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Table of Contents

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
- Define substance abuse and addiction

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 which 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.

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:

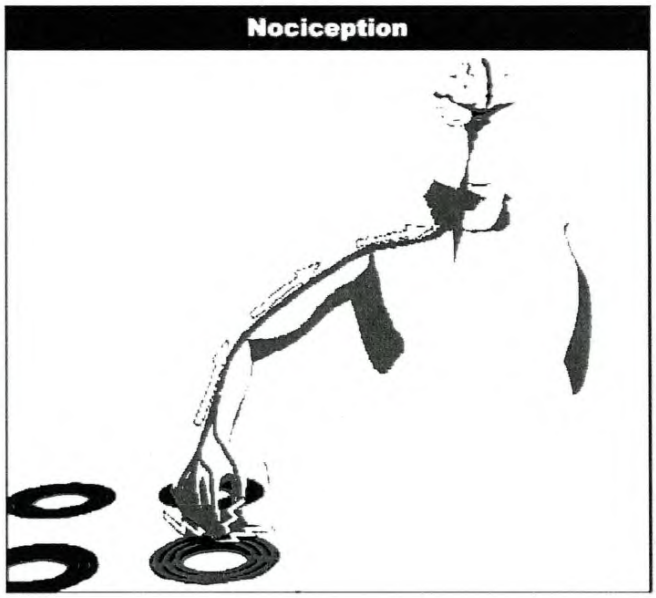
- Nociception
- Transmitting the Pain Sensation to the Spinal Cord
- Connections in the Spinal Cord and Brain
- The Descending Pathways

Nociception

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

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.

Figure 1-1



Transmitting the Pain Sensation to the Spinal Cord

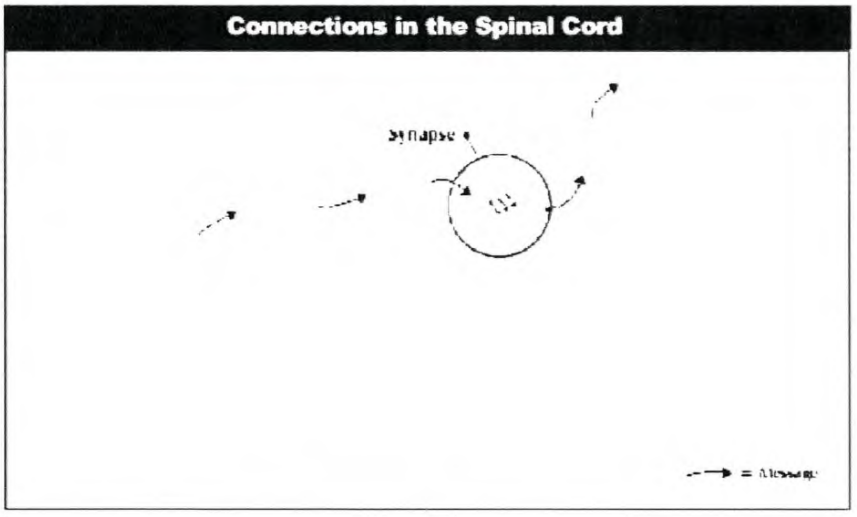
The pain signal travels from the nerve cell (neuron) ending to the spinal cord along a single fiber that is a long branch (also called an axon) off the cell body. Although each individual fiber is microscopically small in diameter, it is long enough to reach from the spinal cord to whatever part of the 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.

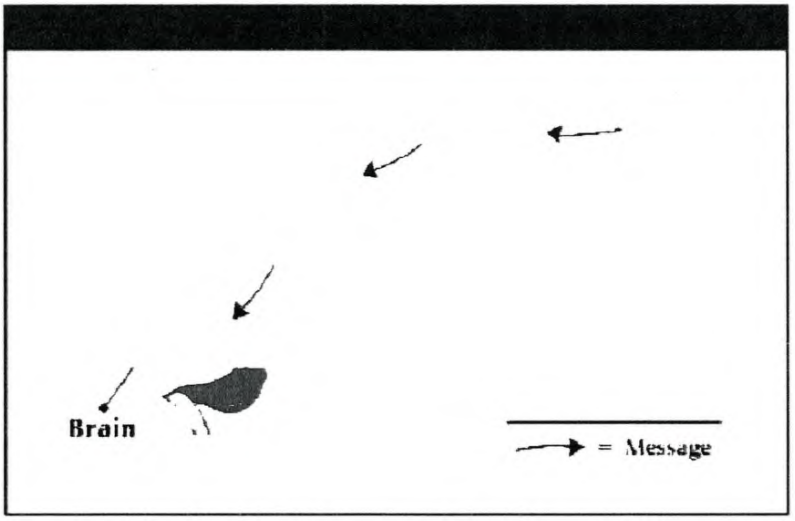
Figure 1-2



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.

Cancer Pain Management

The World Health Organization recommendations for pain management, referred to as the pain ladder, suggests starting with non-steroidal 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)

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. Under-treatment of pain results in patients with a very poor quality of life and may lead to feelings of hopelessness and despondency.

Whereas under-treatment is the most common problem in cancer pain control, a few patients are over-treated 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. Under-treatment 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

- Rheumatoid arthritis
- Migraine headaches
- Chronic back pain

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.

Patients with chronic benign pain could be 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 treated 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 non-opioid 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 non-opioid 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, rheumatologic, 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.

Non-physician 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 some states, nurse practitioners are allowed to prescribe all

Schedule II medications. Nurses often 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 for 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.

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 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).

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 will likely result in the pet's untimely demise.

Lack of Education about Pain and Pain Control

Many practitioners are 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 under-dosing 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 Under-dosing 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 should titrate the dose to the individual patient. Clinicians can also consult pharmacists for advice regarding changing opioids and determining equianalgesic dosing.

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.

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. 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/

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/

Centers for Disease Control and Prevention

http://www.cdc.gov/

Mayo Clinic

http://www.mayoclinic.com/

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

4).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?

True or False

5) Visceral pain arises from muscles, joints, and tendons.
a. True
b. False

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

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

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

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

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

Answers to Self-Assessment Test

1) b
2) a
3) d
4) d
5) b
6) a
7) a
8) a
9) a
10) 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 bother chronic benign and cancer pain.
- List at least 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.

Unfortunately, the treatment these patients receive is often 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?
- A*ggravating 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 a nonprescription

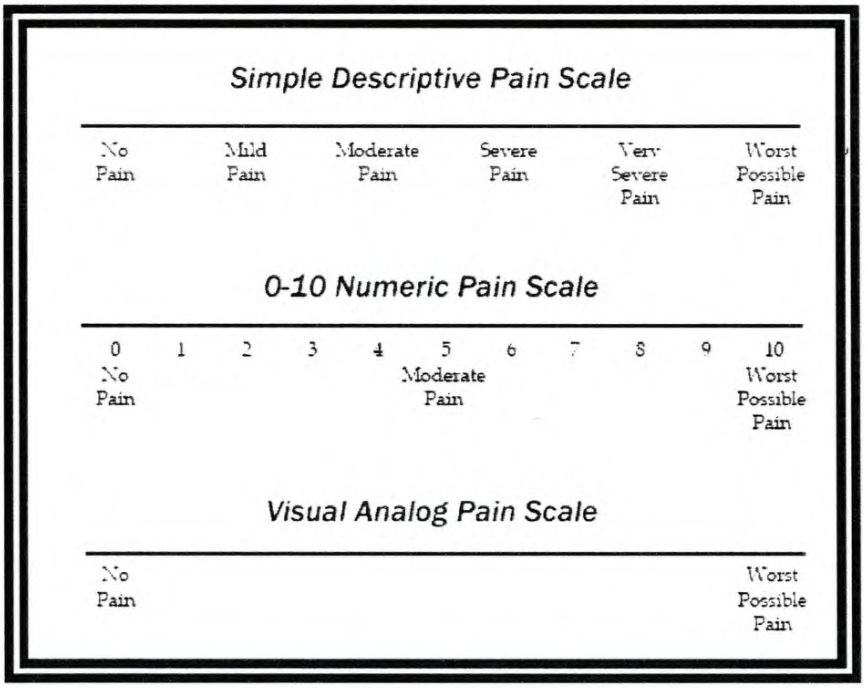
methods or medications to relieve the pain? Were any of the treatments effective?

- *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. 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.

In addition, many 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 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).

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.

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.

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.

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.

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 or not the patient's functional status has improved.

Self-Assessment Test

Circle the best response

1). 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

2). 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
2. a

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 non-opioid analgesics.

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-naive 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 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. In general, these guidelines include using non-opioid 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 non-opioid 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 under-dosing. Conversion tables are notoriously inaccurate and contradictory.

- Non-pharmacologic 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 non-opioid analgesics and opioid analgesics. The non-opioid and opioid medications have distinct benefits and drawbacks and these are taken into consideration when choosing a therapy for a patient.

Non-opioid Analgesics

There are 3 general types of non-opioid agents:

- Acetaminophen
- Non-steroidal anti-inflammatory agents (NSAIDs)
- Aspirin

Acetaminophen (APAP)

Acetaminophen is the most widely used non-opioid 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 known. 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, patients who take such medications AND additional acetaminophen are at risk of liver toxicity.

Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

The non-steroidal 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
    - Immediate-release oral tablet
    - Short acting (infusion/injection)
    - Long-acting Epidural
    - Suppository
    - Liquid (immediate acting)
- fentanyl

  - Oral form
  - Transdermal
  - Injection
- sufentanil
- hydromorphone
  - Oral
  - Extended-release oral capsules
  - Infusion/Injection/epidural
- meperidine
  - Oral
  - Injection/infusion
- methadone
  - Oral
- oxycodone
  - Oral tablets
  - Controlled-release oral tablets
  - Oral solution
- hydrocodone
  - Oral tablets or liquid
- levorphanol
  - Oral and parenteral
- codeine (available in various combinations with acetaminophen, aspirin, cold medication preparations, and promethazine)
  - Oral tablets or solution
- propoxyphene
  - Oral tablets
- tramadol
  - Oral tablets
- oxymorphone
  - Injection

- Oral tablet
- Oral extended-release
- Rectal suppository

Mixed agonist-antagonists

- butorphanol
  - Parenteral
  - Nasal spray
- Buprenorphine
  - Parenteral
  - Sublingual tablets
- dezocine
  - Parenteral
- nalbuphine
  - Parenteral
- pentazocine
  - Oral tablet:

Many opioid agonists are used to treat chronic benign 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.

CHAPTER FOUR

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 and pain treatment 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, similar to that experienced by cancer patients. However, they often have a history of these problems existing before they developed chronic pain. Additionally, 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. 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 foremost 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. 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. 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 non-opioid 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. Many people 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, 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 over-prescribing, 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 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.

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.

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.

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.

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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). 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

6). 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

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.

7). Developing tolerance or dependence

8). Over-sedation

9). Chronic nausea

10). Possibility of substance abuse

11). Worry over regulatory criticism

Answers to Self-Assessment

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

CHAPTER FIVE

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.
- 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.

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. Nonetheless, one must always remember that every opioid has at least some abuse potential.

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 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, 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)

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.

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 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)

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. Many 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 some 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. 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. Many 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.

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.

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. Many 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.

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.

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. 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 5-1

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.*

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.

Summary

- 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.

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Self-Assessment Test

Circle the best response

1. 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

2. 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

3. 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%

True or False

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

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

Answers to Self-Assessment Test

1. c
2. b
3. d
4. b (Withdrawal does not automatically imply abuse.)
5. b

CHAPTER SIX

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 opioids 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. Opioid use in pain relief is favored because opioids have a long history of use and demonstrated efficacy.

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 6-1). 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

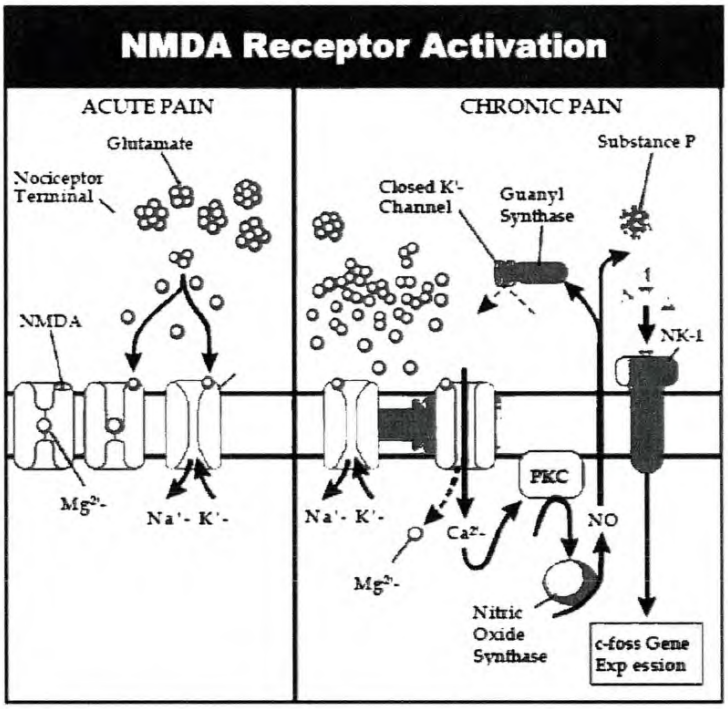
Endogenous peptides are the primary chemical messengers in the antinociceptive system of the body. Endogenous opioids bind to receptors to produce analgesia. Endogenous opioids are composed of three distinct families of peptides, all of which are pharmacologically related to morphine:

- 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 6-1

Adapter from Brookoff, 2000



Opioid Receptors

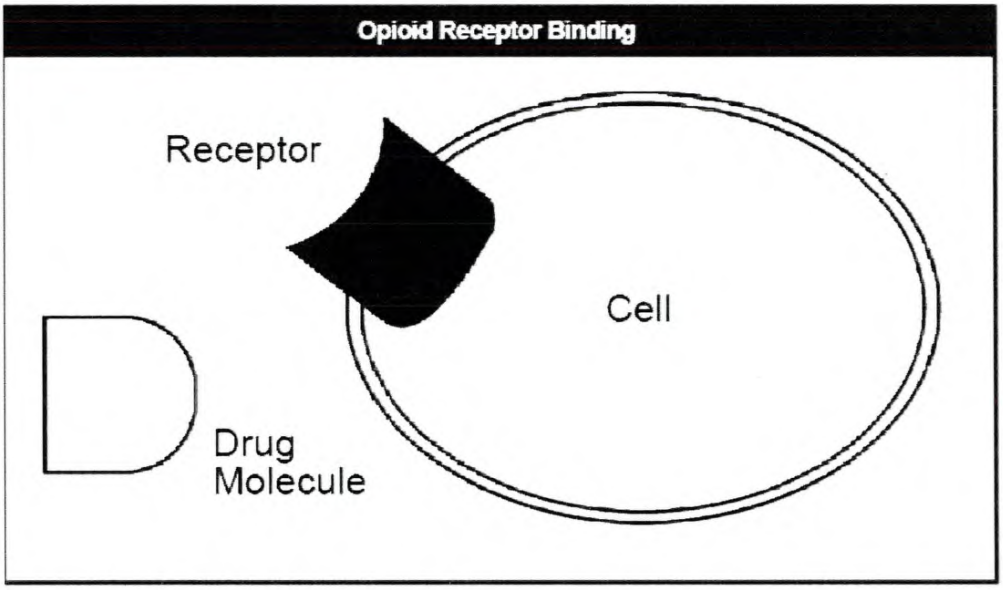
Opioids exert their effects on the body by interacting with specialized macromolecular (large molecule) components in cells called opioid receptors. Opioid receptors are located in the central nervous system (CNS), pituitary gland, the peripheral nervous system (PNS), the gastrointestinal (GI) tract, and a few other locations in the body. They are abundant in the peri-aqueductal 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 6-2). 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 6-2



Opioid Analgesics

Opioids are divided into 3 classes (Table 6-1):

Mu agonists

Most clinically useful opioid analgesics bind primarily to the mu (X) 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 6-1.

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

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 6-2). Analgesia is a beneficial result of mu receptor binding. Side effects are unwanted results of the binding to opioid receptors.

Table 6-2.

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 (Ќ)	Spinal and supraspinal analgesia, respiratory depression, cardiovascular effects, physical dependence, tolerance, impaired GI motility, urinary retention, pruritus, euphoria
Delta (δ)	Spinal and supraspinal analgesia, respiratory depression, cardiovascular effects, physical dependence, tolerance, impaired GI motility, urinary retention, pruritus, euphoria

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 X (mu) receptor activation. There are two distinct subtypes of X receptors, X_1 and X_2. The X_1 receptor is responsible for morphine analgesia at the supraspinal level, whereas the X_2 receptor mediates morphine analgesia at the level of the spinal cord. Morphine given systemically interacts with supraspinal X_1 receptors. Both respiratory depression and constipation are thought to be mediated by X_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. Opioids can cause constricture of the sphincter of Oddi and the biliary tract.

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

Morphine may aggravate pre-existing convulsions in patients with convulsive disorders.

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

Although extremely rare, cases of anaphylaxis have been reported with opioid therapy.

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.

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 antihistamine. 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 6-3.

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).
- 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).
- Respiratory depression.

- Stimulation of histamine release (sweating, flushing, pruritus, red eyes, postural hypotension, wheezing or worsening of asthma symptoms).
- Other possible effects of opioids include aggravating pre-existing convulsions in patients with convulsive disorders and, although extremely rare, cases of anaphylaxis.

Addiction, Dependence, and Tolerance

Misuse, Abuse, and Diversion of Opioids

KADIAN® contains morphine an opioid agonist and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Morphine 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.

Abuse of KADIAN® by crushing, chewing, snorting or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death.

Concern about abuse, addiction, and diversion should not prevent the proper management of pain.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external

factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

Tolerance to Side Effects

Opioid side effects are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. Many of these adverse events will cease or decrease as opioid therapy is continued and some degree of tolerance is developed, but others may be expected to remain troublesome throughout therapy.

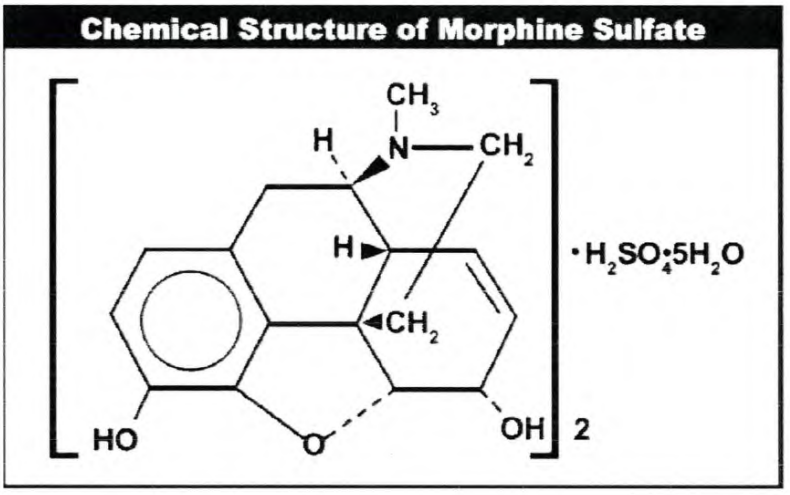
Morphine Pharmacology

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).

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 an 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 6-3.



KADIAN® Pharmacology

KADIAN® is an 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 once or twice a day dosing. KADIAN® capsules are formulated in eight strengths containing 10, 20, 30, 50, 60, 80, 100 or 200mg of morphine sulfate plus inactive ingredients.

KADIAN® Pellet Technology

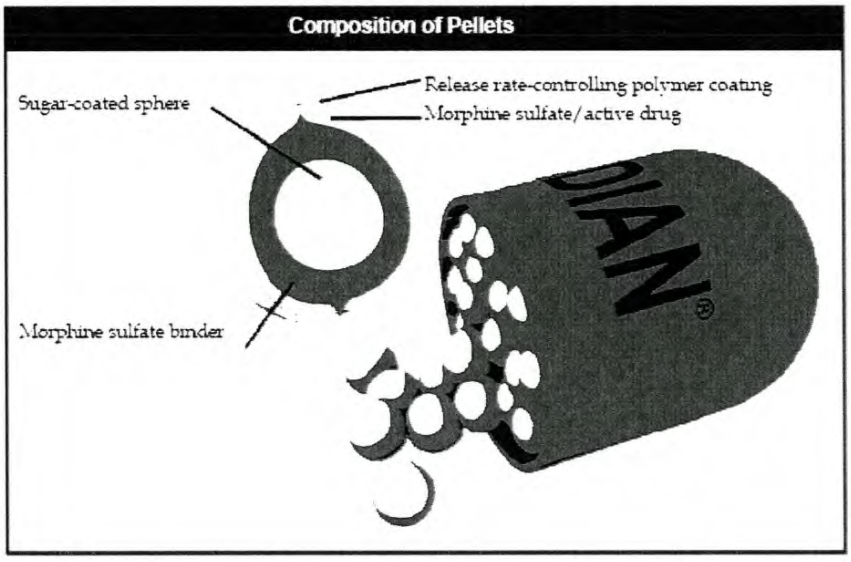
The KADIAN® capsules consist of a hard gelatin shell containing polymer-coated morphine sulfate pellets. The release of morphine from the pellets is pH dependent, with the rate of release increasing as the pH of the medium around the pellet increases.

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 6-4: 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. Patients should be advised that severe constipation could occur as a result of taking morphine and appropriated laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy. 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.

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

CHAPTER SEVEN

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 non-oral 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.

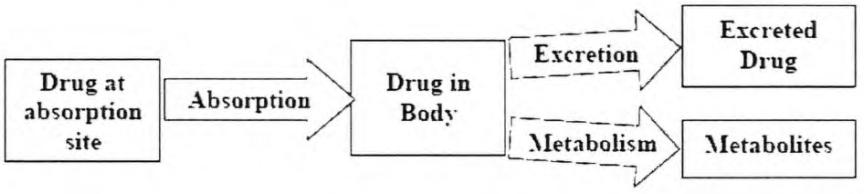
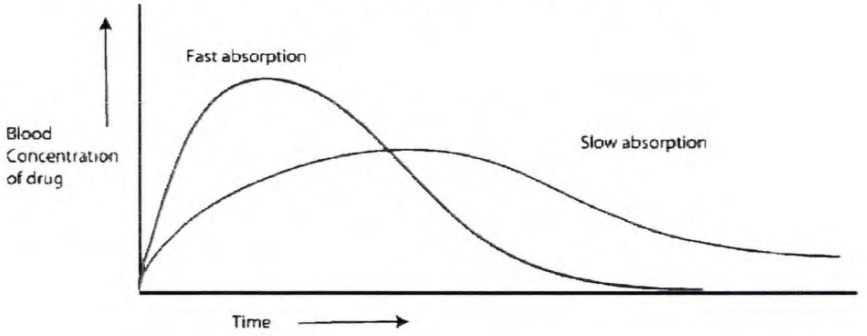


Figure 7-1: Absorption Profiles



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.

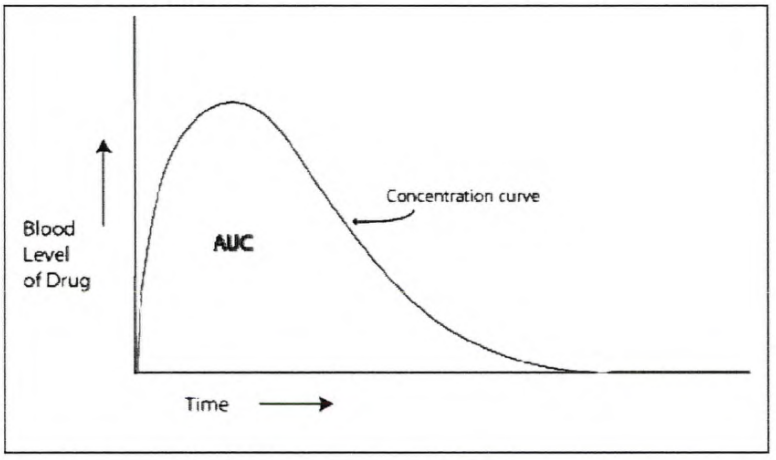
Bioavailability

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 7-1). The AUC is based on the absorption curve of a drug as determined under experimental conditions. In Figure 7-2, 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

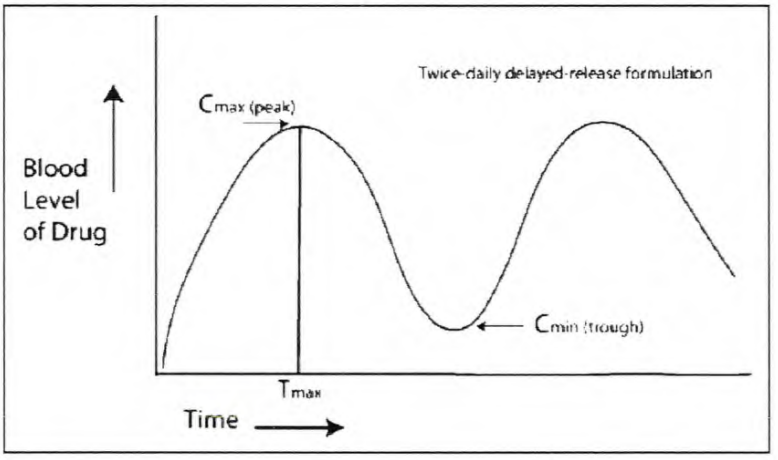
amount of the full dose given to the patient. In reality, any amount of drug that is not bioavailable (e.g., not absorbed) would not end up in the serum and would not be represented by the gray area.

Figure 7-2: 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 7-3).

Figure 7-3: 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 = 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.

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 effective terminal half-life of morphine after IV administration is reported to be approximately 2.0 hours. Longer plasma sampling in some studies suggests a longer terminal half-life of morphine of about 15 hours.

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

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 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

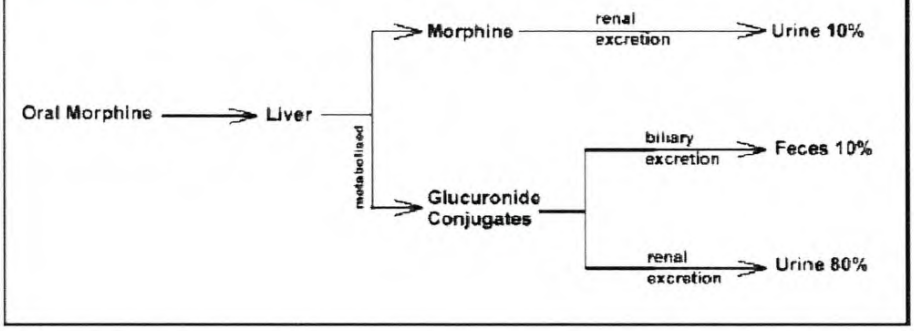
M3G has no significant analgesic activity. M6G has show to have opioid agonist and analgesic activity in humans.

Excretion

Approximately 10% of morphine dose is excreted unchanged in the urine. Most of the dose is excreted in the urine as M3G and M6G. A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic cycling. Seven to 10% of administered morphine is excreted in the feces.

Figure 7-4

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. KADIAN® 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 mean adult plasma clearance is about 20 30 mL/minute/kg. The effective terminal half life of morphine after IV administration is reported to be approximately 2.0 hours. Longer plasma sampling in some studies suggests a longer terminal half life of morphine of about 15 hours.

Pharmacodynamics of Morphine

The pharmacodynamics of a drug describes 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 explores 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 known 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 mg/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-naive 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 mg/mL.
- The effective dose in opioid-tolerant patients may be 10 to 50 times as great (or greater) than the appropriate dose for opioid-naive 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 7-2

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 $\geq 75\%$ 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

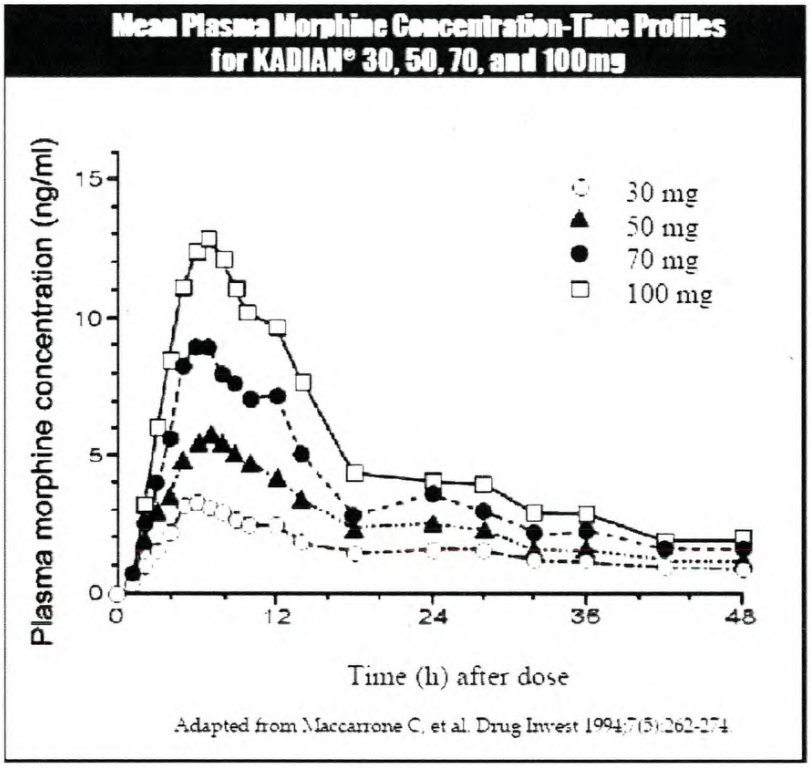
Most drugs have a proportionate relation between drug concentration in the serum and dosing. That is, the amount of drug given relates directly to the serum concentrations. In pharmacokinetic terms, this is called a linear pharmacokinetic profile. This means that serum drug concentrations change proportionally (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 is 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.

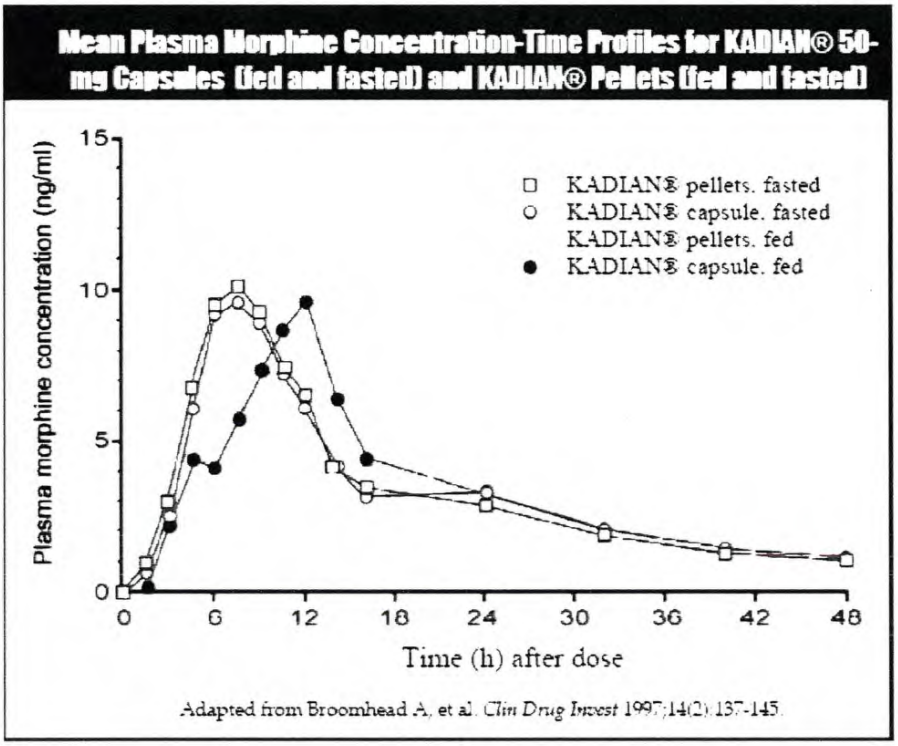
Figure 7-5



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 7-6



Administration by Sprinkling

The rate of release of morphine from the KADIAN® pellets has not been shown to be affected when the pellets are sprinkled 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 7-3

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)
$AUC_{0-\infty}$ (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 C max; 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 alternative 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.

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 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® 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
b. 2
c. 3
d. 4

4). The time to peak plasma concentrations after KADIAN® administration is approximately _____hours.
a. 2
b. 4
c. 6
d. 8

5). Glucuronidation, the major metabolic pathway of morphine, occurs primarily in the _____.
a. Kidneys
b. Liver
c. Brain
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
2. c
3. a
4. d
5. b
6. b
7. c
8. b
9. a
10. b
11. b
12. b
13. b
14. a

CHAPTER EIGHT

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 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.
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.
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 an 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. The range of doses is not suitable for the treatment of very young pediatric patients. The 100 mg and 200 mg capsules are for use only in opioid-tolerant patients.

KADIAN® is not indicated for administration pre-operatively for the management of post-operative pain, or for pain in the first 12 to 24 hours following surgery for patients not previously taking the drug, because its safety in these settings have not been established.

KADIAN® is only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

Care should be taken to use low initial doses of KADIAN® in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications.

Whole Capsule Administration

KADIAN® capsules should be swallowed whole. The capsules or pellets should not be chewed, crushed, or dissolved as this leads to the rapid release and absorption of a potentially fatal 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. 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) onto a small amount of applesauce. Applesauce should be room temperature or cooler.
3. Use immediately.
4. The patient must be cautioned not to chew or crush the pellets which could result in the immediate release of a potentially toxic or fatal dose of morphine.
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.

THE ADMINISTRATION OF KADIAN® PELLETS THROUGH A NASOGASTRIC TUBE SHOULD NOT BE ATTEMPTED

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.

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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 10-mg or 20-mg strength dosage. The dose usually should not be increased by more than 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 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.

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 formulations to KADIAN®

Patients on other oral morphine formulations may be converted to KADIAN® by administering one-half of the patient's total daily oral morphine dose as KADIAN® capsules every 12 hours (twice-a-day) or by administering the total daily oral morphine dose as KADIAN® capsules every 24 hours (once-a-day). KADIAN® should not be given more frequently than every 12 hours.

Conversion from Parenteral Morphine or Other Parenteral or Oral Opioids to KADIAN®

KADIAN® can be administered to patients previously receiving treatment with parenteral morphine or other opioids. While there are useful tables of oral and parenteral equivalents in cancer analgesia, there is substantial inter-patient variation in the relative potency of different opioid drugs and formulations. For these reasons, it is better to underestimate the patient's 24-hour oral morphine requirement and provide rescue medication, than to overestimate and manage an adverse event. The following general points should be considered:

1. Parenteral to Oral Morphine Ratio: It may take anywhere from 2-6 mg of oral morphine to provide analgesia equivalent to 1 mg of parenteral morphine. A dose of oral morphine three times the daily parenteral morphine requirement may be sufficient in chronic use settings.

2. Other Parenteral or Oral Opioids to Oral Morphine Sulfate: There is a lack of systematic evidence bearing on these types of analgesic substitutions. Therefore, specific recommendations are not possible. Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate. In general, it is safest to give half of the estimated daily morphine demand as the initial dose, and to manage inadequate analgesia by

supplementation with immediate-release morphine. (See discussion which follows.)

The first dose of KADIAN® may be taken with the last dose of any immediate-release (short-acting) opioid medication due to the long delay until the peak effect after administration of KADIAN®.

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 a patient to adequate analgesia using an extended-release morphine, it is ordinarily advisable to begin treatment using an immediate-release morphine formulation.

Individualization of Dosage

The best use of opioid analgesics in the management of chronic malignant and non-malignant pain is challenging and well-described in materials published by the World Health Organization (WHO), and the Agency for Health Care Research and Quality. 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 "floor" or "platform" from which to manage breakthrough pain. When a patient has reached the point where comfort cannot be provided with a combination of non-opioid 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 morphine equivalent.

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 twice a day dosing.

Doses are titrated to pain relief, and so no ceiling can be given as to the recommended maximal dose especially in patients with chronic pain of malignancy. In such cases, 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 and pellets 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 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 is a copy of the boxed warning approved by 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.

- KADIAN® contains morphine an opioid agonist and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

- Morphine 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.

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 (light brown) capsules. KADIAN® capsules are administered orally once or twice daily (Q12 or Q24 hours). KADIAN® capsules and pellets 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 fatal 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.
- KADIAN® contains morphine an opioid agonist and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.
- Morphine 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.
- Patients on other oral morphine formulations may be converted to KADIAN® by administering one-half of the patient's total daily oral morphine dose as KADIAN® capsules every 12 hours (twice-a-day) or by administering the total daily oral morphine dose as KADIAN® capsules every 24 hours (once-a-day). KADIAN® should not be given more frequently than every 12 hours.

- KADIAN® can be administered to patients previously receiving treatment with parenteral morphine or other opioids. While there are useful tables of oral and parenteral equivalents in cancer analgesia, there is substantial interpatient variation in the relative potency of different opioid drugs and formulations. For these reasons, it is better to underestimate the patient's 24-hour oral morphine requirement and provide rescue medication, than to overestimate and manage an adverse event.

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.
- KADIAN prescribing information. Morristown, NJ: Actavis Elizabeth LLC

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.

True or False

3). In patients who have not previously received opioids, the initial KADIAN® dose is:
a. 10mg or 20 mg every 24 hours
b. 30 mg every 24 hours
c. 20 mg twice daily
d. 30 mg twice daily

4). Any breakthrough or incident pain may be treated with a short-acting opioid analgesic.
a. True
b. False

5). A patient's KADIAN® dose can be increased every 24 hours.
a. True
b. False

6). 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
2. a
3. a
4. a
5. b
6. b

CHAPTER NINE

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.
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.
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,
- apnea
- circulatory depression,
- cardiac arrest,
- hypotension, and/or
- shock

The less severe adverse effects include

- drowsiness,
- dizziness,
- constipation, and

- nausea and vomiting.

Adverse reactions are more likely to occur in opioid-naive 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, many adverse effects are temporary. They will cease or decrease as opioid therapy is continued and some KADIAN® 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. Some patients, particularly the elderly, debilitated or bedridden patients may become impacted. Tolerance does not usually develop to this side effect. Thus, it requires an aggressive preventive approach and regular assessment, and aggressive management if symptoms are detected. The most common approach is to use a laxative and stool softeners regularly. Exercise, adequate fluid intake, eating bulk-containing foods, and taking natural colon stimulants such as prune juice may also help to prevent constipation. Treatment for this side effect 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 suitable antiemetic (with the awareness that sedation may result) 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 Excessive Drowsiness

Most patients receiving KADIAN® will experience initial drowsiness. This usually disappears within 3-5 days and is not a cause of concern unless it is excessive, or accompanied by unsteadiness or confusion. Dizziness and unsteadiness may be associated with postural hypotension, particularly in elderly or debilitated patients, and has been associated with syncope and falls in non-tolerant patients started on opioids.

Excessive or persistent sedation should be investigated. Factors to be considered should include: concurrent sedative medications, the presence of hepatic or renal insufficiency, hypoxia or hypercapnia due to exacerbated respiratory failure, intolerance to the dose used (especially in older patients), disease severity and the patient's general condition.

The dosage should be adjusted according to individual needs, but additional care should be used in the selection of initial doses for the elderly patient, the cachectic or gravely ill patient, or in patients not already familiar with opioid analgesic medications to prevent excessive sedation at the onset of treatment.

KADIAN® Clinical Safety

Adverse Events – Single Dose and Repeated Dose

In controlled clinical trials in patients with chronic 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

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 an 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. Close monitoring for respiratory depression is needed in opioid-naive patients or when another pain intervention, such as an anesthetic block, takes away the pain stimulus.

Antagonists

The pure opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression which results from opioid overdose. Since the duration of reversal would be expected to be less than the duration of action of KADIAN®, the patient must be carefully monitored until spontaneous respiration is reliably re-established. 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. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given as directed by the manufacturer of the product.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Such agents should be administered cautiously to persons who are known, or suspected to be physically dependent on KADIAN®. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome.

Opioid-tolerant Individuals

In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal. The severity of the withdrawal produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist should be reserved for cases where such treatment is clearly needed. If it is necessary to

treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

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 ®, or in any situation where opioids are contraindicated, because of the risk of anaphylaxis.
- Patients with acute or severe bronchial asthma and those with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings). 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 with moderate or severe pain who require more than several days continuous treatment with a potent opioid analgesic. KADIAN® is not intended for "as needed" use. 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

Patients taking KADIAN® who are scheduled for cordotomy or other interruption of pain transmission pathways should have KADIAN® ceased 24 hours prior to the procedure and the pain controlled by parenteral short-acting opioids. In addition, the post-procedure titration of analgesics for such patients should be individualized to avoid either oversedation or withdrawal syndromes.

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.

Driving and Operating Machinery

KADIAN® may impair the mental and/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 KADIAN® with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol.

Special Populations

Geriatric: The elderly may have increased sensitivity to morphine and may achieve higher and more variable serum levels than younger patients. In adults, the duration of analgesia increases progressively with age, though the degree of analgesia remains unchanged. KADIAN® pharmacokinetics have not been investigated in elderly patients (>65 years) although such patients were included in the clinical studies.

Nursing Mothers: Morphine is excreted in the maternal milk, and the milk to plasma morphine AUC ratio is about 2.5:1. The amount of morphine received by the infant depends on the maternal plasma concentration, amount of milk ingested by the infant, and the extent of first pass metabolism.

Pediatric: Infants under 1 month of age have a prolonged elimination half-life and decreased clearance relative to older infants and pediatric patients. The clearance of morphine and its elimination half-life begin to approach adult values by the second month of life. Pediatric patients old enough to take capsules should have pharmacokinetic parameters similar to adults, dosed on a per kilogram basis.

Gender: No meaningful differences between male and female patients were demonstrated in the analysis of the pharmacokinetic data from clinical studies.

Race: Pharmacokinetic differences due to race may exist. Chinese subjects given intravenous morphine in one study had a higher clearance when compared to caucasian subjects (1852 + 116 mL/min versus 1495 + 80 mL/min).

Hepatic Failure: The pharmacokinetics of morphine were found to be significantly altered in individuals with alcoholic cirrhosis. The clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G

to morphine plasma AUC ratios also decreased in these patients indicating a decrease in metabolic activity.

Renal Insufficiency: The pharmacokinetics of morphine are altered in renal failure patients. AUC is increased and clearance is decreased. The metabolites, M3G and M6G accumulate several fold in renal failure patients compared with healthy subjects.

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 studies have reported that morphine is non-mutagenic in the Ames test with Salmonella, and induces chromosomal aberrations in human leukocytes and lethal mutation induction in Drosophila. Morphine was found to be mutagenic in vitro in human T-cells, increasing the DNA fragmentation. In vivo, morphine was mutagenic in the mouse micronucleus test and induced chromosomal aberrations 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 non-exposed individuals and in heroin users enrolled in long term opioid maintenance programs.

Pregnancy

Teratogenic Effects (Pregnancy Category C)

Teratogenic effects of morphine have been reported in the animal literature. High parental doses during the second trimester were teratogenic in neurological, soft

and skeletal tissue. The abnormalities included encephalopathy and axial skeletal fusions. These doses were often maternally toxic and were 0.3 to 3-fold the maximum recommended human dose (MRHD) on a mg/m2 basis. The relative contribution of morphine-induced maternal hypoxia and malnutrition, each of which can be teratogenic, has not been clearly defined. Treatment of male rats with approximately 3-fold the MRHD for 10 days prior to mating, decreased litter size and viability.

Nonteratogenic Effects

Morphine given subcutaneously, at non-maternally toxic doses, to rats during the third trimester with approximately 0.15-fold the MRHD caused reversible reductions in brain and spinal cord volume, and 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 have demonstrated delayed growth, motor and sexual maturation and decreased male fertility. Chronic morphine exposure of fetal animals resulted in mild withdrawal, altered reflex and motor skill development, and altered responsiveness to morphine that persisted into adulthood.

There are no well-controlled studies of chronic in utero exposure to morphine sulfate in human subjects. However, uncontrolled retrospective studies of human neonates chronically exposed to other opioids in utero, demonstrated reduced brain volume which normalized 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 CO2 and increased risk of sudden infant death syndrome. KADIAN® should only be used during pregnancy if the need for strong opioid analgesia justifies the potential risk to the fetus.

Labor and Delivery

KADIAN® is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which 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 which 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

Chronic maternal use of opiates or opioids during pregnancy coexposes the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NWS). Manifestations 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 addictive 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

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.

Geriatric Use

Clinical studies of KADIAN® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

KADIAN® Drug Interactions

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. When combined

therapy is contemplated, the initial dose of both agents should be reduced by at least 50%.

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.

Diuretics

Morphine reduces the efficacy of diuretic drugs (which increase urine output) by stimulating the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism. In patients receiving KADIAN® and diuretics, either an increase in diuretic dosage or an alternative therapy should be considered.

Mixed Agonist/Antagonist Opioid Analgesics

Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as KADIAN®. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of KADIAN® and/or may precipitate withdrawal symptoms in these patients.

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.

FDA Safety Warnings for KADIAN®

The following are included in the boxed warnings approved by 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 OPIOIDTOLERANT 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 common 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 over-dosage 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

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