAN® capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The pellets in the capsules are not to be chewed, crushed, or dissolved due to the risk of rapid release and the absorption of a potentially fatal dose of morphine.

Summary

- As with any potent opioid, the dosage regimen of KADIAN® must be adjusted according to the needs of each individual patient, bearing in mind the factors outlined that should be considered when determining dosage. Some groups are also at special risk of the adverse effects of morphine, such as the elderly or debilitated and patients with Addison's disease, myxedema, hypothyroidism, renal or hepatic impairment, prostatic hypertrophy, or urethral stricture.
- KADIAN® should be administered with caution to patients with central nervous system depression, toxic psychosis, acute alcoholism, and those with biliary disease. Patients should be warned that morphine may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery, and of the potential combined effects of morphine with other central nervous system depressants, including other

opioids, phenothiazines, sedatives or hypnotics, and alcohol.

- Pregnant patients should be given KADIAN® only when the benefits clearly outweigh the potential risks to the fetus. KADIAN® is not recommended for use in women during and immediately before labor, and women should not breastfeed their infants when taking KADIAN®.
- Because of the risk of interactions, KADIAN® should not be administered to patients receiving monoamine oxidase inhibitors or mixed opioid antagonists/agonists and should be administered with caution in patients taking other central nervous system depressants or diuretics.

Self-Assessment Test

Circle the best response

1) The most troublesome adverse effect of chronic therapy with KADIAN® and other opioid analgesics is _____.
   a. Sedation
   b. Respiratory depression
   c. Constipation
   d. Nausea

2) Which of the following is true regarding nausea and vomiting associated with morphine therapy?
   a. Nausea and vomiting is most common at onset of therapy or with dosage changes.
   b. Occurrence of nausea and vomiting requires discontinuation of the medication.
   c. Vomiting often accompanies nausea even when constipation is well controlled.
   d. Prophylactic treatment of nausea is recommended.

3) Which of the following is true regarding the concomitant use of gastrointestinal agents that decrease the acidity of the stomach with KADIAN®?
   a. KADIAN® absorption is influenced by changes in stomach pH.
   b. Concomitant administration of gastrointestinal agents affects the magnitude and duration of analgesia provided by KADIAN®.
   c. Clinical trials evaluating the efficacy of KADIAN® in patients concurrently receiving antacids or gastric acid secretion inhibitors have been conducted.
   d. Drugs that lower the pH of the gut could theoretically interfere with the release of morphine from KADIAN®.

4) Which of the following patients is not at increased risk of respiratory depression with KADIAN®?
   a. Elderly patients
   b. Severe asthmatics
   c. Hypothyroid patients
   d. Patients with prostatic hypertrophy

5) KADIAN® may cause severe hypotension in patients whose ability to maintain blood pressure is already compromised by :
   a. Increasing blood volume
   b. Vasodilation
   c. Hypertension
   d. Constricting blood vessels

6) Acute overdosage with morphine results in:
   a. Agitation
   b. Somnolence
   c. Dilated pupils
   d. Increased respiratory rate

7) Opioid agonist-antagonists should not be administered with morphine because
   a. Additional opioid analgesics should not be needed.
   b. Opioid agonist-antagonists block the mu receptor potentially causing withdrawal.
   c. Respiratory depression will occur.
   d. Analgesic tolerance will develop.

8) KADIAN® should be administered with caution to patients with _____.
   a. Central nervous system depression
   b. Depression
   c. Diabetes
   d. Hypertension

9) KADIAN® classification as a category C in pregnancy means
   a. It should never be administered in pregnancy.
   b. Morphine has inconclusive data defining the risk in pregnancy.
   c. There are no data showing morphine has teratogenic effects on the fetus.
   d. Morphine should be given only if the potential benefit justifies the risk to the fetus.

10) Signs of neonatal withdrawal syndrome include
   a. Abnormal sleep pattern
   b. Excessive weight gain
   c. Dilated pupils
   d. Constipation

Self-Assessment Test continued

True or False

11) Qualitatively, the adverse effects of KADIAN® are essentially the same as those of other opioid analgesics including morphine sulfate solution.
True
False

12) Patients should be administered prophylactic therapy for constipation at the outset of KADIAN® treatment.
True
False

13) KADIAN® is recommended for administration to women during and immediately before labor.
True
False

14) The most common serious adverse effects of morphine are respiratory depression and apnea.
True
False

15) KADIAN® has many drug interactions due to its cytochrome P450 metabolism.
True
False

16) Patients who require a potent opioid analgesic for more than a few days are not suitable candidates for KADIAN®.
True
False

17) KADIAN® should not be given to patients with acute or severe biliary obstruction.
True
False

Answers to Self-Assessment Test

1. c	10. a
2. a	11. a
3. d	12. a
4. d	13. b
5. b	14. a
6. b	15. b
7. b	16. b
8. a	17. a
9. d	

SECTION THREE

Product Comparison

- Chapter 11: Opioid Product Comparison
- Chapter 12: Clinical Research Papers
- Glossary

CHAPTER ELEVEN

Opioid Product Comparison

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- List each of the other opioid products and their role in chronic pain management.
- Describe the differential features of each of the other opioid products.
- List the modified-release formulations of the other opioid products and their active ingredients and formulations.
- Discuss the advantages and disadvantages of each of the other modified-release opioid products currently on the market.
- State the case for using KADIAN® in preference to the other opioid products for the treatment of chronic pain.

Introduction

Optimizing analgesic treatment with opioids relies on individualization of therapy and an understanding of comparative pharmacology. Several factors can determine the opioid of choice, including mechanism and site of action, pharmacokinetics (including those of different drug formulations), metabolism, and adjuvant drug administration.

Conventional, immediate-release formulations of opioids have been available for a long time. The challenge in improving chronic pain management has not been in the development of new drugs with new actions or better potency, but rather in the way in which the drug is delivered. This chapter will review the commonly prescribed agents used to manage chronic pain and compare these medications with KADIAN®.

Opioid receptors

Opioid receptors in the central nervous system are the point at which opioid drugs (and endogenous opioids) exert their pharmacologic action. Different types of opioid drugs act as agonists or antagonists at these different receptors. Because activation or blockage of different receptors results in different clinical responses, understanding a drug's actions at these receptors makes it easier to understand the benefits and adverse effects of different opioid drugs.

There are three main classes of opioid receptors, mu, kappa, and delta, and each class has subtypes (e.g. mu1 and mu2). Most opioids primarily activate mu receptors, but some opioids interact with kappa receptors as well. When activated by an agonist, the mu receptor mediates analgesia, decreases respiratory function, decreases transit time in the digestive tract, and causes sedation. Some subtypes of kappa receptors also mediate analgesia and decrease digestive tract transit time, but they also can trigger hallucinations and increase urination (agonist actions). Receptor antagonists block these actions; therefore, a mixed agonist/antagonist agent may block some of these effects (e.g., analgesia) while activating others. Although the mixed agonist/antagonist drugs have clinical usefulness in other settings, they are not generally used for chronic pain management, in part because of their ceiling effect for analgesia and antagonist activity at the mu receptor.

KADIAN® Review

(Alpharma Pharmaceuticals, LLC)

Indication

KADIAN® is recommended for the management of moderate to severe pain when treatment with an opioid analgesic is indicated for more than a few days.

Available Strengths

Color-coded gelatin capsules in 8 strengths: 10 mg (light blue), 20 mg (yellow), 30 mg (blue violet), 50 mg (blue), 60 mg (pink), 80 mg (light orange), 100 mg (green), and 200 mg (brown).

Delivery System

KADIAN® capsules contain polymer-coated, sustained-release pellets of morphine sulfate in a capsule. The gelatin capsule dissolves quickly in the stomach, freeing the polymer-coated pellets. As the pellets pass into the less acidic small intestine, morphine release is greatly accelerated. The pellets develop minute holes through which the morphine diffuses. The pellets are formulated so that morphine is released over several hours, resulting in plasma morphine concentrations that are maintained for up to a 24-hour period.

Dosage and Administration

KADIAN® is administered once or twice daily (Q12 or 24 hrs). Patients who do not have a proven tolerance to opioids should be started on only the 20-mg strength. Dosage increases should generally be separated by 48 hours. As with all long-acting opioids, breakthrough pain may require supplementation with short-acting (immediate-release) morphine.

In general, capsules (and pellets) should be swallowed whole and should not be chewed, crushed, or dissolved. As alternatives to ingesting whole capsules, capsules may be opened and the pellets ingested with a small amount of applesauce or administered through a 16-French or larger gastrostomy tube (G-tube) with a small amount of water. The administration of KADIAN® pellets through a nasogastric tube (NG) should not be attempted.

The safety and effectiveness of KADIAN® in pediatric patients below the age of 18 has not been established. The range of dose may not be appropriate for this patient population. Sprinkle administration is not a suitable alternative for these patients.

Pharmacokinetics

After the administration of KADIAN®, approximately 50% of the morphine absorbed reaches the systemic circulation within 8 hours. This absorption is minimally affected by the presence of food. The product continues to release medication up to 24 hours.

KADIAN® is distributed to the skeletal muscle, kidneys, liver, gastrointestinal tract, and brain. It is also secreted into breast milk and crosses the placenta. Morphine does not accumulate in tissues when given in normal doses.
Morphine is 30% to 35% bound to plasma protein, which makes it a low-protein-binding drug.

Morphine is conjugated into M3G and M6G glucuronides in the liver. 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. M6G possess significant analgesic activity.

The pharmacokinetics of morphine are altered in hepatic and renal disease. Adjustment of morphine doses may occasionally be necessary in hepatically or renally impaired patients to prevent drug accumulation including accumulation of metabolites.

Side Effect Profile

- Constipation, drowsiness, nausea and vomiting, and dizziness or light-headedness are the most common adverse effects in normal doses.
- Other adverse effects include cardiovascular alterations (e.g., flushing of the face, bradycardia, tachycardia, palpitations), central nervous system effects (e.g., confusion, hallucinations, restlessness, vertigo), gastrointestinal tract effects (e.g., anorexia, biliary colic), genitourinary tract effects (e.g., urinary retention, hesitancy, inappropriate antidiuretic hormone secretion), visual disturbances (e.g., blurred vision, diplopia, nystagmus, miosis), hypothermia, dermatological effects (e.g., urticaria and pruritus), allergic and anaphylactic reactions, and the withdrawal (abstinence) syndrome.

- Major hazards in large doses are respiratory depression, circulatory depression, respiratory arrest, and cardiac arrest or shock.

Contraindications/Precautions

Contraindications are similar to immediate-release morphine, with the addition of gastrointestinal obstruction and particularly paralytic ileus. Caution should be used when administering KADIAN® within 24 hours of cordotomy or similar surgery.

Black box warning:

KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

KADIAN® Capsules are NOT for use as a prn analgesic.

KADIAN® 100 mg and 200 mg Capsules are for use in opioid-tolerant patients only. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. KADIAN® capsules are to be swallowed whole or the contents of the capsules sprinkled on apple sauce. The pellets in the capsules are not to be chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine.

Alcohol use warning: KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Advantages

- KADIAN® contains morphine, which is the gold standard analgesic for moderate

to severe chronic pain.

- Oral delivery of medication is the preferred route in chronic pain management. KADIAN® is available in 8 strengths of oral morphine that allow titration in 10-mg increments.
- KADIAN® has flexibility in administration by oral, sprinkle, and G-tube routes.
- KADIAN® is not metabolized by the cytochrome P450 system. Therefore, there is no need to monitor drug interactions through this system.
- There is little potential for drug interactions involving protein binding due to low binding of morphine (30% to 35% protein bound).
- The plasma morphine profile following KADIAN® administration is characteristic of a extended-release formulation. The maximum concentration C_{max} is reduced and the time to maximum concentration (t_{max}) is delayed with respect to immediate-release morphine.
- The pharmacokinetics of morphine are linear over the dosing range of 30 to 100 mg. Thus, increases in doses provide predictable increases in plasma concentrations.
- KADIAN® administered once daily may improve compliance compared with that for other controlled-release formulations administered more often.
- The KADIAN® adverse event profile is similar to that for other opioid analgesics.
- The q24h dosing interval allows KADIAN® to be synchronized with the patient's sleep cycle to improve sleep and minimize side effects. Peak levels, which are more often associated with side effects, are delayed 8 hours from administration, and this peak effect may occur during the night if dosing is timed appropriately.

Long-Acting Opioid Product Comparison: Duragesic®, Methadone, OxyContin®

Disadvantages

- Morphine doses may require adjustment in renal and hepatic disease to prevent drug accumulation.
- Morphine is associated with slightly more gastrointestinal side effects than are other opioids.

Duragesic® (transdermal fentanyl patch)

Fentanyl is a synthetic opioid that was first introduced as an alternative to morphine in 1960. For the next 30 years, it was available only in an injectable form and was used primarily as an anesthetic. It is not effective orally because the liver breaks it down quickly. In 1990, it was introduced in a skin patch (Duragesic®) that delivers a steady level of medication for 72 hours (Table 11-1).

Indication

The transdermal product is used in the management of chronic pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteroidal analgesics (NSAIDs), or PRN dosing with short-acting opioids and that requires continuous opioid administration for an extended period of time. The fentanyl patch should be used only in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose of at least the equivalent of fentanyl 25 mcg/h.

Table 11-1

Formulation	Products (Manufacturers)	Dosing Interval
Transdermal patch	Duragesic® 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h Fentanyl Transdermal Patch (generic) 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h	q48 to 72 h

Contraindications/Black box warnings:

Duragesic® contains a high concentration of a potent schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (Duragesic®) may be a particular target for abuse and diversion.

Duragesic® is indicated for management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

Duragesic® should only be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to Duragesic® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, Duragesic® (fentanyl transdermal system) is contraindicated:

- in patients who are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain [e.g., use on an as needed basis (prn)]

Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid tolerant patients, during the initial application period.

The concomitant use of Duragesic® with potent cytochrome p450 3a4 inhibitors (ritonavir, Ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving Duragesic® and potent cyp3a4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted.

The safety of Duragesic® has not been established in children under 2 years of age. Duragesic® should be administered to children only if they are opioid-tolerant and 2 years of age or older.

Duragesic® is only for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory expression. Overestimating the Duragesic® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of Duragesic®, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

Duragesic® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing Duragesic® in situations where the healthcare professional is concerned about increased risk of misuse, abuse or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Duragesic® patches are intended for transdermal use (on intact skin) only. Using damaged or cut Duragesic® patches can lead to the rapid release of the contents of the Duragesic® patch and absorption of a potentially fatal dose of fentanyl.

Interactions with alcohol: fentanyl may be expected to have additive CNS depressant effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Pharmacology

Fentanyl citrate is a synthetic mu agonist with pharmacologic effects similar to morphine and meperidine. Its chemical structure most closely resembles meperidine. Fentanyl is 50 to 100 times as potent as morphine on a weight basis; fentanyl 0.1mg is approximately equivalent in analgesic activity to morphine 10mg or meperidine 75mg.

Available data indicate that histamine release, which can cause hypotension, tachycardia, and erythema, rarely occurs with fentanyl, even with use of large doses (50 to 150 mcg/kg).

Delivery System

Duragesic® (fentanyl transdermal) is a skin patch that contains a reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose. The system delivers less than 0.2 milliliters of ethanol over the 72-hour period of use. Fentanyl is delivered to the skin forming a depot of drug in the upper layers, from which it enters the circulation. An ethylene-vinyl acetate copolymer membrane controls the rate of delivery of fentanyl to the skin surface. The delivery rate is directly proportional to the area of the membrane in contact with the skin, and using patches with different membrane surface areas achieves different infusion rates. Thus, each of the 5 available strengths has a different surface area (See Table 11-2).

The membrane of the patch is coated with a silicon-based bioadhesive that holds the patch in intimate contact with dry or hydrated skin for up to 3 days in temperatures ranging from 0^0 to 40^0C. If properly applied, the patch will adhere while the patient bathes or showers.

Table 11-2

Duragesic® Patch Surface Area and Rate of Delivery		
Patch Size	Fentanyl Content	Rate of Delivery
5 cm^2	1.25 mg	12.5 mcg/h
10 cm^2	2.5 mg	25 mcg/h
20 cm^2	5.0 mg	50 mcg/h
30 cm^2	7.5 mg	75 mcg/h
40 cm^2	10 mg	100 mcg/h

An increasing body of evidence supports the fact that Duragesic® prescription abuse is less common than with some other opioids. The drug may be difficult to extract from the patch. Quantities that are extracted, however, are large enough to kill even opioid-tolerant abusers. The reservoir nature of the patch prevents the abuser from

accurately extracting a specific amount of drug (refer to Chapter 6).

Dosing and Administration

The transdermal patch has a broad equivalency range to oral morphine. See Table 11-3 for corresponding morphine doses. In controlled clinical trials in opioid-tolerant patients, 60mg/day oral morphine was considered to provide analgesia approximately equivalent to Duragesic® 25 mcg/h. Doses greater than 25 mcg/h should not be used for initiation of therapy in non-opioid-tolerant patients. When doses greater than 100 mcg/h are required, multiple patches are used. Due to the broad equivalency ranges, 50% of Duragesic® patients will require a dose increase shortly after the start of therapy.

Table 11-3

Duragesic® Equivalency to PO Morphine	
PO 24 hour Morphine (mg/day)	Duragesic® Dose (mcg/h)
60-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

Duragesic® requires patient education regarding proper patch application. The patch must be applied to an intact, nonirritated, clean, nonhairy site on the upper torso or upper arm. It must be held in place for a minimum of 30 seconds to ensure adhesion.

Patients and healthcare workers must be instructed on the disposal of the patch. Current instructions state that the patch must be disposed of properly by folding the patch in half (with the adhesive side adhering to itself inside the fold) and flushing it in the toilet.

Duragesic has been studied in doses of 25 mcg/h and higher in children aged 2 to 19 years who had been previously receiving daily opioid doses of at least 45 mg of oral morphine (or the equivalent). Initiation of therapy in patients aged 2 to 18 years who were on less than 60 mg/day of morphine has not been studied. Duragesic® has not been studied in children under the age of 2 years. Duragesic® should only be administered to children who are opioid tolerant and are 2 years old or older.

Pharmacokinetics

The uptake of fentanyl through the skin is relatively slow and constant, even when the location of the system is varied. The skin does not metabolize the drug, and 92% of the dose is delivered into the bloodstream as intact fentanyl. Body temperature can accelerate the absorption of fentanyl (increasing body temperature from 37° to 40°C has been shown to increase absorption by up
to 33%).

Serum fentanyl concentrations are measurable within 2 hours after application of the first patch, and analgesic effects can be observed 8 to 16 hours after application. This delay is required to establish a reservoir of fentanyl in the stratum corneum of the skin. It can take 12 to 72 hours for serum fentanyl concentrations to level off. Steady state is not reached until after several sequential patch applications.

Fentanyl is highly soluble in lipids. It accumulates in skeletal muscle and fat and is slowly released into the blood. Plasma half-life is 3 to 4 hours after parenteral administration. However, after removal of the Duragesic® patch, systemic absorption of residual fentanyl in the skin continues. Serum drug levels fall slowly with a variable half-life of about 17 hours (range 13-22 hours). In other words, serum fentanyl levels will fall to 50% in approximately 17 hours.

Fentanyl is rapidly metabolized, primarily by dealkylation, to inactive metabolites in the liver. It is excreted mostly as metabolites in the urine. The presence of inactive metabolites makes it a preferred drug in patients with liver dysfunction.

Drug Interactions

Fentanyl is a CYP3A3/4 enzyme substrate. Medications that inhibit these enzymes (erythromycin, ketoconazole, itraconazole, and protease inhibitors) may increase serum concentrations of fentanyl. Drugs that increase metabolism through CYP3A3/4, (carbamezapine, phenobarbital, and rifampin) may decrease serum levels of fentanyl by increasing its metabolism. However, whether these interactions are clinically significant is unknown. (See Appendix 11-2 for further information.)

Side Effect Profile

- The side effect profile of fentanyl is similar to morphine, although fentanyl is less likely to cause nausea and vomiting when used in equivalent doses. Unfortunately, the conversion from oral morphine to Duragesic® is so broad that patients are often given aggressive doses of Duragesic® and nausea becomes a problem. As with all opioids, tolerance does develop to side effects (except constipation).
- At high doses, fentanyl can produce marked muscular rigidity. However, this side effect is typically associated with rapid IV infusion and not with Duragesic® patches.
- Fentanyl transdermal delivery eliminates first-pass metabolism in the liver.
- Because transdermal delivery eliminates absorption from the GI tract, constipation has been reported to be less frequent than that seen with other opioids.
- Skin rash around the patch is a common side effect. However, this can often be prevented by pretreating the skin with a steroid spray (e.g., the kind that is used in steroid inhalers for asthma). Clinically, the incidence of patch intolerance is believed to be greater than the 3% to 10% reported in the package insert.
- Adverse effects can persist for up to 36 hours after removal of the patch because of continued absorption of the drug in the skin.

Advantages

- Fentanyl is a potent opioid. It is less likely than morphine to cause nausea and vomiting when used in equivalent doses.
- Duragesic® is a good alternative for those who cannot take oral medications.
- In the current sustained-release market, fentanyl is the drug of choice in patients with liver dysfunction.

- The incidence of rash, itching, flushing, and hypotension is lower than for morphine because of minimal histamine release.
- The transdermal patch is believed to be less abusable than OxyContin® and MS Contin®.
- Available as a generic

Disadvantages

- No tablet or capsule formulation of fentanyl is available.
- Patients require education regarding patch application.
- Dose increase should only occur every 6 days.
- Equivalent dosing to morphine is difficult to determine.
- The analgesic effect cannot be evaluated during the first 24 hours because of the delay of onset of Duragesic® patch.
- Patches often do not last 72 hours, requiring more frequent change and increasing cost.
- Some patients, particularly the elderly, may have difficulty remembering what day to change their patch.
- Patients may have allergies to the patch adhesive.
- With the Duragesic® patch, patients must use short-acting analgesics for the first 24 hours as needed.
- Duragesic® cannot be used for acute pain because of the difficulty in titrating the dose.
- Large dose strength patches are quite wide (2-3 inches across).
- Doses greater than 100 mcg/h require multiple patch applications, which can be very expensive.
- Patients with adverse reactions to Duragesic® should be monitored for at least 12 hours after patch removal.
- Patients should be advised to avoid exposing the Duragesic® application site to direct external heat sources (e.g., heating pads, heat lamps, hot tubs, etc). There is a potential for temperature-dependent increases in fentanyl release from the patch. Theoretically, fever may also increase fentanyl release from the patch.
- There has been no systematic evaluation of Duragesic® as an initial opioid in the treatment of pain.

Advantages of KADIAN® Over Duragesic®

- No patient education regarding appropriate application of the product is required before administration of KADIAN®.
- KADIAN® is not metabolized by cytochrome P450 3A4 like Duragesic®, therefore avoiding drug interactions through this system. (*See* Appendix 11-2 for more information.) Drug interactions may lead to less efficacy or greater adverse events associated with drugs that use the P450 3A4 cytochrome system for metabolism.
- Duragesic® 25 mcg may be equivalent to 60 mg daily of oral morphine (12 mcg patch is now available). Morphine can be initiated at a much lower dose.
- The rate of drug delivery from KADIAN® is not increased by external heat sources.
- Steady state is achieved in 2 days with KADIAN® versus approximately 1 week with Duragesic®. Dose titration can be done much more rapidly with KADIAN®.
- Dose titration is easier with KADIAN®. KADIAN® is available in capsules containing 10, 20, 30, 50, 60, 80, 100, and 200 mg of morphine. The 10-mg capsule is the lowest available strength of extended-release morphine.
- At steady state, Duragesic® provides the same blood level at all times. KADIAN® can be administered so that peak blood levels occur at the most opportune time—either during sleep to minimize side effects, or at the time of day when the patient has the most severe pain.
- Oral administration is the preferred route for treatment of pain due to cost and convenience. Duragesic® is not available in an oral formulation and costs more than KADIAN®.

Methadone

Methadone was first synthesized in Germany at the end of World War II and was specifically designed for the treatment of severe chronic cancer pain. In the middle 1960s it became widely used to treat drug addicts because it can suppress drug-craving in this population with one daily dose. Because of this, it has developed a reputation as a medication that is linked to addiction. Actually, it is an excellent pain medication that probably has lower abuse potential than some other opioids (refer to Chapter 6).

Indication

Methadone is indicated for the management of severe pain. It is also used in detoxification and maintenance treatment of narcotic addiction. If used for detoxification and maintenance treatment of narcotic addiction, it must be part of an FDA-approved program.

Contraindications/Black box warnings:

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids.

Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks.

Table 11-4

Available Methadone Products		
Formulation	Products (Manufacturers)	Dosing Interval
Tablets	Dolophine® 1 mg, 5 mg, 40 mg Methodose® 5 mg, 10 mg, Methadose Dispersible Tablet 40 mg Diskets Orodispersable Tablet 40 mg	q3 to 8h
Oral solution	Methadose Concentratione Liquid 10 mg/mL Methadone Solution 10mg/5mL	q3 to 8h

Pharmacology

Methadone is a potent mu agonist with a unique chemical structure. It is considered by some to be the best strong alternative for morphine-intolerant patients. Because it has effects on other receptors (NMDA receptors) in addition to opioid receptors, methadone is sometimes effective for treating pain that does not respond to other opioid medications.

Methadone is a true long-acting opioid. It has a half-life of up to 55 hours in some patients. Other long-acting opioids are modified-release formulations for short half-life drugs.

In single doses, methadone is only marginally more potent than morphine: 10 mg IM or 20 mg PO is equivalent to morphine 10 mg IM or 60mg PO. In repeated doses, methadone is several times more potent than morphine; oral doses of 20-30 mg are equianalgesic to 60-90 mg or more of morphine PO. However, the equianalgesic conversions for methadone are considered less reliable than for most other opioids.

The peak respiratory depression effect of methadone occurs later and lasts longer than the peak analgesic effect. Thus, adequate analgesia could potentially be associated with a delayed respiratory depression effect, particularly in the early dosing period. This can contribute to iatrogenic (induced inadvertently by medical treatment) overdose.

NOTE: Conversion to methadone from other opioids is notoriously unpredictable. For this reason, the American Society of Addiction Medicine has recently recommended that methadone be started at no more than 25% of the expected conversion dose.

Dosing and Administration

Methadone is unique in that its dosing intervals do not correlate with its half-life. Drugs with long half-lives usually are dosed once daily. Methadone requires divided doses to maintain analgesic efficacy. The duration of action of methadone is approximately 4 to 6 hours following oral administration (i.e., similar to morphine). The duration of action may extend to 6 to 8 hours after repeated administration. Typical starting doses range from 5 to 30mg daily in divided doses. Onset of analgesia varies from 30 minutes to 4 hours with peak concentrations occurring at 2 to 4 hours. Methadone is occasionally used every 3 to 8 hours as a PRN medication.

Dose titration is more difficult with methadone than with morphine. The patient must be stable for 2 to 3 days before gradual increases in the dose are initiated. In some cases, the methadone dose may need to be decreased 3 to 5 days after initiation to prevent toxic effects due to drug accumulation in the tissues.

Pharmacokinetics

Methadone is readily absorbed from the gastrointestinal tract, reaching peak concentrations after about 4 hours. After therapeutic doses, about 90% of methadone is bound to plasma protein. It is widely distributed in tissues. Methadone is found in low concentrations in blood and brain, with higher concentrations in kidney, spleen, liver, and lung. It readily crosses the placenta; concentrations in amniotic fluid approach those of maternal plasma.

Methadone is extensively metabolized in the liver, mainly by *N*-demethylation. This appears to be mediated by several cytochrome P450 enzymes, which means there is a potential for drug interactions if the patient is taking other drugs that are metabolized by the P450 enzymes (*see* Appendix 11-2). The major metabolites are excreted in the bile and urine. Terminal half-life is extremely variable (15 to 55 hours); therefore, accumulation is possible and dosing intervals need to be carefully monitored.

Methadone appears to be firmly bound to protein in various tissues, including the brain. After repeated administrations, there is gradual accumulation in tissues. The

risk of accumulation is more likely in patients with impaired renal or hepatic function, because both organs are involved with the metabolism of methadone.

Like morphine, methadone displays wide variability between individuals in concentrations of drug achieved in the blood and rate of elimination of drug from the body after parenteral administration. Dosage schedules of methadone must therefore be individualized for each patient.

Drug Interactions

Methadone is a CYP1A2, 2D6, and 3A3/4 enzyme substrate and a CYP2D6 enzyme inhibitor. CYP3A3/4 and CYP2D6 enzyme inhibitors may increase serum methadone concentrations, potentially leading to toxicity, although no cases are reported in the literature. Enzyme inducers decrease serum methadone concentrations via enhanced hepatic metabolism. Inducers such as phenytoin, pentazocine, ritonavir, and rifampin may increase the metabolism of
methadone, which could lead to inadequate pain control. See appendix 11-2 for more information.

Due to high protein binding of methadone, it is possible that methadone interacts with other highly protein-bound drugs such as digoxin and warfarin; however, no such interactions have been reported in the literature. Drugs that are highly protein-bound may be displaced from their binding sites by competition with other protein-bound drugs. This can lead to unpredictable levels of unbound drug (available drug).

Side Effect Profile

- The side effect profile of methadone is similar to that of morphine, but methadone has a greater respiratory depressant effect than morphine.
- Pulmonary edema after overdosage is a common cause of fatalities among addicts.
- Deaths from methadone overdose have been on the rise. A public health data base in Utah found that methadone use for pain treatment had increased 727% and was associated with a 1770% increase in methadone-related deaths. Several theories to the dramatic increase in death exist. (Sims 2007) One theory is that patients switched to methadone from other highly abused opioids misuse the product. The accumulation of the drug in the tissue makes it a very unpredictable product when not used appropriately.
- Recently, methadone has been associated with QT interval elongation and

torsades de pointes, an atypical rapid ventricular tachycardia, at an average dose of 400 mg per day.

- A black box warning from the FDA states that both cardiac and respiratory deaths have been reported during initiation and conversion of pain patients to methadone.

Advantages

- The extended duration of action is advantageous for patients with chronic benign pain except for the tendency of the drug to accumulate.
- Methadone is sometimes effective for treating pain that does not respond to other opioid medications as the result of activity at NMDA and other receptor sites.
- Tolerance may develop more slowly to methadone than to morphine in some patients.
- Methadone is less expensive than other long-acting opioids.
- Methadone is very effective in suppressing withdrawal symptoms in patients dependent on opioids.

Disadvantages

- The sedative properties of methadone are greater than those of morphine.
- Respiratory depression effects typically occur later and persist longer than the peak analgesic effects, particularly in the early dosing period.
- Repeated administration may lead to accumulation of the drug (with potential for significant toxicity) because of very long half-life.
- Produces less intense but more prolonged withdrawal symptoms than morphine.
- Use should be restricted to patients intolerant of morphine and should be closely monitored in the elderly and in patients with hepatic or renal dysfunction, all of whom are more likely to experience accumulation of the drug.
- There is potentially an increased risk of torsades de pointes or QT interval prolongation with methadone administration.
- Methadone is known to have several cytochrome P450-mediated drug interactions that may increase or decrease methadone levels. Methadone potentially has protein-binding interactions as well.
- Methadone should be used cautiously in patients whose compliance or communication with the prescribing clinician is in question, such as confused or demented patients.

Advantages of KADIAN® over Methadone

- The half-life of methadone varies from 15 to 55 hours depending on the individual. This variability of response between patients makes the duration of analgesia and dosing requirements difficult to determine. KADIAN® pharmacokinetics are predictable and titration is convenient.
- Deaths with methadone have increased in proportion to the increase in prescription methadone use, likely due to the unpredictable pharmacokinetics profile of the drug, including the delayed respiratory depression effects.
- KADIAN® dosing is q24h or q12h. Methadone is commonly dosed q8h to q6h. Methadone occasionally requires more frequent dosing than q6h.
- Sedation is more common with methadone than with morphine.
- Methadone side effects may not become apparent for weeks after starting the drug.
- Because of its association with addiction, many patients feel uncomfortable when filling prescriptions for methadone and some pharmacies are not willing to stock it.
- In many areas, methadone is only available as 10-mg tablets, so patients may need to take 8 or 10 tablets of methadone per day.
- KADIAN® is not metabolized by cytochrome P450 3A4 like methadone is, therefore avoiding potential drug interactions through this system.
- There is potentially an increased risk of torsades de pointes or prolongation of the QT interval with methadone administration.
- High protein binding of methadone makes it susceptible to protein-binding drug interactions.

OxyContin® (controlled-release oxycodone)

Oxycodone is a semi-synthetic opioid. Since 1994, it has been available as a long-acting medication (OxyContin®) that is dosed every 8 or 12 hours. The short-acting forms of oxycodone are usually manufactured in combination with acetaminophen (e.g. Percocet®, Tylox®, Roxicet®) or aspirin (e.g. Percodan®).

Indication

OxyContin® is indicated for around-the-clock management of moderate to severe pain when an analgesic agent is needed for an extended period of time.

Contraindications/Black box warnings:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. OxyContin® Tablets are NOT intended for use as a PRN analgesic.

OxyContin® 80 mg tablets are for use in opioid-tolerant patients only. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin® tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin® tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

Alcohol use warning: Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Pharmacology

Oxycodone is a potent semi-synthetic opioid agonist derived from morphine.

Table 11-5

Available OxyContin® Products		
Formulation	Products (Manufacturers)	Dosing Interval
Tablet, controlled-release	OxyContin® 5 mg, 10 mg, 20 mg, 40 mg, 80 mg Oxycodone Extended-Release Tablet 10 mg, 20 mg, 40 mg , 80mg	q8 to 12h

Delivery System

This formulation has a biphasic absorption pattern. OxyContin® is designed to deliver up to one-third of its contents in the first hour and then to slowly release the remainder over 8 to 12 hours. Because of this, it has a much quicker onset of action than some controlled-release medications. This may also explain the increase in side effects that sometimes occurs when patients are taking higher dosages of this medication. In addition, the initial OxyContin® drug release mimics short-acting medications. Short-acting medications should be reserved for PRN use. There is a trend towards eliminating short-acting medications in chronic pain treatment.

Dosing and Administration

The recommended starting dose of OxyContin® for opioid-naïve patients is 10mg every 12 hours. For patients already taking opioids, obtain the equivalent total daily dose of oral oxycodone from an equianalgesic dose table and round down to the closest tablet strength. OxyContin® is indicated for q12h dosing.

OxyContin® is not intended for use as a PRN analgesic. OxyContin® tablets must be swallowed whole and should not be broken, crushed, or chewed. Taking broken, chewed, or crushed controlled-release tablets leads to rapid release and absorption and is potentially fatal.

Pharmacokinetics

The absorption of oxycodone is greater than for morphine. Oxycodone is well absorbed from OxyContin® tablets with an oral bioavailability of 60% to 87%. In normal volunteers, the $t_{1/2}$ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin® exhibits a biphasic absorption pattern with two

apparent absorption half-times of 0.6 and 6.9 hours. This describes the initial release of oxycodone from the tablet followed by a prolonged release. The apparent elimination half-life of oxycodone after the administration of OxyContin® was 4.5 hours compared with 3.2 hours for immediate-release oxycodone.

Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality or bioavailability has been established for the 10-mg, 20-mg, 40-mg, 80-mg, and 160-mg strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC).

Oxycodone is a "pro-drug," which means it must be metabolized by the liver in order to become effective. The liver enzyme responsible for this metabolism is cytochrome P450 2D7. Approximately 8% of whites, 3% of African Americans, and 1% of Asians are poor metabolizers of cYP2D6 and produce no CYP2D6 or undetectable levels of it. Poor metabolizers will experience little or no analgesia from oxycodone.

Oxycodone is metabolized primarily to oxymorphone and noroxycodone. Noroxycodone is the major circulating metabolite of oxycodone. Oxymorphone possesses analgesic activity but is present in low plasma concentrations.

Oxycodone and its metabolites are excreted primarily by the kidney.

Drug Interactions

Medications that interfere with cytochrome P450 2D6 liver enzyme (including some antidepressants such as Prozac® and Paxil®) (SSRI's), may reduce the effectiveness of oxycodone. Case reports in the literature support the clinical significance of these interactions (*see* appendix 11-2).

Side Effect Profile

- Same as for morphine.
- Oxycodone generally has fewer gastrointestinal side effects than morphine.

Advantages

- An effective oral opioid alternative to morphine for moderate to severe pain.
- Oxycodone may have fewer gastrointestinal side effects.

Disadvantages

- Deaths from overdose have been reported after misuse by crushing OxyContin® and thus destroying the delivery system.
- OxyContin® serum levels rise sharply in the first hour because of the early release of 33% of the dose. This peak may be associated with increased side effects, but faster relief of pain.
- The biphasic release of OxyContin® makes serum levels less stable than with other controlled-release opioids, which may result in uneven pain relief.
- Some patients are deficient in the cytochrome P450 2D6 enzyme required for oxycodone conversion to active metabolites. Other patients take medications that interact at the 2D6 site. As a result, neither patient population may be able to convert oxycodone to active drug.
- Many patients require q8h dosing with OxyContin® to maintain analgesic efficacy.

Advantages of KADIAN® over OxyContin®

- KADIAN® dosing is q24h or q12h. OxyContin® is dosed q12h. OxyContin® occasionally requires more frequent dosing than q8h.
- KADIAN® is not metabolized by cytochrome P450 3A4 like OxyContin®, therefore avoiding potential drug interactions through this system.
- Some patients may not be able to convert OxyContin® to active drug because of a deficiency of cytochrome P450 2D6 enzyme.
- OxyContin® has biphasic absorption with 33% of the drug being released within the first hour.
- OxyContin® is associated with a high rate of abuse.
- Because of the high street value of OxyContin®, patients may be at risk of having their medication stolen. Some pharmacies are no longer willing to stock OxyContin® because of the risk of armed robbery.

Long-Acting Morphine Product Comparison: MS Contin®, Oramorph SR®, Avinza®

MS Contin® (Purdue Pharma)

Indication

MS Contin® is indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesic over periods of more than a few days.

Contraindications/Black box warnings:

Ms Contin® contains morphine sulfate, an opioid agonist and a schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Ms Contin® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Ms Contin® tablets are a controlled-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Ms Contin® tablets are not intended for use as a PRN analgesic.

Ms Contin® 100 and 200 mg tablets are for use in opioid-tolerant patients only. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Ms Contin® tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed Ms Contin® tablets leads to rapid release and absorption of a potentially fatal dose of morphine.

Alcohol use warning: Morphine may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Available Strengths

- Color-coded tablet in 5 strengths: 15 mg (blue), 30 mg (lavender), 60 mg (orange), 100 mg (gray), and 200 mg (green).
- Generic products are also available.

Delivery System

MS Contin® tablets are film-coated and contain wax-coated controlled-release granules of hydroxyalkyline cellulose to which morphine sulfate is absorbed. Gastric juices dissolve the tablet surface and expose the wax-coated granules. The wax coating slowly dissolves and exposes the cellulose carrying the morphine. Morphine then diffuses from the cellulose and is absorbed into the bloodstream. Thus, morphine release is controlled by means of the time it takes the tablet to disintegrate, the wax to dissolve, and the morphine to diffuse from the cellulose.

Dosage and Administration

MS Contin® is approved for 8-hour or 12-hour administration, but clinical experience suggests that 8-hour administration is necessary for some patients. There has been no systematic evaluation of MS Contin® as an initial opioid in the treatment of pain. Breakthrough pain may require supplementation with short-acting (immediate-release) morphine or shortening the dosing interval of MS Contin® to q8h.

Tablets should be swallowed whole and should not be broken, chewed, or crushed. The 200-mg tablets are for use in opioid-tolerant patients only.

Pharmacokinetics

The extent of absorption of MS Contin® is comparable with that of other morphine products but the rate is slower than oral immediate-release morphine sulfate. On average, 50% of absorption occurs in 1.5 hours. Food does not affect the bioavailability of the medication.

MS Contin® has a greater fluctuation in plasma morphine levels than KADIAN® (See Comparative Pharmacokinetics). The maximum plasma concentration is reached in 2.5 hours. Steady state is achieved in about one day.

Comparative Pharmacokinetics

Two important studies comparing the pharmacokinetics of KADIAN® with MS Contin® have been completed by Gourlay and colleagues: one involving once-a-day dosing and one involving twice-a-day dosing. Both studies were conducted in patients with cancer pain after a lead-in period in which the dose of morphine was stabilized at an effective dose. The data from the once-a-day study are presented below. These data show that KADIAN® has fewer fluctuations in plasma concentration than does MS Contin®.

Study Design and Population

The study was a randomized, double-blind, double-dummy, 2-treatment, 2-crossover study with a lead-in period. Twenty-four patients with moderate to severe cancer pain completed the study. After a lead-in period to achieve stabilization at an effective dose, patients were randomly assigned to receive either KADIAN® q24 hr or MS Contin® q12 hr. Blood samples were drawn on the last day of each treatment period. All doses were corrected to 100mg for comparison purposes. The study parameters are listed in Table 11-3.

Table 11-6

Mean Steady-State Pharmacokinetic Parameters for Morphine Following KADIAN® or MS Contin® (AUC, C_{max}, C_{min} corrected to 100 mg dose)		
Parameter	KADIAN® q24h	MS Contin® q12h
AUC (ng/ml)/h	500.9 + 193.2	457.3 + 184.7
C_{max} (ng/ml)	37.3 + 14.0	36.9 + 15.5
C_{min} (ng/ml)	9.9 + 5.2*	7.6 + 4.6
t_{max}(h)	10.3 + 3.3*	4.4 + 2.3
$t > 0.75\ C_{max}$ (h)	6.0 + 3.0*	4.8 + 2.8
Fluctuation	1.4 + 0.4*	1.6 + 0.5

*Statistically significantly different from MS Contin® q12h ($p<0.05$ by ANOVA)

Study Results

Dose normalization to 100 mg permitted a direct comparison of the pharmacokinetics parameters of the 2 formulations. The differences in AUC values were not statistically significant, which indicates that the extent of absorption from the 2

products is similar. The C_{max} values were also similar. However, the other pharmacokinetics parameters differed significantly.

KADIAN® exhibited a higher C_{min} and less fluctuation in plasma morphine concentrations. A longer time to maximum plasma concentration (t_{max}) was observed with KADIAN®. KADIAN® has a longer time that the plasma concentration remained about 75% of the C_{max} when compared with MS Contin®, as well. The authors concluded that KADIAN® given once daily has a superior pharmacokinetic profile when compared with MS Contin® twice daily.

Advantages of KADIAN® over MS Contin®

- KADIAN® allows dose titration at lower doses in 10-mg increments.
- KADIAN® is approved for sprinkle and G-tube administration. MS Contin® tablet technology does not allow this type of administration.
- Labeling supports the use of MS Contin® q12h to q8h. KADIAN® is rarely dosed more than q12h in clinical practice.
- KADIAN® 10-mg and 20-mg formulations allow a physician to begin therapy at a lower dose than the 30-mg lowest strength of MS Contin®.
- KADIAN® provides steady and consistent blood plasma concentrations with less fluctuation than MS Contin®.
- KADIAN® exhibits a higher C_{min} and less fluctuation in plasma morphine concentrations than MS Contin® does. A longer time to maximum plasma concentration (t_{max}) was observed with KADIAN®. In addition, KADIAN® has a longer time that the plasma concentration remains above 75% of the $\mathbf{C}_{max}$ when compared with MS Contin®. KADIAN® given once daily has a superior pharmacokinetic profile when compared with MS Contin® twice daily (Gourlay et al, 1997).

Comparative Clinical Efficacy

Two double-blind, multiple-dose, active controlled studies of the efficacy of KADIAN® in patients with cancer pain have been carried out. Gourlay et al (1997) evaluated KADIAN® q24h versus MS Contin® q12h. Broomhead et al (1997) evaluated KADIAN® administered q24h versus KADIAN® administered q12 h versus MS Contin® q12h.

Neither study showed a statistical difference in pain control or the occurrence of breakthrough pain (as evidenced by the percentage of patients requiring rescue

medication and the timing of rescue medication) between KADIAN® administered once or twice daily and MS Contin® administered q12h.

The 1997 Gourlay et al study also evaluated patient preference for KADIAN® q24h versus MS Contin® q12h and found there were no statistically significant differences in patient preference ratings between the 2 treatment groups.

Patient preference for once-daily KADIAN® or twice-daily MS Contin® were evaluated in an open label study of the two formulations in patients with cancer pain by Kerr and Tester in 2000. In this study there was a clear preference for KADIAN® q24h over MS Contin® q12h. Of the 104 patients for whom evaluative data were available, 57 (55%) preferred KADIAN® q24h, 34 (33%) preferred MS Contin®, and 13 (12%) had no preference. A clear patient preference for KADIAN® daily over MS Contin® q12h was identified in this study.

Oramorph SR® (Roxane Labs)

Indication

Oramorph SR® is indicted for the relief of pain in patients who require opioid analgesics for more than a few days.

Contraindications/Black box warnings:

This is a sustained release dosage form. Patient should be instructed to swallow the tablet as a whole; the tablet should not be broken in half, nor should it be crushed or chewed.

The sustained release of morphine from Oramorph SR should be taken into consideration in event of adverse reactions or overdosage.

In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist in such a person should be avoided. If necessary to treat serious respiratory depression in a physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Alcohol use warning: Morphine should not be taken with alcohol or other CNS depressants (sleep aids, tranquilizers) because additive effects, including CNS depression, may occur. A physician should be consulted if other prescription and/or over-the-counter medications are currently being used or are prescribed for future use.

Precautions

Contraindications for Oramorph SR® are similar to those for immediate-release morphine, with the addition of paralytic ileus.

Available Strengths

- White tablet embossed in 4 strengths: 15 mg, 30 mg, 60 mg, 100 mg.

Delivery System

Oramorph SR® tablets contain sustained-release granules of hydroxypropyl methylcellulose to which morphine sulfate is adsorbed. Gastric juices dissolve the tablet surface and expose the coated granules. The coating slowly dissolves and exposes the cellulose carrying the morphine. Morphine then diffuses from the cellulose and is absorbed into the bloodstream.

Dosage and Administration

Oramorph SR® is approved for administration every 12 hours. The dosing interval should not be extended beyond 12 hours or shortened to less than 8 hours. The 30-mg tablet strength is recommended for the initial titration period for patients with a daily morphine requirement of 120mg or less. For patients with low daily morphine requirements, the 15-mg tablet should be used. There has been no systematic evaluation of Oramorph SR® as an initial opioid in the treatment of pain. Tablets should be swallowed whole and should not be broken, chewed, or crushed.

Oramorph SR® has not been evaluated in children and therefore its use in the pediatric population is not recommended.

Pharmacokinetics

The pharmacokinetics of Oramorph SR® show considerable intersubject variation. For example, time to peak plasma concentrations averages around 4 hours. The range for this average varies from 1 hour to 7 hours. However, there are fewer fluctuations

between single-dose peak plasma morphine concentrations compared with immediate-release morphine. Steady-state plasma concentrations are achieved in 1 to 2 days.

The extent of absorption of Oramorph SR® is comparable with that of other morphine products but the rate is slower than oral immediate-release morphine sulfate. On average, 50% of absorption occurs in 1.5 hours. Oramorph SR® does not release morphine continuously over the course of the dosing interval. The possible effect of food on bioavailability has not been evaluated. Dose proportionality or bioavailability has not been established for currently available strengths.

Advantages of KADIAN® over Oramorph SR®

- Titration is more difficult with 15, 30, 60, and 100 mg Oramorph SR®. KADIAN® allows dosing titration in 10-mg increments at some doses.
- KADIAN® is approved for sprinkle and G-tube administration. Oramorph SR tablet does not allow this type of administration.
- Clinical practice supports the use of Oramorph SR® q12h to q8h. KADIAN® is rarely dosed more than q12h in clinical practice and pharmacokinetically does not require more frequent dosing.

Avinza® (King Pharmaceuticals)

Indication

Avinza® is indicated for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time.

Contraindications/Black box warnings:

Avinza® capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The capsule beads are not to be chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine.

Patients must not consume alcoholic beverages while on Avinza® therapy. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on Avinza® therapy. Consumption of alcohol while taking Avinza® may result in the rapid release and absorption of a potentially fatal dose of morphine.

Alcohol use warning: Morphine may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. In vitro studies performed by the FDA demonstrated that when Avinza® 30 mg was mixed with 900 mL of buffer solutions containing ethanol (20% and 40%), the dose of morphine that was released was alcohol concentration-dependent, leading to a more rapid release of morphine. While the relevance of in vitro lab tests regarding Avinza® to the clinical setting remains to be determined, this acceleration of release may correlate with in vivo rapid release of the total morphine dose, which could result in the absorption of a potentially fatal dose of morphine.

Precautions

Contraindications are similar to those for immediate-release morphine, with the addition of gastrointestinal obstruction, particularly paralytic ileus. Caution should be used when administering Avinza® within 24 hours of cordotomy or similar surgery.

Available Strengths

Color-coded gelatin capsules in 4 strengths: 30 mg (yellow), 60 mg (bluish-green), 90 mg (red), and 120 mg (blue-violet).

Delivery System

Avinza® capsules contain polymer-coated, sustained-release beads of morphine sulfate. The capsules use the proprietary SODAS (Spheroidal Oral Drug Absorption System) technology to produce an extended-release component of Avinza®. As the capsule passes through the GI tract, soluble polymers of ammoniomethacrylate dissolve, leaving pores within the outer membrane. Fluid enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the dissolution phase.

The diffusion of the dissolved solution within the beads is mediated by fumaric acid, which acts as an osmotic agent and a local pH modifier. Fumaric acid increases the acidity of the drug (decreases the pH) and serves as an osmotic agent that controls the rate of osmotic diffusion. Fumaric acid is used in small amounts as a food additive to increase acidity. The safety of large amounts of fumaric acid (as are found in doses of Avinza® over 1600mg/day) has not been established. Large doses of fumaric acid may result in serious renal toxicity. In rats, fumaric acid monoethylester leads to

concentration defects (during water deprivation) and reduced glomerular filtration rates (Hohenegger, 1989).

Dosage and Administration

Avinza® should not be given more frequently than every 24 hours. The 30-mg capsule strength is recommended for the initial titration period. There has been no systematic evaluation of Avinza® as an initial opioid in the treatment of pain, although efficacy studies have included patients in the study population who were not previously taking opioids. Capsules should be swallowed whole and should not be broken, chewed, or crushed. Doses above 1600mg per day contain a quantity of fumaric acid that has not been shown to be safe and that may result in serious renal toxicity.

As alternatives to ingesting whole capsules, capsules may be opened and the beads ingested with a small amount of applesauce (sprinkle administration).

The safety and effectiveness of Avinza® in pediatric patients below the age of 18 years have not been established. The range of dose may not be appropriate for this patient population. Sprinkle administration is not a suitable alternative for these patients.

Side Effect Profile

In controlled trials for malignant and nonmalignant pain, the most serious adverse events reported with administration of Avinza® were vomiting, nausea, death, dehydration, dyspnea, and sepsis. Deaths occurred in patients treated for pain due to underlying malignancy. The common adverse events seen on morphine initiation are similar to those for other opioid products.

Pharmacokinetics

Avinza® consists of two components, an immediate-release component that rapidly achieves plateau morphine concentrations and an extended-release component that maintains plasma concentrations throughout the 24 hour dosing interval. The extent of absorption is comparable with that of other extended-release morphine formulations. Bioavailability is not affected by presence of food. Dose proportionality has been established in chronic pain patients over the range of 30 to 180mg.

The maximum plasma concentration of Avinza® is achieved in 0.5 hours after oral administration. Steady-state plasma concentrations are reached in 2 to 3 days.

Advantages of KADIAN® over Avinza®

- The KADIAN® 10-mg formulation allows clinicians to begin therapy at a lower dose than the 30-mg lowest strength of Avinza®.
- Avinza® is only indicated for q24h dosing. KADIAN® allows the flexibility of q24h and q12h dosing.
- KADIAN® allows dosing titration in 10-mg increments.
- Avinza® is not approved for G-tube administration.
- The dose of Avinza® is limited to 1600 mg per day due to potential renal toxicity from the fumaric acid component. KADIAN® does not contain fumaric acid.
- Avinza® contains an immediate-release component that peaks in 0.5 hours. This mimics short-acting medications. Short-acting medications should be reserved for PRN use. In addition, there is a trend towards eliminating short-acting medications in chronic pain treatment.

Summary of KADIAN® Advantages

Contains morphine in an oral formulation:

- The oral route is recommended by the World Health Organization for treatment of pain.
- The oral route has a more rapid onset of analgesic action than does transdermal delivery (advantage vs. Duragesic®).
- No maximum dose (advantage vs. Avinza®).
- Easily titratable (advantage vs. Duragesic® and Methadone).
- Titration can occur in 10-mg increments at lower doses when small increases in the dose are more likely to be needed (advantage vs. MS Contin®, Oramorph SR®, and Avinza®).
- Known manageable side effects.
- No special patient education required before administration of KADIAN®

(advantage vs. Duragesic®).

Desirable Pharmacokinetic Profile

- KADIAN® does not require cytochrome P450 2D6 for conversion to active drug (advantage vs. OxyContin®).
- KADIAN® is not metabolized by the cytochrome P450 system, therefore avoiding poleutial drug interactions through this system (advantage vs. Duragesic®, OxyContin®, and Methadone).
- KADIAN® pharmacokinetics are predictable and titration is convenient (advantage vs. Duragesic® and Methadone).
- KADIAN® has no risk of torsades de pointes (advantage vs. Methadone).
- KADIAN® does not have a short-acting component (advantage vs. OxyContin® and Avinza®).
- Easy to manage at home – less restrictive and invasive than parenteral therapy.
- KADIAN® is more cost-effective in terms of savings in nursing time vs. infusion devices. KADIAN® requires less nursing time for administration than Duragesic®.

Has a capsule formulation:

- Tasteless (advantage vs. morphine solution).
- KADIAN® has not been associated with a dramatic increase in death rate from overdose (advantage vs. Methadone).

Is an extended-release formulation:

- Allows the option of dosing every 24 hours and should not require dosing more often than q12h (advantage vs. OxyContin®, Methadone, MS Contin®, and Oramorph SR®).
- KADIAN® given once daily has a superior pharmacokinetic profile when compared with MS Contin® twice daily (Gourlay 1997).
- Can be given without regard to meals.
- Capsule can be opened and the pellets sprinkled on small amount of applesauce for ingestion (advantage vs. Duragesic®, Methadone, OxyContin®, MS Contin®, and Oramorph SR®).
- The KADIAN® capsule can be opened and the pellets mixed with a small

amount of water and administered through a 16-French (or larger) G-tube(advantage vs. Duragesic®, Methadone, OxyContin®, MS Contin®, Oramorph SR®, and Avinza®).

Is formulated for dosing every 24 hours:

- Reduced dosing frequency relative to immediate-release morphine tablets or solution and some controlled-release formulations (MS Contin®, Oramorph SR®, OxyContin®, and Methadone).
- Patient preference for KADIAN® q24h over MS Contin® q12h has been documented in clinical trials (Kerr and Tester 2000).
- May facilitate uninterrupted sleep for some patients (advantage vs. MS Contin®)

Is available in 8, easily discernible, color-coded strengths:

- Eight strengths allow precise dosage: 10 mg (light blue), 20 mg (yellow), 30 mg (blue-violet), 50 mg (blue), 60 mg (pink), 80 mg (light orange), 100 mg (green), and 200 mg (brown).

Possible Objections to KADIAN®

Versus other Morphine Preparations

- Breakthrough pain requires therapy with immediate-release morphine preparations (also true of other controlled-release opioid products).
- Perceived as expensive compared with oral morphine sulfate solution and generic MS Contin®. Depending on total number of daily doses of the other products, KADIAN® may be comparable in price. Education is required regarding cost-effectiveness.

Versus Nonopioid Preparations

- Fear of the use of opioids among medical practitioners and patients; the market requires education.
- Adverse effects of morphine require use of other medications, e.g., prophylaxis for constipation. This is inconvenient and adds to costs.
- Morphine is a regulated substance and its usage introduces prescribing complications for clinicians.

Summary

- Extended- and controlled-release morphine preparations occupy a variable share of the oral morphine market. Of the extended- and controlled-release preparations presently on the market, MS Contin® is the longest established and OxyContin® is the most widely used. All of the extended- and controlled-release formulations of morphine, oxycodone, and transdermal fentanyl are suitable for relief of chronic cancer and nonmalignant moderate to severe pain.
- The advantages of the extended-release preparation KADIAN® can be summarized as follows:
- KADIAN® is suitable for administration every 12 to 24 hours, whereas the recommended dosing interval for MS Contin® is every 8 to 12 hours and OxyContin® is every 12 hours. Avinza® is every 24 hrs.
- KADIAN® has been shown to be as effective as 4-hour immediate-release morphine formulations and 12-hour controlled-released morphine tablets for relief of moderate to severe chronic pain.
- KADIAN® can be administered by opening the capsule and sprinkling the pellets on a small amount of applesauce. Also, the pellets can be mixed with a small amount of water and administered through a 16-French (or larger) G-tube.
- KADIAN® has fewer fluctuations in plasma concentrations.

Literature Cited

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- Kerr RO, Tester WJ. A Patient Preference Study Comparing Two Extended-Release Morphine Sulfate Formulations (Once-Daily Kadian(R) versus Twice-Daily MS Contin(R)) for Cancer Pain. Clinical Drug Investigation. 2000;19:25-32.
- Sims SA, Snow LA, Porucznik CA. Surveillance of methadone-related adverse drug events using multiple public health data sources. J Biomed Inf. 2007;40:382-389.

Table 11-7 REFERENCE - LONG-ACTING OPIOID COMPARISON TABLE

	KADIAN®	OxyContin®	MS Contin®	Duragesic®	Avinza®	Methadone
Dosing	10 20, 30, 50, 80, 60, 100, 200 mg QD or BID	10, 20, 40, 80 mg BID*	15, 30, 60, 100, 200 mg BID*	25, 50, 75, 100 mcg 72hrs.*	30, 60, 90, 120 mg QD (1600/day max)	5, 10, 40 mg, q6-8h (dosing varies)
Monophasic vs. Biphasic Absorption	Monophasic	Biphasic	Monophasic	Monophasic	Biphasic	Monophasic
Technology	Polymer-coated pellets	Matrix	Matrix	Reservoir patch (transdermal)	Copolymer beads (fumaric acid)	Immediate--release long half-life drug
Metabolism	M3G & M6G glucuronide metabolites	P450	M3G & M6G glucuronide metabolites	P450 3A4 isoenzyme	M3G & M6G glucuronide metabolite	CYP1A2, 2D6, and 3A 3/4 enzyme substrate; CYP2D6 enzyme inhibitor
Most Common Adverse Events	Drowsiness, constipation, nausea, dizziness, anxiety (<10%)	Constipation, nausea, somnolence, dizziness, pruritus, vomiting	Constipation, dizziness, sedation, nausea, vomiting, dysphoria, euphoria	Nausea, vomiting, constipation, dry mouth, somnolence, confusion (<10%)	Vomiting, nausea, death, dehydration, dyspnea, sepsis	Lightheadedness, dizziness, drowsiness, nausea, vomiting, constipation, hypotension, weakness (<10%)
Titration	24-48 h	24-48 h	24-48 h	72 h	24-48 h	q48-72h once stable (stability achieved in 3 to 5 days)
Plasma Fluctuations	Steady-state, no bolus	Bolus	Peaks & trough	Steady	Bolus	Steady
Routes	Oral, sprinkle, G-tube	Oral	Oral	Patch	Oral, sprinkle	Oral

*Refer to the Royal Abstract (*see* Appendix 11-1) for information on dosing in clinical practice.

Self-Assessment Test

Circle the best response

1) Which of the following statements support morphine as the gold standard potent opioid for the treatment of pain?
   a. 60% to 85% of patients respond adequately to regular administration of morphine.
   b. Morphine is available orally, parenterally, and transdermally.
   c. Morphine has a ceiling effect.
   d. Morphine has known and predictable side effects.

2) Which of the following is a potential drawback compared with morphine for the use of methadone in the continuous treatment of chronic cancer pain?
   a. Repeated administration of methadone could lead to accumulation of the drug.
   b. Methadone produces more intense and more prolonged withdrawal symptoms than does morphine.
   c. Methadone has not been shown to have as much analgesic efficacy as morphine.
   d. Methadone causes more pruritus than does morphine.

3). Which of the following statements is true regarding mixed agonist-antagonists?
   a. Mixed agonist-antagonist enhance analgesic efficacy when given in conjunction with a mu agonist.
   b. Mixed agonist-antagonists have a lower risk of psychotomimetic effects.
   c. Mixed agonist-antagonists are recommended for use in chronic pain because of their good side effect profile.
   d. Mixed agonists-antagonists potentially reduce analgesia or precipitate withdrawal symptoms when administered to patients taking mu agonists.

4) Which of the following statements is true regarding Duragesic®?
   a. Onset of analgesic activity is delayed by 6 hours.
   b. Duragesic® patches may be changed every 48 hours.
   c. Duragesic® is easily titratable.
   d. Fentanyl levels clear quickly after removal of the Duragesic® patch.

5) Which of the following is not an advantage of KADIAN®?
   a. KADIAN® can be given without regard to meals.
   b. KADIAN® allows more flexibility in dosing intervals than do other morphine formulations.
   c. KADIAN® can be administered by G-tube.
   d. KADIAN® delivers medication up to 24 hours.
   e. All of the above are advantages.

True or False

6) Methadone is effective in suppressing withdrawal symptoms in patients with opioid dependency.
   True
   False

7) The extent of KADIAN® absorption is unaffected by the presence of food.
   True
   False

8) MS Contin® has a C_{min} that is similar to that of KADIAN®.
   True
   False

9) KADIAN® contraindications and warnings are generally the same as for morphine except that KADIAN® is contraindicated in paralytic ileus and GI obstruction.
   True
   False

10) KADIAN® and OxyContin® both exhibit biphasic absorption.
   True
   False

Answers to Self-Assessment Test

1. d	6. a
2. a	7. a
3. d	8. b
4. b	9. a
5. e	10. b

Appendix 11-1: Royal Abstract

Clinical practitioners often use long-acting opioids more often than indicated. There are several reasons for this practice. The primary reason is that patients experience pain at the end of many recommended dosing intervals. Some practitioners believe that many patients actually use breakthrough doses of instant-release medication to provide pain relief during the interval between long-acting doses, rather than for true breakthrough pain. This end-of-dose pain can be reduced by increasing the number of daily doses of controlled-release medication. An additional (although theoretical) advantage is that blood levels often vary less with more frequent dosing.

Recently, a professor of Internal Medicine and Anesthesiology/Pain Management at the University College of Medicine in Oklahoma collected data to support this practice.

A retrospective chart review was performed evaluating the use of various long-acting opioid preparations, including Duragesic®, MS Contin®, KADIAN®, OxyContin®, and methadone. The purpose of the review was to determine the percentage of patients who required more frequent dosing than the labeling for each opioid. Three hundred and sixty charts were reviewed. Primary pain diagnoses varied from nociceptive to neuropathic pain. The use of immediate-release morphine (MSIR) for breakthrough pain was also evaluated.

The review found that patients often used long-acting opioid formulations more frequently than recommended by manufacturers. Of the oral formulations, KADIAN® was most likely to be dosed either QD or BID (94.2%), whereas MS Contin® and OxyContin® were dosed more frequently than BID in 70.5% and 87.2%, respectively. Nearly one-fourth of patients taking Duragesic® required q48h dosing. KADIAN® maintained a less frequent dosing schedule than other extended-release opioid preparations. In addition, breakthrough medication requirements were reduced with KADIAN®.

Table 11-8

Frequency of Dosing for Common Long-Acting Opioids						
	Total # of Patients	QD%	BID%	TID%	QID	MSIR% (breakthrough)
Duragesic®	77	NA	72 hr 76.6	48 hr 23.4		58.4
Ms Contin®	68	1.5	27.9	67.6	2.9	48.5
KADIAN®	69	60.9	33.3	2.9	2.9	43.5
OxyContin®	86	0	12.8	59.3	27.9	57.0
Methadone	60	0	11.7	28.3	60.0	56.7

Royal M, Jensen M, Gunyea I, et al. Retrospective assessment of the frequency of dosing of sustained-release opiate preparations in chronic pain patients. 2002

Appendix 11-2: Substrates and Inhibitors of Cytochrome P450 Subtypes

Many drugs (and other chemicals, including toxins) undergo enzymatic biotransformation in the liver. The transformation may activate or deactivate the drug, depending on the chemical structure of the drug. The major group of enzymes responsible for drug biotransformation in the liver is the cytochrome P450 monooxygenase system of enzymes. These are often called the P450 or CYP 450 enzymes, for short. There are a number of individual enzymes in the CYP group, including 2D6, 3A4, and 1A2, which are important in this process, although 3A4 is the most commonly involved in drug metabolism.

It is important to know which drugs are metabolized by the P450 system because the system can be saturated. If the system is saturated by a drug or other substrate (the material that is transformed by the enzymes), it is not available to metabolize other drugs. That can lead to either a lack of activated forms of the drug (if P450 enzymes activate that drug) or excessive levels of the drug (if P450 enzymes deactivate the drug). It is not always predictable which drug will have excessive or insufficient levels if more than one drug that affect this system is given.

The P450 system can also be induced, which means its activity levels can be increased by chronic exposures to substances, such as with chronic drug therapy. In those cases, the P450 system becomes more active, resulting in excessive or

insufficient drug levels, depending on whether the system deactivates or activates a particular drug.

The prescribing information on drugs that are affected by the P450 system includes detailed information on the effects of the P450 system on that particular drug and also includes a list of other drugs that are expected to be affected if the patient is taking them concurrently.

KADIAN® does not invoke the P450 system, but rather is metabolized to morphine-6-glucuronide through glucuronidation. This means that it is not as complicated for the clinician to determine what drugs might cause alterations in the drug levels of KADIAN® and it is not as complicated to predict how the pharmacodynamics of other drugs a patient is taking would be affected.

CYP2D6

Substrates

METHADONE
OXYCODONE
Antidepressants
- Amitriptyline (Elavil)
- Clomipramine
- (Anafranil) Desipramine
- (Norpramin) Doxepin
- (Adapin, Sinequan)
- Fluoxetine (Prozac)
- Imipramine
- (Tofranil)
- Nortriptyline
- (Pamelor) Paroxetine
- (Paxil)
- Venlafaxine (Effexor)

Antipsychotics
- Haloperidol (Haldol)
- Perphenazine (Etrafon,
- Trilafon) Risperidone
- (Risperdal)
- Thioridazine (Mellaril)

Beta blockers
- Metoprolol
- (Lopressor)
- Penbutolol (Levatol)
- Propranolol (Inderal)
- Timolol (Blocadren)

Opioids
- Codeine, tramadol (Ultram)

Inhibitors (decrease metabolism of substrates)

Antidepressants
- Paroxetine (Paxil)

Fluoxetine (Prozac) Sertraline (Zoloft) Fluvoxamine
- (Luvox) Nefazodone

(Serzone)
- Venlafaxine (Effexor)

Clomipramine (Anafranil)
Amitriptyline (Elavil)
Antipsychotics
- Fluphenazine (Prolixin)
- Haloperidol (Haldol)
- Perphenazine (Etrafon,

Trilafon) Thioridazine
- (Mellaril)

Cimetidine (Tagamet)

CYP3A4

Substrates

- FENTANYL
- METHADONE
- Antidepressants
  - Amitriptyline (Elavil)
  - Imipramine (Tofranil)
- Sertraline (Zoloft)
- Venlafaxine (Effexor)
- Nefazodone (Serzone)
- Benzodiazepines
  - Bupropion (Wellbutrin)
  - Alprazolam (Xanax)
  - Triazolam (Halcion)
  - Midazolam (Versed)
- Calcium blockers
  - Carbamazepine (Tegretol)
  - Cisapride (Propulsid)
  - Dexamethasone (Decadron)
  - Erythromycin
  - Ethinyl estradiol

(Estraderm, Estrace)

  - Glyburide (Glybnase,

Micronase)

  - Ketoconazole (Nizoral)
  - Lovastatin (Mevacor)
  - Terfenadine (Seldane)
  - Astemizole (Hismanal)
  - Verapamil (Calan, Isoptin)
  - Testosterone
  - Theophylline
- Protease inhibitors (HIV agents)
  - Ritonavir (Norvir)
  - Saquinavir (Invirase)
  - Indinavir (Crixivan)
  - Nelfinavir (Viracept)

Inhibitors

- Antidepressants
  - Nefazodone (Serzone)
- Fluvoxamine (Luvox)
- Fluoxetine (Prozac)
  - Sertraline (Zoloft)
  - Paroxetine (Paxil)
  - Venlafaxine (Effexor)
- Azole antifungals
  - Ketoconazole (Nizoral)
  - Itraconazole (Sporanox)
  - Fluconazole (Diflucan)
- Cimetidine (Tagamet)
- Clarithromycin (Biaxin)
- Diltiazem
- Erythromycin
- Protease inhibitors

Inducers increase metabolism of substrates)

- Carbamazepine
- Dexamethasone
- Phenobarbital
- Phenytoin (Dilantin)
- Rifampin (Rifadin, Rimactane)

CYP1A2

Substrates

METHADONE
Antidepressants
- Amitriptyline (Elavil)
- Clomipramine (Anafranil)
- Clozapine (Clozaril)
- Imipramine (Tofranil)

Other
- Propranolol (Inderal)
- R-warfarin
- Theophylline
- Tacrine (Cognex)

Inhibitors

Fluvoxamine (Luvox)
Grapefruit juice
Quinolones
Ciprofloxacin (Cipro)
Enoxacin (Penetrex) > norfloxacin (Noroxin) >
Ofloxacin (Floxin) > lomefloxacin (Maxaquin)

Inducers

Omeprazole (Prilosec)
Phenobarbital
Phenytoin (Dilantin)
Rifampin (Rifadin, Rimactane)
Smoking
Charcoal-broiled meat

CHAPTER TWELVE

Clinical Research Papers

Learning Objectives

After reading this chapter, you should be able to:

- List and describe the phases of the Pharmaceutical Investigation.
- Describe the anatomy of a clinical research paper and the importance of each part.

Terminology

Exclusion criteria:	variables used to eliminate patients from the study.
Inclusion criteria:	variables used to define the patient population.
***n*:**	the number of patients participating in the experiment.
Reliability:	a measure of the extent to which the experiment produces the same result.
Validity:	extent to which the experiment measures the specified objectives.
Variance:	extent to which variables or characteristics of the subject population differ.
Randomization:	a selection procedure used to eliminate the bias in a subject population.
Placebo:	pharmacologically inactive pill.
Open label:	both patient and physician are aware of actual treatment.
Single blind:	only the physician is aware of actual treatment.
Double blind:	neither the patient nor the physician is aware of actual treatment.
Single group:	one subject group with one treatment.
Multiple group:	one or more subject groups (usually one group is a control group).
Parallel group:	two or more subject groups studied simultaneously.
Crossover group:	each subject is given each treatment (double crossover repeats crossover design).
Objective criteria:	clearly defined variables with exact measurements. *Example: visual and numeric analog pain scales.*
Subjective criteria:	variables that are less well defined (typically exhibiting great intrapatient differences). *Example: patient self-report.*

Introduction

Reviewing the investigation and anatomy of clinical research papers will facilitate an understanding of the general information that a clinical study provides. This chapter reviews the phases of pharmaceutical investigation and the anatomy of clinical research papers.

Phases of Pharmaceutical Investigation

Preclinical

- Evaluation of animal and *in vitro* pharmacology.

Phase I

- Evaluation of safety in healthy humans.
- Determination of dose.
- Evaluation of human pharmacology.

Phase II

- Clinical evaluation of specific patient population.

Phase III

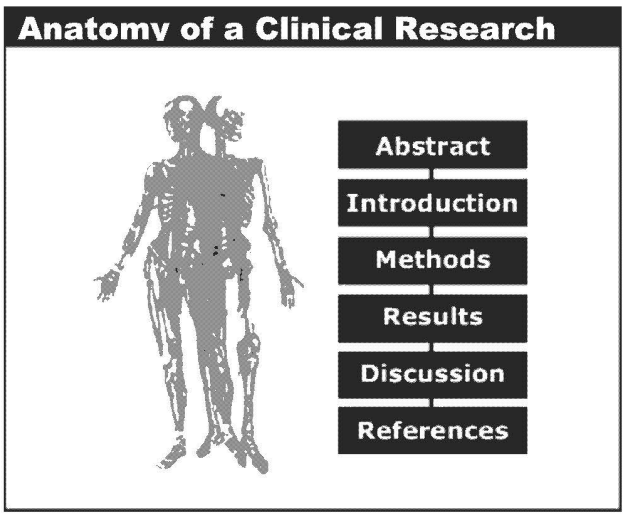
- Evaluation of safety and efficacy in larger numbers of patients.

Phase IV

- Postmarketing evaluation with larger population.

Anatomy of a Clinical Research Paper

Figure 12-1



Abstract

A brief summary of the study.

- ***Key Information***
- Abstract provides directions for navigating the study.
- Contains purpose statement, information about methods, results, discussion.

Introduction

The introduction section reviews information about the subject and establishes the purpose for the study.

Methods

The methods section describes what procedures and designs were used in conducting the research.

- ***Key Terms***
- **Reliability-** a measure of the extent to which the experiment produces the same result.

- **Validity-** extent to which the experiment measures the specified objectives.
- Patient Population
- ***n***- the number of patients participating in the experiment.
- **Inclusion criteria**- variables used to define the patient population.
- **Exclusion criteria**- variables used to eliminate patients from study.
- **Variance-** extent to which variables or characteristics of the subject population differ.

- ***Control Methods***
- **Randomization**- a selection procedure used to eliminate the bias in a subject population.
- **Placebo** - pharmacologically inactive pill.
- **Open label** - both patient and physician are aware of actual treatment.
- **Single blind** - only the physician is aware of actual treatment.
- **Double blind**- neither the patient nor the physician is aware of actual treatment.

- ***Experimental Design***
- **Single group** - ones subject group with one treatment.
- **Multiple group** - one or more subject groups (usually one group is a control group).
- **Parallel group** - two or more subject groups studied simultaneously.
- **Crossover group** - each subject group is given each treatment (double crossover repeats crossover design).

- ***Measurement Parameters***
- **Objective criteria** - clearly defined variables with exact measurements. Example: visual and numeric analog pain scales.
- **Subjective criteria**- variables that are less well defined (typically exhibiting great intrapatient differences). Example: patient self-report.

Results

The results section of the study reports the collected data and emphasizes the statistical significance of the findings (also used to state means, standard deviation, etc.).

Discussion

The discussion portion of the study is used to interpret the value and applications of the results.

References

The reference section of the study contains documentation for sources of information.

Glossary

Absorption:	The taking in or assimilation of a substance (e.g., a drug or food) into body tissues.
Abuse :	The use of a prescription medication in a manner other than that for which it was prescribed. This can include recreational use of a prescription drug.
Acetylcholine:	Neurotransmitter at cholinergic synapses in the central sympathetic, and parasympathetic nervous systems.
Acidic:	A pH less than 7.0
Action potential:	Short-lived electrical nerve impulse, created when a neuron is stimulated. The impulse spreads like a wave along the length of the nerve cell.
Acupuncture:	A procedure that originated in Far Eastern medical traditions that involves inserting needles into specific locations of the body to relieve pain and other symptoms. This is different than dry needling and moxibustion.
Acute pain:	Short-term pain experienced after surgery or a traumatic injury
Acute:	Having a short course.
Addiction:	(see Psychological dependence)
Addison's disease:	A deficiency of the adrenal cortex and therefore the hormones produced in this area.
Adenoma:	Benign tumor which arises from or resembles glandular tissue.
Adjuvant:	Adjuvant drugs are medications that are not analgesics, but that may reduce pain or improve other symptoms associated with chronic pain. The term adjuvant itself means an aid or assistant and the adjuvant drug is typically given as an additional medication to augment pain control.
Adsorption:	A process by which a thin layer of a material is attached to another, as when molecules of medication are attached to beads. This term is similar in spelling, but different in meaning, to the more familiar term, absorption.
Afferent:	Conducting toward the center (e.g., sensory nerve).
Affinity:	Goodness of fit.
Agonist:	Drug that binds to and stimulates physiological activity at cell receptors normally stimulated by naturally occurring substances.
Agonist-antagonist:	Medication that has one effect at low doses and a different effect at higher doses. For example, at low doses, the drug may act as an agonist, but acts as an antagonist at higher doses. Example: Buprenorphine
Alkaline:	A pH greater than 7.0
Allergy:	Unusual hypersensitivity when exposed to a particular substance (allergen).
Allodynia:	Condition in which ordinarily nonpainful stimulus evokes pain.
Amblyopia:	Weakness in vision in one eye that can cause it to relax and drift relative to the other (also called lazy eye).
Ambulatory:	Walking or able to walk.
Amenorrhea:	Lack of menstrual periods.
AMES test:	A test for potential carcinogenic properties of a drug. It uses the rate of genetic mutations caused in a strain of the bacterium Salmonella.

Amphetamine: Powerful synthetic central nervous system stimulant.

Amylase: An enzyme that occurs in saliva and pancreatic juice and aids the digestion of starch. Amylase will also hydrolyze glycogen to yield glucose and other sugars.

Analgesia: Absence of pain.

Analgesic ceiling effect: A limitation of analgesic effect due to other effects of the drug. Opioid analgesics theoretically have no limit to the analgesic effects mediated by the mu receptor. However, opioids stimulate additional receptors that cause side effects that limit the maximum dose that can be given. For example, while morphine could theoretically be titrated upward indefinitely to control pain, high doses can cause respiratory depression, thus the actual maximum dose that can be given is limited by the risk of respiratory depression (and/or other side effects).

Analgesic: Relieving pain without causing loss of consciousness, or an agent that produces the same.

Analogue: A compound that resembles another in structure, but is nor necessarily an isomer.

Anaphylaxis: An unusual or exaggerated allergic reaction that may be life threatening.

Anatomical pathology: The actual physical disturbances in the body. For example, a broken leg is the anatomical pathology and leg pain is the symptom.

Anesthetic: Pertaining to loss of feeling or sensation, or an agent that produces the same.

Anorexia: Lack of a desire to eat. (The term is similar to 'anorexia nervosa' but these are different medical conditions.)

Antagonist: Drug that binds to a receptor site, inhibiting its action.

Anticoagulant: Stops blood clotting, or an agent with this effect.

Anticonvulsant: Preventing fits or convulsions, or an agent with the effect.

Antiemetic: A drug that prevents nausea.

Antisympathetic: Producing effects resembling those of interruption of the sympathetic nerve supply, or an agent which does the same.

Antitussive: Effective at relieving coughing. Antitussive effects associated with opioids are due to μ-receptor and possibly κ-receptor stimulation.

Anxiolytic: Reducing or preventing anxiety.

Apnea: Cessation of breathing.

Arrhythmia: Disturbance of the heart beat or rhythm.

Arthralgia: Joint aching.

Arthritis: Inflammation of a joint.

Ataxia: A lack of coordinated muscular movements that can result from neurologic disorders.

Atelectasis: Collapse of the alveoli (tiny air sacs) in the lungs.

Atrophy: Wasting away.

AUC: Area under the curve. Graphically, this is the area under a drug's absorption curve. It represents the amount of drug absorbed after a dose.

Autonomic nervous system: Part of the nervous system concerned with regulation of activity of heart muscle, smooth muscle, and glands.

Axial skeletal fusion: Calcification of the spinal column that leads to calcified connections between the bones, leading to a loss of motion.

Barbiturates: Group of sedatives derived from barbituric acid.

Baroreceptor reflex: A reflex response to activation of a sensory nerve terminal that is stimulated by changes in pressure. These receptors are located in the blood vessel walls.

Baroreceptors: Receptors that detect blood pressure.

Baseline dose: A dose of pain medication that is given consistently to achieve an acceptable level of pain control in a given patient. The pain control is effective most of the time in most situations but may require supplementation (e.g., the pain relief is effective during both the peaks and troughs of the serum drug levels).

Bedsore: An ulceration due to prolonged pressure from lying immobile in bed for too long (also known as decubitus ulcer).

Bile: A greenish-yellow bitter fluid produced in the liver and stored in the gall bladder. Bile which flows in bile ducts from the gall bladder to the intestine helps in the digestion and absorption of fat.

Biliary colic: Pain due to an obstruction(and subsequent increases in pressure) in the gallbladder or bile collecting system in the liver. This medical condition can be an adverse effect of opioid drugs. A few opioids, such as meperidine, fentanyl, and butorphanol, produce less pronounced increases in biliary tree pressure than morphine.

Biliary: Of the bile or bile ducts.

Bioavailability: The degree to which a drug will become available in the system after it is taken orally or injected (parenterally).

Bioequivalent drugs: Two drugs that are similar in absorption and physiologic activity.

Biofeedback: Process by which an individual is provided with information on the state of one or more physiological variables, such as heart rate or skin temperature; this often enables the individual to gain some voluntary control over them.

Biopsy: Removal and examination (usually through a microscope) of tissue from the living body to establish a precise diagnosis.

Biphasic absorption pattern: An absorption pattern of a drug that demonstrates two phases, with two distinct and separate serum drug peaks. This is seen in drug formulations in which some of the drug is released shortly after it is administered and the other part of the drug is released later.

Black box warnings: Warnings required by the FDA for a product. They are called "Black Box" because they are required to be placed in a black box in a prominent position in the pharmaceutical information for a given drug ("package insert").

Bleeding time: The amount of time it takes blood to clot.

Blood-brain barrier: Selective barrier which prevents substances in the blood from entering the central nervous system.

Bolus: large amount.

Brachial: Pertaining to the arm.

Bradycardia: Low heart rate.

Bradykinin: A naturally produced substance which dilates blood vessels, constricts to smooth muscle and stimulates pain receptors.

Brainstem: Stemlike portion of the brain connecting the cerebral hemispheres with the spinal cord; comprised of the pons, medulla (oblongata), and the midbrain.

Breakthrough pain: Pain that occurs before the next scheduled dose of analgesic. Can also refer to episodic pain that is not fully controlled with the current pain control regimen.

Bronchial: Pertaining to the bronchi (singular bronchus), i.e., the larger passages conveying air to the lungs.

Bronchoconstrictor: Substance which narrows airways.

Cachexia: General weight loss and wasting occurring in the course of chronic disease or emotional disturbance.

Carcinogenic: Any substance producing cancer.

Carcinoma: Malignant growth of epithelial cells.

Cardiac muscle: Muscle of the heart, composed of striated muscle fibers.

Cardiac: Pertaining to the heart.

Cardiogenic: Any substances producing cancer.

Cardiovascular: Pertaining to the heart and blood vessels.

Carpal tunnel syndrome: Entrapment of a large nerve at the wrist, causing pain and numbness in the palm and fingers.

CAT scan: (see Computerized axial tomography).

Catheter: Flexible tube passed through body channels for withdrawal of fluids from or introduction of fluids into a body cavity.

Causalgia: Burning pain, allodynia and disruption of the actions of the sympathetic nervous system in the affected region.

Ceiling affect (for analgesia): Property of a drug, which means that further increases in dose above a certain level will not result in increases in analgesia.

Central nervous system: Brain and spinal cord.

Central pain: Pain that results from injury or disease in the spinal cord or brain.

Cerebral cortex: Outermost convoluted layer of gray matter covering each cerebral hemisphere; responsible for conscious location of sensory stimuli, evaluation of sensory stimuli received from lower parts of the brain, sending instructions to muscles, organs, and glands, and intellectual processes and emotional responses.

Cerebral ventricular system: Interconnected system of spaces within the brain filled with cerebrospinal fluid.

Cerebrospinal fluid: Liquid which circulates around the brain and spinal cord.

Cerebrum: Main portion of the brain, occupying the upper part of an organ (e.g., of the uterus).

Chemoreceptor trigger zone: Region of the medulla which, when stimulated, activates the adjacent emetic center which is responsible for vomiting.

Chemotherapy: Treatment of disease by chemical agents.

Chronic benign pain: Pain from problems that are neither fatal nor curable.

Chronic obstructive pulmonary disease (COPD): Condition in which irreversible damage to lung tissue, generally as a result of smoking, leads to a reduction in respiratory capacity.

Chronic: Persisting for a long time.

Cimetidine: A drug that reduces the production of stomach acid (also called Tagamet®).

Circulatory depression: A reduction in the activity of the heart and normal tone of the blood vessels and can be a side effect of opioids. The clinical findings are low blood pressure and a slow pulse.

Circulatory shock: Failure of the circulatory system to maintain adequate blood supply to vital organs.

Cirrhosis: Progressive disease characterized by diffuse damage to parenchymal cells, especially of the liver.

Clearance: Volume of plasma cleared of a drug per unit of time. It is a measure of the body's ability to eliminate a drug from the body.

Cmax: Maximum concentration in the blood of a drug after dosing.

Cmin: Minimum concentration in the blood of a drug after dosing.

Coanalgesics: Pain-relieving agents used in conjunction with other analgesics.

Colic: Severe, cramping, visceral pain caused by spasm of smooth muscles in the wall of hollow organs.

Compliance: Adherence to a prescribed regimen.

Computerized axial tomography (CAT, CT) scan: Technique which provides cross-sectional images of internal structures from information obtained by passage of x-rays through the body.

Congener: (also spelled cogener) A substance that is chemically related to another. A member of the same kind, class, or group.

Conjugation: This is one of the metabolic processes performed by the liver to deactivate drugs in preparation for elimination. The reaction joins a drug with another molecule to produce a form that can be eliminated by the kidney. A drug changed by this type of metabolism is sometimes referred to as a conjugate.

Constriction: Narrowing.

Contracture: Abnormal shortening of muscle tissue, rendering the muscle highly resistant to passive stretching.

Contraindication: Circumstance which means a drug should not be considered appropriate treatment.

Contralateral: On the other side.

Contrast media: A substance which when injected into blood vessels can be seen on x-ray film. It can help define the position, size, and shape of tumors.

Controlled-release drug: The rate at which an oral drug is absorbed depends partly on how quickly it is dissolved in and absorbed from the digestive tract. A drug can be chemically altered (e.g. the pH is altered, causing absorption to be delayed) or placed into a delivery system that alters the rate of release of the drug into the digestive tract in a predictable manner, allowing control over how quickly the drug is absorbed into the system.

Coping skill: A means of dealing with difficult or stressful situations.

Cordotomy: A surgical procedure involving the division of the spinothalmic tract. The spinothalmic tract contains the nerve fibers responsible for transmitting the sensation of pain up the spinal cord.

Cor pulmonale: Heart disease which develops as a result of lung disease, leading to thickening of the walls of the chamber of the heart (right ventricle) which pumps blood to the lungs.

Corticosteroid: A hormone produced by the outer layer (cortex) of the adrenal gland, or any synthetic equivalent; used clinically to reduce inflammation and for other purposes.

Corticotropin-releasing factor: Hormone released from the hypothalamus which is responsible for the synthesis and release into the bloodstream of hormones from the pituitary gland.

Cough reflex: Involuntary protective mechanism for explosively removing foreign matter or sources of irritation from the air passages of the lungs.

Counter-irritation: Irritation or much inflammation of the skin exerted for the purpose of relieving symptoms of an inflammation of the deeper structures.

Cranial nerves: Twelve pairs of nerves directly connected with the brain, including the nerves of sight, smell, eye movement, hearing, etc.

Craving: An extremely strong psychological desire to use a substance.

Cross-dependence: The "transfer" of dependence on one substance (e.g., opioid) to another.

Crossover abuse: Shifting patterns of abuse from one substance to another, for example, an individual stops using cocaine but starts drinking heavily.

Crossover group: Each subject is given each treatment (double crossover repeats crossover design).

Cross-tolerance: The "transfer" of tolerance from one substance (e.g., opioid) to another.

CT scan: (see Computerized axial tomography).

Cytochrome (CYP) P450 system: This refers to a family of liver enzymes involved in the metabolism of various substances in the body, including drugs. The term is often abbreviated to CYP and then the number of the specific member of the family is given. These enzymes include CYP3A3/4, CYP1A2, and CYP2D6, which are involved in the metabolism of various opioids.

Deafferentation pain: Pain which results from instability and spontaneous discharge of spinal cord nerves that have lost normal incoming sensory stimuli.

Dealkylation: To remove a chemical alkyl group from a chemical structure. This is one way the body metabolically alters drugs into inactive forms.

Decubitus ulcer: An ulceration of the skin caused by pressure over a bony prominence. (Bed sore)

Delayed gastric emptying: Slow transit of stomach contents out and into the intestine. This can result from drug side effects or disease states.

Delayed release: A drug formulation that delays the release of a drug until it has passed out of the stomach and into the intestine.

Delirium tremens: An alcohol withdrawal syndrome that results in confusion and hallucinations. (DTs)

Demographics: Distribution throughout the population.

Dendrite: Extension of the neuron which receives and conducts nervous impulses towards the cell body of a neuron.

Dependence: A state in which the usual or increasing doses of a drug are required to prevent the onset of withdrawal symptoms. A state in which a withdrawal syndrome develops if a medication is stopped suddenly.

Dermatome: Area of skin supplied with nerve fibers from a single spinal nerve root.

Descending pathways: Nerve fibers that travel down the spinal cord from the brain and inhibit incoming pain signals.

Detoxification: Tapering a medication to prevent withdrawal symptoms.

Detrusor muscle: The muscle in the bladder that contracts to initiate urination.

Diagnosis: Determination of the nature of a cause of a disease.

Diaphoresis: Sweating.

Dilation: Increase in diameter or caliber.

Diplopia: Double vision.

Disc (intervertebral): Layer of fibrous cartilage between adjacent vertebrae.

Distention: Swelling out by pressure from within.

Distraction: Diversion of attention (e.g., from pain)

Distribution: The extent of and processes by which a drug enters and remains in different areas (compartments) of the body.

Diuretic: Increasing urine output, or agent which has the same effect.

Diversion: The act of giving one's prescription drugs to others for their use. This may be done in exchange for money.

Dorsal horn:	Horn-shaped structure of the gray matter of the spinal cord, of particular importance in receiving incoming sensory impulses from the periphery and the transmission of outgoing motor impulses to the appropriate peripheral nerves.
Dose Titration:	Adjustment of a dose to achieve the best therapeutic response with a minimum of undesirable side effects.
Dosing interval:	The time between administration of doses.
Double blind:	Neither the patient nor the physician is aware of actual treatment.
Drug holiday:	A period during which a drug is not used to allow restoration of normal function of tissues which are adversely affected by the drug.
Drug metabolism:	The process of changing a drug from an active form to a less-active or inert form before it is eliminated from the body. This can occur by means of enzymes in the liver or the kidney.
Duodenum:	First part of the small intestine.
Dura mater:	Outermost membrane surrounding the brain and the spinal cord.
Dysesthesia:	An unpleasant abnormal sensation produced by normal stimuli or abnormal sensations experienced in the absence of stimulation.
Dyspepsia:	Impairment of the function of digestion; usually applied to epigastric discomfort after meals.
Dysphagia:	Difficulty in swallowing.
Dysphoria:	Disquiet, restlessness, anxiety.
Dysplasia:	Abnormality of development, size, shape, or organization of cells.
Dysplastic:	Pertaining to dysplasia.
Dyspnea:	Labored or difficult breathing, “breathlessness”.
Edema:	Excessive accumulation of fluid in a tissue.
Efferent:	Conveying away from a center.
Elimination half-life:	The amount of time it takes the body to eliminate half of a dose of a drug that has been fully absorbed.
Embryocidal:	Causes death of an embryo in pregnant women.
Emesis:	Vomiting.
Encephalopathy:	A disease or process causing abnormalities in the tissue of the brain.
Endocrine:	Pertaining to hormones.
Endogenous:	Produced within or caused by factors within the body.
Endorphins:	General term for the endogenous opiate-like (opioid) neurotransmitters.
Enema:	Solution introduced into the rectum to promote evacuation of feces.
Enkephalin:	Endogenous opiate-like (opioid) neurotransmitter.
Enterohepatic:	Pertaining to the intestine and liver.
Enzyme:	Protein produced in a cell which is capable of greatly accelerating a chemical reaction.
Epidemic:	Affecting a large number of individuals within a population.
Epidural:	External to the dura mater, the outermost membrane surrounding the brain and the spinal cord.
Epigastrium:	The upper and midline region of the abdomen.
Epithelium:	Cellular covering of internal and external body surfaces.

Equianalgesic dose: The dose of a given drug that is required to reach the same degree of activity as another drug. In the case of opioids, morphine is the standard used to compare potency. Doses of other opioids are often compared to morphine to determine doses that offer equivalent activity.

Equianalgesic: Producing the same degree of analgesia.

Exclusion criteria: Variables used to eliminate patients from the study.

Excrete: The process of actively eliminating a molecule from inside a cell into a cavity for the purpose of removing it from the system. For example, a drug molecule may be excreted by a kidney cell into the collecting system of the kidney where it will be transported into the urine.

Excretion: The elimination of a substance, such as a drug, from your body.

Extended-release: A drug formulation that releases the drug over an extended period of time.

Extent of absorption: The degree to which a dose of medication is taken up into the system from the site of administration.

Fellowship trained: Having 1 year or more of additional medical training specifically in pain management in an accredited pain management program. The term also applies to subspecialty training of other types that goes beyond the usual residency training period.

Fibrosis: Formation of thickened, scar-like tissue, usually as a result of injury.

Fibrous tissue: Common connective tissue of the body, i.e., tissue which binds together and is the ground substance of the various parts and organs of the body.

First-pass metabolism: Metabolism of a drug that occurs during its first passage through the liver in the circulation, right after absorption from the intestine.

Fixation: Process of making immovable.

Flaccidity: A decrease in muscle tone.

Focal: Localized to specific areas.

Formulation: The form a drug is in for administration. For example, an oral formulation is a form that is meant to be taken orally (by mouth).

French: A measurement scale used for denoting the external diameter of catheters, sounds, and other tubular instruments. The scale is expressed in units, and each unit equals about 0.33mm. Thus, a 16-French catheter has a 5.3-mm external diameter (16 X 0.33mm).

Gamma knife: Specialized machine that projects a very tightly focused beam of radiation.

Gastric emptying: The process of the body moving the contents of the stomach into the small intestine.

Gastric stasis: A relaxation of the stomach that causes it to not digest or propel its contents into the small intestine.

Gastric: Pertaining to the stomach.

Gastrointestinal: Pertaining to the stomach and the intestines.

Gastrostomy tube: A tube inserted through a gastrostomy opening into the stomach of a patient used for feeding. It is also known as a "G-tube" or a "feeding tube." There is a small balloon on the tube that is inflated within the stomach to prevent the tube from falling out and a closed port on the end of the external section of the tube that can be opened to allow fluids and medications to be administered. Water and other fluids can be flushed through the tube from the opening of the port to clear obstruction or to make sure all the material introduced has fully passed through into the stomach.

Gastrostomy: The creation of an opening in the stomach through which a tube is placed to allow administration of fluids, food, and medications in individuals who cannot swallow.

Genitourinary: Of or pertaining to the urinary and genital systems.

Gland: An aggregation of cells specialized to release materials not related to their ordinary metabolic needs.

Half-life ($t_{1/2}$): Time required for an organism to eliminate one-half of a substance that has been introduced into it.

Hematological: Pertaining to blood.

Hematopoiesis: Formation of blood cells.

Hepatic: By or of the liver.

Hepatitis: Inflammation of the liver.

Heredity: Genetic transmission of particular qualities or characteristics from parents to offspring.

Herpes zoster: Reactivation of dormant chickenpox virus in spinal nerve roots, leading to blistering and severe pain (herpetic neuralgia) in the dermatone of the affected nerve root.

Herpetic neuralgia: (see Herpes zoster). Post-herpetic neuralgia

Hesitancy: Difficulty in starting urination.

Histamine: Endogenous substance which has a number of activities, including dilation of small blood vessels, reduction of blood pressure, and mediation of certain hypersensitivity reactions.

Histology: Microscopic anatomy of tissues.

Histopathology: Microscopic anatomy or investigation of diseased cells.

Hormone: Chemical messenger produced in the body, and carried in the blood to another organ or part which has a specific effect on the activity of certain cells or organs.

Hospice: Organization that provides palliative and supportive care for terminally ill patients and their families.

Hydrophilic: Literal translation is "water-loving." This refers to the ability of a chemical or agent to easily dissolve into water.

Hyperalgesia: Abnormal sensitivity to pain that causes normal sensations to be interpreted as pain and painful sensations to be more intense.

Hypercalcemia: Abnormally high levels of calcium in the blood.

Hypercapnia: The presence in the blood of an unusually high concentration of carbon dioxide.

Hypercathia: Exaggerated subjective response to painful stimuli.

Hyperesthesia: Increased sensitivity to stimulation.

Hyperpyrexia: Increased body temperature (fever).

Hyperreflexia: Excessively increased reflexes.

Hypersensitivity: State in which the body overreacts exaggeratedly to a foreign agent, e.g., a drug or chemical.

Hypertension: Elevated blood pressure.

Hypertrophy: Enlargement.

Hypnotic: Produces drowsiness and/or sleep.

Hypophysectomy: Removal of the pituitary gland.

Hypotension: Low blood pressure.

Hypothalamus: Part of the brain lying, above the pituitary gland; it is responsible for activating, controlling, and integrating peripheral autonomic mechanisms, endocrine activities, and many somatic functions.

Hypothyroidism: Low levels of thyroid hormones.

Hypoxemia: Abnormally low blood oxygen levels.

Hypoxia: A deficiency of oxygen in a tissue.

Ileus: Paralysis (usually temporary) of the bowels, which typically leads to constipation and abdominal distention. More severe ileus can cause nausea and vomiting as well.

Immediate-release: A drug that is absorbed quickly after administration.

Immunity: The body's natural defense system.

Immunocompromised: State of impaired immunity.

Impaction: State of being wedged in firmly.

In vitro: Within a test tube.

In vivo: Within the living body.

Inappropriate ADH secretion: A syndrome in which antidiuretic hormone (ADH) is secreted abnormally.

Incidence of abuse: The frequency that a certain drug is reported to be abused by legal agencies. Overdoses, overdose deaths, and arrests for illegal sales are the usual sources of such numbers.

Incidence: The rate at which disease occurs.

Incident pain: Pain that occurs in addition to a chronic-pain patient's usual pain. An example would be cancer pain that is intensified by extra physical activity.

Inclusion criteria: Variables used to define the patient population.

Incontinence: Inability to control discharge of urine or feces.

Indication: Approved reason for using a drug.

Infarction: Death of tissue that occurs when its arterial blood supply is cut off; the tissue dies because of lack of oxygen.

Inflammation: A protective response to injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissues. The classical signs of acute inflammation are pain, heat, redness, and loss of function.

Innervation: Distribution or supply of nerves to a part.

Intercostal: Between the ribs.

Internist: Specialist in internal medicine.

Intracerebral: Within the brain (specifically the cerebrum).

Intracranial pressure: Pressure within the cranium.

Intracranial: Within the skull

Intractable: Resistant to cure, relief, or control.

Intramuscular: Into the muscle. This term is used for injections of medications that require administration deep into the muscle tissue.

Intranasal: Within the nose.

Intraperitoneal: Within the membrane of the abdominal cavity.

Intraspinal: Within the spine.

Intrathecal: Within the cerebrospinal fluid.

Intravenous: Within a vein.

Jaundice: Yellowness detectable in the skin and the whites of the eyes due to excessive amounts of bile pigments in the blood and tissue fluids. Jaundice may be the result of a liver disorder, gallstones blocking the flow of bile, or a number of other disorders.

Kappa receptor: (also spelled κ receptor) One of the 3 major opioid receptor types in the central nervous system. This receptor is a molecule on the nerve cell that, when activated by an agonist (e.g. morphine), leads to decreased pain signal transmission. This has been named the OP2 receptor by the International Union of Pharmacology.

Kyphoscoliosis: Deformity involving forward and sideways curvature of the spine.

Lancinating: Tearing, darting, or sharply cutting; said of pain.

Large intestine (bowel): The part of the gastrointestinal tract which extends from the small intestine to the anus; it includes the cecum, the colon, and the rectum.

Larynx: Voice box.

Laxative: Agent which promotes evacuation of feces from the bowel.

Lethargy: Extreme drowsiness from which it is difficult to rouse an individual.

Leukocytes: White blood cells.

Limbic area: Primitive area of the brain which is primarily associated with the sense of smell, autonomic functions, and certain aspects of emotion and behavior.

Linear accelerator: A machine that projects a beam of radiation.

Linear pharmacokinetics: Having absorption and elimination properties that lead to a proportional relation between dosing and serum drug concentrations.

Lipid: Fat or fat-like substance.

Lipophilic: Literal translation is "fat-loving." This refers to the ability of a chemical or agent to easily dissolve in lipids, fats, or oils. These agents easily cross cell membranes, because cell membranes are composed of lipids and proteins.

Lumbar spine: The five vertebrae (L1 to L5) in the posterior wall of the abdominal region which connect the thoracic vertebrae to the sacrum. The lumbar vertebrae are the largest vertebral bodies in the spine.

Lumbosacral: Usually pertaining to the joint between the lowest lumbar vertebra and the sacrum, or that general area.

Luteinising hormone: One of several hormones included in the menstrual process.

Lymph nodes: Accumulations of lymphoid tissue along the course of lymphatic vessels; they serve as a defense mechanism by removing noxious agents from the lymph.

Lymph: Transparent yellowish fluid collected from tissues and returned to the blood via lymphatic vessels.

Lymphatic system: Lymphatic vessels and lymphoid tissue, considered collectively.

Lymphatic vessels: Channels for carrying lymph back to the blood.

Lymphocytes: Cells specialized for fighting infection and cancer.

Magnetic resonance imaging (MRI): Technique which provides images of internal structures from information obtained by application of a magnetic field to tissues.

Malaise: A generalized uncomfortable feeling that may be accompanied by physical discomfort.

Malignancy: Cancer, i.e. tumor(s) with malignant properties.

Malignant: Threatening life or tending to cause death. When referring to tumors: Having the properties of anaplasia, invasiveness, and metastasis.

Mastectomy: Surgical removal of a breast.

Matrix: The substances, other than the active drug, contained in a pill or capsule.

Medulla (oblongata): Part of the brain continuous with the pons above and the spinal cord below.

Melanin: Dark pigment of the skin, hair, and other parts of the body.

Meningeal: Pertaining to the membranes covering the brain and the spinal cord (the meninges).

Metabolism: 1.) The physical and chemical processes essential for an organism to live, and also the transformation by which energy is made available for the use of the organism. 2.) The interactions of a drug with the body's biochemical processes. It usually results in a drug's structure and properties changing.

Metabolite: A product of metabolism. A byproduct of a drug that has undergone chemical changes due to biochemical processes in the body.

Metastasis: Secondary site of cancer which develops as a result of spread of cancer cells from the primary site to other parts of the body.

Metastatic tumor: A tumor that has spread to a distant site from the original tumor.

Micturation: Voiding of urine.

Midbrain: Uppermost part of the brainstem, connecting the latter to the cerebral hemispheres.

Migraine: Intense, throbbing headache, usually confined to one side of the head, caused by dilation or blood vessels in the head.

Miosis: Constriction of the pupil of the eye.

Misuse : Using a prescribed drug for a reason other than that for which it was prescribed or in a manner other than that for which it was prescribed.

Mixed agonist-antagonist: Drug which acts as an agonist at one receptor but an antagonist at another.

Monoamine oxidase inhibitor: A type of drug used to treat depression.

Morphine-3-glucuronide (M3G): The predominant metabolite of morphine that has opioid antagonistic effects.

Morphine-6-glucuronide (M6G): A metabolite of morphine that has analgesic properties.

Motility: Ability to move spontaneously.

Motor: Producing or subserving motion

Mouse micronucleus test: This is a commonly used test that determines whether a compound is able to cause chromosome aberrations in mice. It is used to predict genotoxicity (teratogenicity) of a new drug.

MRI: (see Magnetic resonance imaging).

Mu receptor: (also spelled μ receptor): One of the 3 major opioid receptor types in the central nervous system. This receptor is a molecule on the nerve cell that, when activated by an agonist (e.g. morphine), leads to decreased pain signal transmission. This has been named the OP3 receptor by the International Union of Pharmacology.

Mucous membrane: Membrane which secretes mucus, a slime composed of the secretions of glands, dead cells, white blood cells, etc.

Multimodality treatment: Combination of chemotherapy, radiotherapy and surgery for treatment (of cancer).

Multiple group: One or more subject groups (usually one group is a control group).

Multiple sclerosis: Disease in which patchy loss of myelin throughout the white matter (mostly) of the central nervous system leads to weakness, lack of coordination, paresthesias, speech disturbances, and visual complaints.

Mutagenic: An agent that increases the rate of mutation.

Mutation: Permanent change in genetic makeup, i.e., DNA.

Myalgia: Pain in the muscles.

Mydriasis: Dilation of the pupil.

Myelin: Lipid substance surrounding the axons of myelinated nerve fibers which facilitates orderly and rapid transmission of nerve impulses along the axon.

Myelopathy: Disease or disorder of the spinal cord.

Myoclonic jerks: Mild to moderate muscle contractions.

Myoclonus: Spasmodic muscle contractions.

Myxedema: A dry firm waxy swelling of the skin and subcutaneous tissues found in patients with underactive thyroid glands.

n or N: The number of patients participating in the experiment.

Naloxone/naltrexone: Two opioid antagonists; medications that reverse the effects of opioids.

Narcotic: (see opioid) 1.) Having the property of depressing activity of the central nervous system and, in large doses, inducing sleep. 2.) Legal term for opioid agent. 3) Abused substances

Nasogastric tube: A tube of soft rubber or plastic that is inserted through a nostril into the stomach. This tube is used for various problems, including decompressing/draining the stomach of gas or digestive fluids if it becomes distended due to obstruction. Nasogastric tubes are of a relatively small diameter to maintain patient comfort, therefore are prone to blockage if material (e.g. medications or food) are administered through them.

Necrosis: Death of cells, tissue or part of an organ.

Neonate: Newborn infant.

Neoplasia: New or abnormal growth of tissue.

Neoplasm: Tissue formed by neoplasia.

Nerve block: An injection of anesthetic near a major nerve. A steroid may be added to the injection for therapeutic or diagnostic purposes.

Nerve fiber: A long, typically singular branch of the nerve cell that relays messages to and from the area it serves. These branches can be several feet long in the extremities. A fiber is also called an axon.

Nerve roots: Paired bundles of nerve fibers which emerge at each level of the spinal cord.

Nerve tract: A bundle of nerve axons that run together within the spinal cord or brain, functioning in a manner similar to a nerve.

Nerve: A bundle of nerve axons (outside the brain or spinal cord) that run together within a connective tissue sheath.

Nervous system: Organ system which (along with the endocrine system) correlates the adjustment and reactions of the body to its internal and external environment; comprised of the central and peripheral nervous systems.

Neural blockage: (see Nerve block).

Neural: Pertaining to nerves.

Neuralgia: Pain in the distribution of a single injured or irritated nerve.

Neuralgic pain: Localized pain resulting from damage to a single nerve.

Neuroendocrine system: Collective name for elements of the nervous and endocrine systems, particularly as they interact in the control of body functions.

Neuroleptic: Antipsychotic or psychotropic.

Neurological: Originating from the nerves or nervous system.

Neurology: Science of the nervous system.

Neurolytic: Destruction of nerves.

Neuroma: Tumor or new growth of nerve cells and nerve fibers.

Neuron: A nerve cell, including its body and its dendrites (very short branch-like extensions of the cell body) and axon.

Neuropathic pain: Pain which arises from diseased or damaged nerves.

Neuropathic: Generated by the nerves. Neuropathic pain is that which is generated as a result of damage to a nerve.

Neurosurgery: Surgery of the nervous system.

Neurotoxic: Damaging to nerve tissue.

Neurotransmitter: A chemical substance released from the end of a nerve cell which diffuses across a synaptic cleft to excite or inhibit a target cell (another nerve cell or an organ cell)

NMDA receptor: A subtype of glutamate receptor on neurons. Binding with N-methyl-D-aspartate (NMDA) to these receptors opens calcium channels, allowing signal transmission (e.g. pain signal transmission).

Nociception: The detection of noxious stimuli and transmission of information (nervous impulses) about these in sensory nerves. The perception of pain.

Nociceptive: Relating to the perception of pain. A nociceptive receptor is a pain signal receptor.

Nociceptor: Receptor stimulated by injury or noxious stimulus (pain receptor).

Nomenclature: Classified system of names.

Noncardiogenic pulmonary edema: A build-up of fluid in the lungs that is not caused by heart failure.

Nonlinear pharmacokinetics: Having absorption and elimination properties that lead to a nonproportional relation between dosing and serum drug concentrations. This means that responses to changes in doses are more difficult to predict.

Nonopioid analgesic: A medication that reduces pain through mechanisms other than through stimulating or blocking opioid receptors on nerve cells in the central nervous system. The mechanisms of action of various nonopioid analgesics differ. Barbiturates, such as butalbital, inhibit the gamma-aminobutyric acid neurotransmitter receptors to block signal transmission. Acetaminophen is conjugated with arachidonic acid to form N-arachidonoylphenolamine, a compound known as an endogenous cannabinoid which is responsible for its analgesic effect. Acetominophen has also been thought to exert its analgesic effect by inhibiting prostaglandin synthesis in the brain (the prostaglandin inhibition results in a minimal amount of anti-inflammatory effect that is not clinically significant and does not contribute to the analgesic

effect). The release of phospholipid from injured cell membranes is converted to arachidonic acid, which in turn is metabolized by a cyclooxygenase or lipoxygenase to produce prostaglandins and other chemicals that mediate inflammation. Non-steroidal anti-inflammatory drugs, such as naproxen sodium, inhibit prostaglandin production, thereby reducing pain signal transmission, and reduce inflammatory responses that contribute to pain.

Nonsteroidal: Drugs that reduce inflammation but which are not anti-inflammatory corticosteroids agents (NSAIDs). (Nonsteroidal Anti-Inflammatory Drugs)

Noradrenaline: Neurotransmitter and hormone; plays chief role (norepinephrine) in the transmission of information in the sympathetic nervous system, and is also a powerful blood pressure-elevating substance.

Noxious: Hurtful, injurious.

Nystagmus: An abnormal sideways or up-and-down movement of the eyes that is associated with neurologic abnormalities or disease of the vestibular apparatus of the ear.

Objective criteria: clearly defined variables with exact measurements. Example: visual and numeric analog pain scales.

Occult: Hidden, unrecognized.

Oliguria: Diminished urine output.

Oncologist: A physician specializing in cancer treatment.

Open label: Both patient and physician are aware of actual treatment.

Opiate: Alkaloids (morphine and codeine) obtained from the opium poppy plant.

Opioid naïve: This refers to a patient who is not currently or who has not recently been treated with opioids. Opioid-naïve patients have not developed tolerance to the effects of opioids and therefore are started at the low recommended doses.

Opioid phobia (opiophobia): Irrational fear of using strong opioids, especially morphine.

Opioid receptors: A receptor is a group of cell membrane proteins in nerve cells that cause certain responses in the cell when stimulated or blocked by ligands. Opioid receptors are stimulated or blocked by opioids. There are different classes of opioid receptors, including delta opioid receptors (also known as OP1 receptors), kappa opioid receptors (also known as OP2) receptors, and mu opioid receptors (also known as OP3). Activation of these receptors stimulates specific activities within the activated cell, causing effects such as analgesia, nausea, or somnolence. Blockage of the effects of some types of receptors can cause effects such as anorexia or decreased prolactin release.

Opioid tolerant : This refers to a patient who has been taking opioids and has developed physical tolerance to some of the effects of opioids, such as respiratory depression.

Opioid: A drug that is chemically similar to or derived from opium. These drugs act at opioid receptors on nerve cells in the central nervous system to reduce transmission of painful stimuli/impulses.

Oral: Pertaining to or by the mouth.

Oralet: Medication in a lozenge form.

Organ: A relatively independent body part that performs a special function, e.g., brain, liver, heart.

Orthopedic: Pertaining to the skeletal system (bones, muscles, joints, etc).

Orthostatic hypotension: Drop in blood pressure upon standing.

Osmosis: Process of spontaneous movement of a substance through a membrane from a solution of higher concentration to one of lower concentration.

Osteoclasts: Cell that breaks down bone.

Pain behaviors: Exaggeration or magnification of the effects of pain.

Palliative: Attempting to relieve symptoms without curing the disease.

Pallor: Paleness.

Palpitations: Discernible irregularities of heart beat.

Pancreas: Large gland in the abdomen that secretes digestive enzymes and hormones.

Pancreatic duct: Channel through which secretions from the pancreas empty into the intestine.

Pancreatitis: Inflammation of the pancreas.

Pancuronium: A drug used in anesthesia that paralyzes skeletal muscle.

Parallel group: Two or more subject groups studied simultaneously.

Paralytic ileus: A side effect of opioids that manifests as a functional stoppage of the bowel. The bowel stops all contractions in response to the drug and rather than being digested, the contents build up, leading to severe bloating, constipation, and vomiting. In rare cases of severe paralytic ileus with massive dilation of the colon, decompression with colonoscopy and selective use of neostigmine may be necessary. In select patients who cannot be treated with decompression, percutaneous endoscopic colostomy or other invasive procedures may be necessary.

Paraneoplastic effects: Tumor-induced changes produced in tissues remote from a tumor or its metastases.

Paraspinal: Beside the spine.

Parasympathetic nervous system: Part of the autonomic nervous system which innervates the heart, smooth muscle, and glands of the head and neck, and the thoracic, abdominal, and pelvic viscera, usually decreasing their activity.

Parenteral: A non-oral route of administering medicine. This includes intravenous, intramuscular (an injection), rectal suppository, or transcutaneous (through the skin, as with a skin patch).

Paresthesia: Disordered, abnormal sensation, e.g., burning, prickling, etc.

Partial agonists: Agents that are only partly effective as agonists. Partial opioid agonists have actions at the opioid receptors that are not as strong as agonists.

Paroxysmal: Relating to a sudden onset of a symptom or disease, especially one with recurrent manifestations.

Pathognomonic: Denoting a sign or symptom that is characteristic enough of a condition that it can be used to diagnose that condition.

Pathological fractures: Fractures caused by tumor invading and destroying bone.

Pathology: Science of disease, including the causes of disease and their effect on the structure and functions of body tissues.

Peptic: Relating to the action of gastric digestive juices (which contain pepsin and acid).

Peptide: A naturally occurring compound of two or more amino acids.

Peptides: Constituents of proteins.

Percutaneous: Performed through the skin.

Peripheral nervous system: Nerves which connect the brain and spinal cord to the rest of the body.

Peripheral neuropathy: Pain in the feet and hands resulting from damage to the long nerve fibers that supply the limbs.

Peristalsis: Propulsive coordinated movements which transport food and the by-products of digestion along the gastrointestinal tract.

pH: A logarithm scale used to measure the degree of acidity or alkalinity of a given substance. A lower pH is associated with acidity and a higher pH is associated with alkalinity.

Phantom limb pain: Sensation, after a limb has been amputated, that the absent part is still present and painful.

Pharmacodynamics: Describes the effects of a drug on the body and the relationship between the size of a dose and the degree of these effects. These effects would include therapeutic effects as well as side effects.

Pharmacokinetics: A branch of pharmacology dedicated to the determination of the fate of substances (primarily drugs) administered to a living organism (usually humans). The term is derived from the greek words "pharmacon" (meaning drug) and "kinetikos" (meaning putting in motion). Specifically, this branch of study focuses on the absorption, distribution, metabolism and excretion of pharmaceutical agents.

Pharmacology: Science of the origin, nature, chemistry, effects, and uses of drugs.

Pharmacotherapy: Treatment of disease with medications.

Phase I reactions: One set of enzymatic processes in the liver that metabolize drugs. Phase I reactions include oxidation, hydrolysis, and reduction.

Phase II reactions: One set of enzymatic processes in the liver that metabolize drugs. Phase II reactions include conjugation to form glucuronides, acetates, or sulfates.

Phenothiazine: One of a group of major tranquilizers.

Physical dependence: State of physiological change that arises through continuous use of a drug.

Physiologic: Originating from the physical processes of the body.

Physiology: Science of normal functions of the body.

Piloerection: Erection of the hair (forming "goose bumps" or "goose flesh").

PISCES: Percutaneous Inserted Spinal Cord Electrical Stimulation.

Pituitary gland (hypophysis): Gland situated below the hypothalamus, divided into anterior and posterior sections (lobes), responsible for the production of several important hormones.

Placebo: An inactive substance or preparation given to satisfy the patient's symbolic need for drug therapy. It is also used as a disguise in drug studies to prevent the patient or the physician from being aware of whether the patient is on active or inactive treatment.

Plasma terminal half-life: The amount of time it takes for the drug levels that are already present plus the drug added by a recent dose to fall to half of the peak level. This is applied to drugs for which a steady level is intermittently augmented with additional breakthrough doses.

Plasma: Fluid portion of blood.

Platelets: Small independent cell-like bodies in the blood that help form clots. They are actually cell fragments that break off a parent cell (megakaryocyte) and form clots by adhering to damaged tissue.

Plexopathy: Disorder or disease of a nerve plexus.

Plexus: Large network of nerves.

Polymer: Compound formed by the linear combination of simpler molecules.

Polyneuropathy: Disease process involving a number of peripheral nerves.

Polypharmacy: Taking multiple drugs concurrently. Polypharmacy may be necessary to manage a patient's medical condition(s), however, it increases the potential for side effects and drug interactions.

Polysubstance abuse: Abusing several different types of drugs, i.e., alcohol and cocaine and opioids, either together or at different times.

Portal circulation: Blood vessels which collect and transport digested substances from the gastrointestinal tract to the liver.

Postherpetic neuralgia: Pain persisting after an attack of herpes zoster.

Postsynaptic neuron: Neuron which receives a neural impulse at a synapse.

Postural hypotension: Decrease in blood pressure on standing.

Potency: The strength of a drug's effects. This is not to be confused with a higher dose. A very potent drug can have powerful effects at very low doses, whereas a drug with low potency will require large doses to have any effect.

Presynaptic neuron: Neuron which transmits a neural impulse before it interacts with another.

PRN: An acronym made from the Latin 'pro re nata', which means as needed. It is typically used in medical orders and prescriptions.

Pro-drug: A drug that must be metabolized by the liver before it becomes active in the body.

Prognosis: Forecast of the probable course and outcome of a disorder.

Prophylactic: Preventive.

Prostaglandins: Naturally occurring compounds with a variety of actions, including some of the local effects of inflammation.

Prostate: Gland surrounding the neck of the bladder and urethra in males.

Prostatic Hypertrophy: Enlargement of the prostate gland.

Protein: Complex compound which is the principal constituent of cells and which also makes up enzymes, structural elements, hormones, etc.

Protein-binding: The property of drugs that causes them to adhere to proteins in the serum.

Pruritus: Itching.

Pseudoaddiction: Behaviors (that mimic addiction behaviors) exhibited by patients with inadequately treated pain.

Psychogenic pain: Pain which arises "from the mind".

Psychological dependence: Behavioral pattern characterized by a craving for the drug (addiction) and an overwhelming concern with obtaining it.

Psychological: Originating from the conscious or subconscious mind.

Psychosis (Psychotic disorders): Major mental disorders marked by derangement of personality and loss of contact with reality.

Psychostimulant: Agent that produces increases in cerebral activity.

Psychotomimetic effects: Side effects of drugs that affect mood and thinking.

Psychotomimetic: Something that causes a feeling of depersonalization or dysphoria; producing symptoms similar to psychosis.

Psychotropic: Exerting an effect on the mind.

Pulmonary embolus: A clot or other particulate matter blocking one of the blood vessels to the lungs from the right side of the heart. The usual source of the blockage is material from a deep vein thrombosis.

Pulmonary: Pertaining to the lungs.

Pulmonic: Pertaining to or of the lungs.

Pupillary: Pertaining to the pupils of the eye.

Pyloric sphincter: Ring-like muscle between the stomach and the small intestine.

Q24h/Q12h:	Shorthand for every 24 hours and every 12 hours. Q is an abbreviations for *every* from the Latin quaque.
Radical:	Designed to eliminate all possible extensions of a disease process.
Radicular:	Pertaining to a nerve root.
Radiculopathy:	Disease of nerve roots which is typically painful.
Radiotherapy:	General term for all types of radiation used to treat cancer.
Randomization:	A selection procedure used to eliminate the bias in a subject population.
Receptor:	1.) A structure on the surface or within a cell that recognizes and binds with specific molecules, producing a specific effect in the cell. 2.) A sensory nerve ending that responds to various stimuli.
Recovering:	An ex-abuser who now abstains. Such individuals remain at increased risk of relapse for at least several years.
Rectum:	The final part of the large intestine, terminating at the anus.
Referred pain:	Pain felt in a part of the body which is distant from the tissues causing the pain.
Reflex:	An automatic involuntary response mediated by the nervous system.
Refractory:	Not readily responsive to treatment.
Regional anesthesia:	Nerve block which relieves pain in the area served by that peripheral nerve, nerve root, or plexus.
Relapse:	Returning to substance abuse after a period of abstinence.
Reliability:	A measure of the extent to which the experiment produces the same result.
Remission:	Temporary reduction of symptoms.
Renal:	By or of the kidney.
Rescue dose:	An additional dose of pain medication above the usual baseline dose for times when pain is worsened (e.g., when a patient with otherwise well-controlled pain overexerts himself or the disease/condition has periodic "flares" of symptoms or breakthrough pain).
Rescue medications:	Medications which the patient can take when symptoms are not controlled by the usual fixed regimen.
Resection:	Excision (cutting out) of a portion or all of an organ or other structure.
Resistance:	Natural ability of a normal organism or cell to withstand the effects of a drug that is lethal to most members of its species or to most other cells of its type.
Respiratory depression:	A reduction in the amount of respiratory effort that can be a side effect of opioids in the CNS. If this worsens, it can lead to respiratory arrest (the patient ceases to breathe).
Rheumatoid arthritis:	Chronic systemic disease, primarily involving inflammation of the joints, but also associated with disease in other organs.
Rhinitis:	Inflammation of the mucous membranes of the nose.
Rhizotomy:	Severance or disruption of a nerve root.
Sacrum:	Wedge-shaped bone in the pelvis formed by fusion of five vertebrae below the lumbar vertebrae.
Salicylate:	One of a group of drugs, e.g., aspirin, derived from salicylic acid.
Sarcoma:	Malignant tumor of connective tissue.
Scan:	An image produced suing a moving detector or a sweeping beam of radiation.

Sclerosing agent (sclerosant): Chemical irritant injected to produce inflammation and eventual fibrosis and obliteration of a structure.

Secondary gain: A gain (financial, emotional, or social) resulting from (or secondary to) what would appear to be an unpleasant situation.

Seizure: Sudden attack, e.g., a convulsion (fit).

Sensory nerve: This is a nerve that carries sensation signals, including pain.

Sensory: Pertaining to sensation.

Serotonin: Hormone and neurotransmitter which has a variety of properties, including inhibition of stomach secretions, stimulation of smooth muscles, and production of vasoconstriction. Also known as 5-hydroxytryptamine (5-HT).

Serum half-life: The amount of time it takes for a drug level in the blood to decrease to one-half of the maximum amount reached. This term is sometimes shortened to "half-life."

Serum: Clear portion of blood which remains when cells and other solid elements have been removed.

Shingles: (see Herpes zoster).

Shock: (see circulatory shock).

Sigma receptors: Receptors in the central nervous system that appear to be involved in antidepressant effects and antianxiety effects. These receptors also attenuate the pain response in experimental settings, thus these receptors were originally classified as opioid receptors. They are now felt to constitute a distinct class of receptors.

Signs: Objective evidence of disease.

Single blind: Only the physician is aware of actual treatment.

Single group: One subject group with one treatment.

Skeletal muscle: Striated muscle attached to bone and crossing at least one joint; involved in voluntary activities.

Small intestine (bowel): The gastrointestinal tract immediately following the stomach, and preceding the large intestine; comprised of the duodenum, jejunum, and ileum.

Smooth muscle: Nonstriated muscle which is not under voluntary control.

Socio-environmental: Originating from, or strongly influenced, social or environmental pressures.

Somatic nervous system: Part of the nervous system which carries messages originating from the conscious part of the brain to skeletal muscles.

Somatic pain: Sharp, localized pain originating from the skin, muscles, tendons, ligaments, and bones. This type of pain is usually well-localized and easy to describe.

Somatoform disorders: Psychological conditions that produce physical complaints even though there is nothing physically wrong with the patient that can be identified medically.

Spasm: Sudden involuntary muscular contraction.

Sphincter of Oddi: A circular muscle located where the common bile duct passes through the small intestine that controls the flow of bile into the intestine.

Sphincter: Ring-like muscle around an orifice.

Spinothalmic tract: Group of sensory nerve fibers which transmit information from the spinal cord to the thalamus.

Spleen: Large organ in the upper left part of the abdomen, in which old red blood cells are broken down.

Steady state: Condition of dynamic equilibrium between administration and elimination of a drug.

Stomach atony disorder: A condition caused by a loss of muscle tone in the stomach. It can lead to pain, nausea and vomiting, and distension.

Street value: The price for which a drug is commonly sold for illegally (i.e., "on the street").

Stricture: Abnormal narrowing.

Subcutaneous: Beneath the skin. This term is used for injections of medications that require administration into the looser tissue under the skin.

Subjective criteria: Variables that are less well defined (typically exhibiting great intrapatient differences). Example: patient self-report.

Subjective: Cannot be seen, felt, or shown on laboratory test. A subjective diagnosis is one that is made on the basis of the patient's history rather than a finding on physical exam or by testing.

Sublingual: Beneath the tongue.

Substance abuse: Continued use of a mood-altering substance despite repeated harmful problems associated with its use.

Substance dependence: Substance abuse associated with tolerance and withdrawal symptoms.

Suppository: A formulation of a drug that can be given rectally.

Supraspinal: Occurring at the level of the brain.

Sympathectomy: Disruption or interruption of some portion of the sympathetic nervous pathway.

Sympathetic nervous system: Part of the autonomic nervous system which innervates the heart, smooth muscle, and glands of the entire body, usually increasing their activity.

Symptoms: Subjective evidence of disease or a patient's condition.

Synapse: The junction between two neurons or a neuron and an effector target organ, across which neural impulses are transmitted, usually by chemical means.

Synaptic cleft: Narrow gap at the synapse, across which neurotransmitters are responsible for transmitting nerve impulses.

Syncope: Fainting.

Syndrome: A group of findings or symptoms that commonly occur together.

Systemic: Involving the whole body.

$T_{1/2}$: (see Half-Life).

Tachycardia: Increased heart rate.

T-cells: White blood cells primarily responsible for cell-mediated immunity.

Temporal: The course of a situation or circumstance over time.

Tenesmus: Ineffectual and painful straining to void feces.

TENS: Transcutaneous Electrical Nerve Stimulation.

Tension headache: Headache resulting from prolonged contraction of the muscles of the scalp, generally reflecting chronic stress.

Teratogen: An agent that induces the formation of abnormalities of the fetus.

Therapeutic index: The range of drug dose within which the drug is effective but does not cause unacceptable side effects.

Therapeutic regimen: All of the combined treatments used for a certain condition.

Thoracic spine:	Twelve vertebrae (T1 to T12) in the chest which connect the cervical vertebrae to the lumbar vertebrae. Each of the pairs of ribs attaches to a thoracic vertebrae.
Thoracic:	Of the thorax.
Thorax:	Chest.
Thymus gland:	Lymphoid organ, located in the upper chest/lower neck region, responsible for the production and development of certain lymphocytes.
Tic douloureux:	(see Trigeminal neuropathy).
Titration:	Gradual adjustment of dose of a drug until the desired effect is achieved with
Tmax:	Time required to achieve maximum plasma concentration of a drug.
Tolerance:	The need for increased doses of medication over time to achieve the same level of pain control.
Tonsils:	Small, rounded masses of lymphoid tissue at the rear of the mouth.
Topical:	Pertaining to a particular superficial area only.
Totipotential cells:	Cells which can develop into any cell type.
Toxic psychosis:	Alterations of mental state caused by drug toxicity.
Toxic:	Poisonous.
Trachea:	Windpipe.
Traction:	Act of drawing or pulling.
Transdermal:	Through the skin.
Transcutaneous:	Through the skin.
Transduction:	Stimulation of nociceptors by noxious stimuli.
Tremor:	Involuntary trembling or quivering.
Tricyclic antidepressants:	Group of drugs used to treat depression.
Trigeminal neuropathy:	Nerve pain in the trigeminal nerve distribution (i.e., the face, teeth, mouth, nose).
Trough:	The lowest level of drug concentrations in the blood.
Tumor:	Any abnormal growth of tissue, generally a neoplastic mass.
Ulceration:	Formation of an ulcer, i.e., a local defect, or excavation of the surface, of an organ or tissue.
Ultrasound:	Mechanical radiant energy used to provide images of deep structures of the body.
Unilateral:	On one side.
Ureter:	Tube which conducts urine from the kidneys to the bladder.
Urethra:	Canal through which urine is discharged from the bladder to the exterior of the body.
Urethral stricture:	Narrowing of the passage through which urine is voided.
Urgency:	Urge to pass urine.
Urticaria:	Hives.
US Pharmacopoeia:	A legally recognized compendium of standards for drugs. It includes assays and tests for determination of strength, quality and purity.
Uterus:	Hollow female organ in which the fertilized egg develops into a fetus.
Validity:	Extent to which the experiment measures the specified objectives.
Variance:	Extent to which variables or characteristics of the subject population differ.

Vasoconstriction:	State of decreased caliber (narrowing) of blood vessels.
Vasodilation:	Relaxation of the smooth muscle in the blood vessels that results in an increase in the size of blood vessels.
Vasomotor:	Affecting the caliber of blood vessels.
Vasopressors:	Drugs that stimulate the contraction of blood vessels and therefore bring about an increase in blood pressure.
Vertebra (plural vertebrae):	Any of the 33 bones of the vertebral (spinal) column including the cervical, thoracic, lumbar and sacral vertebrae.
Vertigo:	Dizziness, specifically the type that causes a spinning sensation.
Vestibular:	Involving the inner ear organ which senses bodily equilibrium.
Viscera (singular viscus):	Any of the large internal organs, especially those situated in the abdomen.
Visceral pain:	Poorly localized pain originating from internal organs.
Visual analog scale:	A pain severity rating scale.
Volume of distribution:	A measure that describes the concentration of drug in the body tissues