Opioids as Medications (178)

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Course Summary

The pharmacologic properties of opioids including their mechanisms of action, receptor targets, target tissues, agonists and antagonists. Clinical applications including accepted usage, duration of action, and the minimizing of side effects. Finally, a look at overdose deaths from opioid abuse, cannabis as a harm reduction agent, and patient education about opioids.

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80% or higher on the post test, a completed evaluation form, and payment where required. No partial credit will be awarded.

Course Objectives

When you finish this course you will be able to:

- Comment on the history of poppies and the opium trade.
- Identify the various receptor targets of opioid action and explain how they differ.
- Describe the actions of morphine.
- Identify morphine-like drugs and synthetic derivatives.
- Discuss dependence, tolerance, and addiction in opioids.
- Explain ADME in pharmacokinetics.
- List other opioid analgesics in addition to morphine.
- Distinguish between opioid agonists and antagonists and the ways they are used.
- Summarize the current problem of overdose from prescribed opioids.
- Describe the use of methadone and its relation to overdose deaths.
- Teach a patient how to minimize the negative side effects of opioid use.
- Explain cannabis as an adjunct treatment for chronic pain to reduce the use of opioids.

The Beauty of Poppies, the Allure of Opium

Opium is extracted from the juice of poppies, and it contains a complex mixture of chemicals that are related to morphine, named for Morpheus, the Greek god of dreams. It has been used medicinally and socially for thousands of years to produce euphoria, analgesia, and sleep, and to prevent diarrhea.

The poppy plant Papaver somniferum and its effects were known to the Persian, Egyptian, and Mesopotamian cultures. Poppy plants were first mentioned in Sumerian writing around 4000 B.C., where they were referred to as "plants of joy." A significant advance in opium processing occurred in the sixteenth century when it was discovered that the alkaloids found in opium are significantly more soluble in alcohol than in water. Paracelsus (1490–1541) produced "laudanum" by extracting opium into brandy, creating a tincture of morphine.

Papaver somnifera

By the nineteenth century, vials of laudanum and raw opium were freely available in English pharmacies and grocery stores. In eighteenth- and nineteenth-century Britain, opium was taken orally as a tincture of laudanum, and addiction to it was a sign of social status. British opium imports more than tripled from 45 tons in 1830 to 140 tons by 1860, and despite extensive British control of Indian production, imports of Turkish opium proved to have greater morphine content (A Brief History of Opium, 1999).

Source: Wikimedia Commons.

Opium was also well known in ancient China, where people ate parts of the flower or drank liquid extracts. By the seventh century, Turkish and Islamic cultures of western Asia discovered that the smoking of opium was more powerful. Widespread use of opium in China escalated after pipes for smoking were delivered by Dutch traders in the 1600s. Indians usually ate opium, whereas the Chinese smoked it, with and without tobacco. By the late 1700s, the British East India Company controlled the prime Indian poppy-growing areas and dominated the Asian opium trade and, though demand already existed, they had a created a monopoly and could control both supply and prices.

Opium was already a heavily used recreational drug in China; seeing this as detrimental to the people, the Imperial court banned its importation and use—but smuggling continued. In 1839 the Qing Emperor ordered his ministers to act, initiating the First Opium War with the British. The Chinese were defeated and forced to sign the Treaty of Nanjing in 1842, whereby the British opium trade was to continue, and the Chinese had to pay a large settlement, open five new ports to foreign trade, and cede Hong Kong to Britain.

After 14 years, the Second Opium War started over Western demands to increase the opium trade. China was defeated again by 1860 and opium importation to China was formally legalized, leading to even greater use. By 1900 an estimated 25% of adult male Chinese were addicted (A Brief History, 1999).

* * *

Morphine was first isolated from opium in 1805 by a German pharmacist. Doctors had searched for alternatives to oral administration of drugs, and opium in particular caused unpleasant gastric problems. With the invention of the hypodermic syringe in the mid-nineteenth century, injection of purified morphine was even more potent and rapid acting than opium itself. Morphine addiction became widespread in the United States following its extensive use by maimed soldiers on both sides of the Civil War. Opiates were cheap, legal and prevalent in the United States of the late 1800s. It was mistakenly believed that injecting morphine was not addictive, whereas ending habitual opium use caused flu-like symptoms and depression that morphine could easily alleviate.

From a calendar of 1886. Source: U.S. National Library of Medicine, NIH.

A powerful non-addictive alternative to opium and morphine would be ideal. In 1874 an English pharmacist boiled morphine and acetic acid (vinegar), acetylating both of the hydroxyl groups on morphine, to produce diacetylmorphine. This was synthesized and marketed commercially by the German pharmaceutical giant, Bayer, in 1898. Bayer launched the best-selling drug brand of all time, Heroin, as "the sedative for coughs." The new drug enjoyed widespread acceptance in the medical community and among patients.

Bayer was actively selling Heroin to dozens of countries, with free samples given to physicians. It was several years before the risk of addiction became obvious to doctors, who noted the extraordinary use of Heroin-based cough medicine. Heroin was not the miracle cure for morphine or opium addiction that some had hoped, so in 1913 Bayer halted production and erased the drug from their official company history. Bayer then focused on marketing their second blockbuster drug, aspirin.

Eventually in 1910, after 150 years of failed attempts to rid the country of opium, the Chinese were successful in convincing the British to dismantle the India–China opium trade. By the 1920s, many Western countries had made opiate use illegal, unless by prescription with medical care. As recently as 2007, Afghanistan's poppy production rose an estimated 15% over that in 2006 (Washington Post, 2007). The U.S. State Department's top counter-narcotics official, Tom Schweich, claims that Afghanistan is now "providing close to 95% of the world's heroin."

Voice of America reporter interviewing Afghan poppy cultivators. Source: Wikimedia Commons.

Opioids and Their Receptors

Opioids are chemicals that produce morphine-like effects in the body; these effects are blocked by antagonists of morphine such as naloxone. Agonists for opioid receptors include various neuropeptides (beta-endorphin, dynorphins, enkephalins, endomorphin) and other synthetic compounds that may have very different chemical structures than morphine. Opiates are a subset of opioids and are naturally occurring molecules that have very similar chemical structure to morphine and would therefore not include the neuropeptides.

Early studies with opioids implied that there must be multiple types of target receptors in the human body because different opioid compounds produced varied levels of effects including analgesia, respiratory depression, pupillary constriction, bradycardia (slow heart rate), reduced gastrointestinal GI motility, smooth muscle spasm, euphoria, sedation, and physical dependence.

Opioid receptors are members of the G protein-coupled receptors (GPCRs) that act to inhibit adenylate cyclase and thereby reduce intracellular levels of cyclic adenosine monophosphate (cAMP). Opioids can also have more direct roles in opening potassium channels (preventing nerve hyperpolarization and synapse firing) and to inhibit voltage-gated calcium channels at the cell membrane. Both have the net effect of reducing the excitability of neurons and the release of transmitter calcium to signal other neurons.

Opioid receptors are found extensively in the brain and spinal cord, as well as in vascular, gut, lung airway, cardiac, and some immune system cells.

Mu, Delta, and Kappa Receptors

There are three family members of opioid receptors, with similar protein sequences and structures (Kane et al., 2006). They are all transmembrane proteins of the rhodopsin family of GPCRs, embedded in the cell membrane and crossing it seven times. The Mu opioid receptors (MOR) are thought to give most of their analgesic effects in the central nervous system, as well as many side effects including sedation, respiratory depression, euphoria, and dependence. Most analgesic opioids are agonists on MOR (see table below). The Delta opioid receptors (DOR) are more prevalent for analgesia in the peripheral nervous system. The Kappa opioid receptors (KOR) contribute to analgesia in the spine and may exhibit dysphoria and sedation, but do not generally lead to dependence. Some drugs are relatively KOR-specific (Brunton et al., 2011).

Selectivity of Opioids for Opioid Receptors			
Opioid ligands		**Opioid receptor types**	
Opioid ligands	Mu (MOR)	Delta (DOR)	Kappa (KOR)
Agonists			
Morphine	+++	+	++
Codeine	+	+	+
Meperidine	++	+	+
Hydromorphone	+++		+
Etorphine	+++	+++	+++
Methadone	+++		
Fentanyl	+++	+	
Sufentanil	+++	+	
Partial mixed agonists			
Pentazocine	–	+	++
Nalbuphine	– – –	+	++
Buprenorphine	+		– –
Antagonists			
Naloxone	– – –	–	– –
Naltrexone	– – –	–	– – –
Neuropeptides			
Beta-endorphin	+++	+++	
Dynorphin	++	+	+++
Enkephalins	++	+++	

Selectivity of Opioids for Opioid Receptors			
Opioid ligands		Opioid receptor types	
Opioid ligands	Mu (MOR)	Delta (DOR)	Kappa (KOR)
Endomorphin	+++		

Key: + is agonist, – is antagonist.
Source: Adapted from Goodman and Gilman, 2011, and Molecular Pharmacology, 2000.

At the cellular level, all three receptor types act similarly, though their distribution in the body and sensitivity to various opioid drugs lead to markedly different pharmacologic reactions. In addition, all three of these subtypes are present in some tissues at various levels, further modulating the responses. In the membrane, opiate receptors can form both homo- and heterodimers, altering the pharmacologic properties of the respective receptors. For example, DORs can form heterodimers with both KORs and MORs. Thus, MOR-DOR and DOR-KOR heterodimers show less affinity for highly selective agonists and reduced receptor recycling.

Agonists and Antagonists

Opioids can be classified as agonists (activators), antagonists (blockers), or partial agonist/antagonists on their target receptors. Some opioids act as full agonists on one type of receptor and may be partial or antagonists on another subtype, complicating the pharmacologic responses to a drug (Molecular Pharmacology, 2000). One group of compounds consists of pure agonists, including many of the most common morphine-like drugs. They have high affinity for the mu receptors and varying affinities for the kappa and delta receptors. Some of these (eg, methadone, codeine, dextropropoxyphene) are weak agonists—their maximal pain relief and side effects are much less than those of morphine and they usually do not lead to addiction.

Partial agonists have mixed agonist-antagonist character; for example, nalorphine and pentazocine have a degree of agonism or antagonism on different receptors. Nalorphine can be an agonist in some tissues, yet competitively block the otherwise stronger effects of morphine there. Pentazocine and nalbuphine are antagonists on mu receptors but are partial agonists on KOR and DOR. This class of drugs usually results in dysphoria (emotional state marked by anxiety, depression, and restlessness) rather than euphoria.

Antagonists, including naloxone and naltrexone, have little effect if given on their own but are very effective inhibitors of the actions of other opioids, because they block the binding sites for agonists on the receptors.

Actions of Morphine

Morphine has many effects on the central nervous system:

- **Analgesia**: Morphine is effective for both acute and chronic pain, and is often used before and after surgery. While morphine is effective against nociceptive pain (pain resulting from tissue damage), it is also able to reduce the affective or psychological part of pain perception.
- **Respiratory depression**: The normal analgesic doses of opiates result in respiratory depression and increased concentration of CO2 in arterial blood. Both effects result from action at MOR: the respiratory center in the brain becomes less sensitive to the concentration of CO2 and fails to signal for more intense breathing. This is not usually accompanied by a decrease in the cardiovascular output, so it can be tolerated better than if both had been depressed, as for some other classes of drugs. However respiratory depression does occur at therapeutic doses of opiates and is the most common cause of death with opiate overdose.
- **Euphoria**: Morphine is able to induce a sense of contentment and well-being, which is key to its analgesic benefit. When anxiety and agitation are reduced, the patient can relax. If given intravenously (IV), morphine or heroin can produce a euphoric "rush." The euphoria is dependent on the original state; if the patient has become used to chronic pain, there is usually no euphoria with the pain relief (commonly the case for cancer patients). The euphoria results from opioids at the MOR, while KOR mediates the opposite dysphoria. Therefore a particular drug can have widely varying effects. Codeine and pentazocine do not usually produce euphoria, while nalorphine is associated with dysphoria.
- **Depression of cough reflex**: Cough suppression does not correlate well with pain relief or respiratory depression and thus may use another receptor type. Certain substitutions on the morphine molecule increase the antitussive effects relative to analgesic effects such that codeine is commonly used in cough medicines at sub-analgesic doses. Pholcodine is a more selective antitussive, though it can also cause increased constipation.
- **Nausea, vomiting**: This happens in up to 40% of morphine patients and does not appear to be separable from the analgesic relief. The emetic effect of morphine can be reduced by giving a counteracting antagonist such as naloxone. The nausea and vomiting induced by morphine usually fades away with repeated use.
- **Pupillary constriction**: This is centrally mediated by MOR and KOR receptors stimulating the oculomotor nucleus. Pinpoint pupils is a useful diagnostic in detecting

overdosage of opiates because most other causes of coma and respiratory depression are associated with dilated pupils.

- **Effects on GI tract**: Morphine causes an increased tone and decreased motility in the gastrointestinal tract, leading to potentially severe constipation. In addition, this may retard the absorption of other drugs given orally. Patients with pain associated with gallstones may not benefit and, in fact, have more pain, with slowed GI motility.
- **Other actions of opioids**: Morphine releases histamines from mast cells and may cause itching or urticaria (hives) at the injection site, or exhibit other systemic effects such as bronchoconstriction and hypotension from vasodilation; therefore, asthma patients should not be given morphine or the close structurally related opioids, but may be given synthetic opiates that do not release histamines. There also appears to be some immunosuppression with long-term opioid use, leading to possible increase of infections.

Morphine-Like Drugs and Synthetic Derivatives

Morphine, meperidine, hydromorphone, oxymorphone, methadone, fentanyl, and large doses of oxycodone (OxyContin) are generally used for severe pain relief. Morphine and full agonists have no limiting effectiveness for pain relief until the side effects prohibit any further increase in dose. Generally, any of the opioids can relieve pain if the correct dose is used, though some have undesirable side effects before full relief is achieved.

Morphine is the standard opioid for comparison; there is strong first-pass metabolism by the liver if it is taken orally, limiting the effective time of analgesia unless a sustained-release form is given. This slow-release form must not be broken up or chewed or an overdose may occur (A to Z Drug Facts, 2008).

Meperidine (Demerol) is very similar to morphine in its actions except that it leads to restlessness instead of sedation and can cause dry mouth and blurred vision from its antimuscarinic receptor effects. It does not have strong antitussive properties and can still lead to euphoric and dependence symptoms. Meperidine has a quicker onset of action than morphine, as rapid as 15 minutes and peaking at 1 to 2 hours, but it irritates tissues and is shorter acting.

Repeated dosing with meperidine can lead to accumulation of the metabolite normeperidine, which has a 15- to 20-hour half-life—compared to only 3 hours for meperidine itself—and can cause tremors, dysphoria, irritability, and possible seizures. Therefore repeated doses for more than 48 hours are not recommended. It is preferred for childbirth because it is short acting and does not depress breathing in the child as much as morphine.

Meperidine should not be combined with patients taking monoamine oxidase (MAO) inhibitors or in those with decreased renal function because severe or lethal complications may occur. The most prominent is an excitatory reaction ("serotonin syndrome") with delirium, hyperthermia, headache, hyper- or hypotension, rigidity, convulsions, coma, and death. This reaction may be due to the ability of meperidine to block neuronal reuptake of serotonin, resulting in serotonergic overactivity. Single doses of meperidine also appear to be effective in the treatment of postanesthetic shivering and in controlling reactions to immunotherapies such as Herceptin and interferons.

Methadone (half life = 30 hr) and levorphanol (half life = 16 hr) may be used orally for chronic pain. However, their relatively extended half lives can lead to CNS depression of respiration upon repeated doses. Methadone may also have less sedative action. Presumably the longer acting property arises from being bound to tissues extracellularly and then being slowly released over time. Hence withdrawal symptoms may be less severe than with shorter acting opiates like morphine and others, though psychological dependence can be equivalent.

Weak, long-acting MOR agonists like methadone can be used to wean addicts off of morphine and heroin because they would get no rush from a new injection of those while methadone was present, and yet withdrawal symptoms are less severe over time. (See the problems of increasing methadone overdosing and deaths in a later section.)

Tramadol is an oral opiate agonist that is used for rheumatoid arthritis, restless leg syndrome, and fibromyalgia. It can block reuptake of norepinephrine and serotonin and should not be combined with antidepressants, antipsychotics, or MAO inhibitors because of an increased risk of seizures (A to Z Drug Facts, 2008).

Fentanyl (100x morphine) and **sufentanil** (1000x) are highly potent synthetic phenylpiperidine derivatives, with short acting morphine-like actions, and are often used in anesthesia and in patient-controlled drips. These can give peak analgesic effects within 5 minutes of IV dosing, whereas morphine and meperidine would require 15 minutes. Fentanyl is a very strong opioid, most often used post operatively or for relief of cancer pain. In addition to injectable and patch forms, it also is made as a lollipop for patients to use when there is breakthrough pain even while taking scheduled opioids.

Fentanyl has a relatively small therapeutic index between effective dose and potentially lethal dose. Some patients using the patch (Duragesic transdermal patch) have been overdosed due to increased body temperature with fever and resulting elevated uptake of fentanyl. This has led to depressed respiration and death. Fentanyl has been abused in the illicit drug market, leading to overdose death (CDC, 2008).

Opioids are generally better for nociceptive pain resulting from tissue damage than for neuropathic pain (eg, "phantom limb" pain). Opioid dosage required for relief can vary widely among patients. Generally the dose should be increased until the desired pain relief is accomplished. If side effects become an issue, switching to another opioid is sometimes helpful. For chronic pain treatment, opioids are empirically titrated up to an optimal dose that lasts approximately 4 hours, and then given on a schedule, allowing the patient to skip a dose if it is not needed. Such a schedule works better than waiting for pain to return, when much higher doses may be required for relief. The patient can usually be allowed an option to additional dosing if there is breakthrough pain.

The adverse effects of morphine include CNS respiration depression, sedation, dizziness, nausea, vomiting, itching and constipation. Most serious is the CNS respiratory depression. Tolerance will develop to the emetic and respiration effects, but not the constipation. It is possible to include low doses of amphetamines to combat drowsiness and add stool softeners for the constipation. The transdermal fentanyl patches seem to induce fewer side effects than sustained-release oral morphine. Patients with pulmonary issues (eg, COPD) should be closely monitored for oxygen levels in the early periods of opioid treatment. Patients on multiple medications may be at increased risk for respiratory depression.

Tolerance, Dependence, Addiction, and Risk of Opioid Use Disorder

Regular opioid use leads to ever increasing doses required to get the same effect, which is referred to as tolerance.

Tolerance is the body's physical adaptation to a drug (in this case to opioids) so that greater amounts of the drug are required over time to achieve the initial effect as the body gets used to and adapts to the intake. One way to delay tolerance is to use low doses of opioids in combination with non-opioid pain relievers such as acetaminophen (common products include Vicodin, Percocet). Many opiates are marketed in at least one form with acetaminophen included (A to Z Drug Facts, 2008). Fortuitously, tolerance to the CNS-depressing side effects seems to develop as fast as tolerance to pain relief, so the dose can be escalated. There is often cross tolerance to other opioid agonists, but it is not usually equivalent, so switching drugs and using about a 50% equivalent dose can work to some degree.

Dependence is a term that has been used in the past to include both a physical and psychological need for a drug, but more recently is confined to the physical need. Dependence is a state of adaptation that is manifested by a drug class specific (in this case opioid) withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of a drug, and/or administration of an antagonist. As opioids are used over time, physical dependence will develop and the user will experience withdrawal symptoms if the drug is stopped suddenly. Tolerance is increased at approximately the same rate for analgesia, euphoria, and respiratory depression, while pupillary constriction and constipation show little tolerance and become greater symptoms with increased dose.

In general, patients using an opioid for acute pain management will taper their dosage as the pain decreases thereby avoiding withdrawal symptoms. Classic opioid withdrawal symptoms are described as severe flu-like symptoms and in general are not life threatening, but the user feels like dying if no medical assistance is available. Initial symptoms may begin 6 to 14 hours after the last dose and include anxiety, irritability, perspiration, restlessness, muscle aches, rhinorrhea, frequent yawning and insomnia. As time goes on the user experiences piloerection (goose bumps), diarrhea, abdominal cramping, nausea and vomiting, dilated pupils, tachycardia and high blood pressure. Withdrawal symptoms usually begin to taper after 3 days and should be minimal within a week, however some users may have an extended withdrawal experience.

Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Pseudo addiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudo-addiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated.

Opioid Use Disorder

Due to confusion about the terms *drug dependence* and *addiction*, the new Diagnostic and Statistical Manual of Mental Disorders (DSM5) uses the diagnosis of Substance Use Disorders.

The new terminology for a diagnosis of an opioid addiction is Opioid Use Disorder and it can be categorized as mild, moderate, or severe depending upon the number of diagnostic criteria. It lists eleven diagnostic criteria of which at least two must be met within a 12-month period to make the diagnosis:

1. Opioids are taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid , use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

10. Tolerance*
11. Withdrawal*

*This criterion is not considered to be met if the opioid is taken under appropriate medical supervision.
Source: DSM5, 2013.

Pharmacokinetics (ADME)

The **absorption, distribution, metabolism, and excretion (known commonly as ADME)** are important features of any medication. Absorption of oral opiates varies widely. Morphine is irregular in its oral uptake so it is usually given by IV or intramuscular injection (IM). There is, however, a slow-release oral form for those with chronic pain, though the patient must not chew or otherwise crush these tablets or an overdose will occur. Codeine is well absorbed if taken orally, and is usually used as a cough suppressant. Most opiates are subject to significant first-pass metabolism by the liver and are therefore less potent orally than if delivered by IV or injection.

The half-life of most morphine derivatives given by mouth is 3 to 6 hours, though some of the first-pass liver metabolites (after glucuronidation) still have considerable analgesic effects. Morphine is not well metabolized by neonates and is relatively long acting causing respiratory depression, so it should not be used during childbirth, where meperidine is a safer choice. Respiration can be restored with the opioid antagonist naloxone, as necessary.

For post operative or chronic pain, opioids have been used for **patient-controlled analgesia (PCA)**. Patients receiving IV opioids are able to self-medicate via a pump (with dosing and limits determined by a physician's orders). PCA allows patients to medicate as needed and avoids the potential delay due to other demands on the nurse providing pain medication. The pump has not generally led to overmedication and dependence as originally feared. Instead patients are treated more effectively and tend to self-taper their dosing as the pain resolves.

Acute overdose of morphine results in respiratory depression and even coma, and is characterized by constricted pupils. The antagonist naloxidone can be given by IV but this often leads to severe withdrawal symptoms if the overdose was, as is most common, in a habitual user. As with many other medications, the dosage of opiates for medication must be altered in any patients with reduced renal or liver function, which are especially common in elders with comorbidities.

Other Opioid Analgesics

Diacetylmorphine (**heroin**), discovered in 1894, is produced from morphine by simple chemical acetylation. Heroin, though metabolized to morphine in the body, is more lipophilic than morphine and crosses the blood brain barrier (BBB) more readily, giving a greater rush with IV injection and a relatively shorter time of action (2 hr). It has no real medical benefit over morphine, so its synthesis and sale is banned in most countries.

Codeine (3-methylmorphine) is synthesized from morphine and is better absorbed by mouth, though it has only about 20% of the analgesic potency. It is primarily used for headache or backache and is unlikely to give euphoria or produce addiction. It is commonly used in cough suppressants and can lead to constipation as a side effect. Codeine is avoided in patients taking MAO inhibitors.

Etorphine, discovered in the 1960s, is a morphine-like analog that is 1000x more potent; it is used primarily in the veterinary field to immobilize wild animals; for example one dart can hold enough etorphine to halt an elephant or rhino.

Pentazocine is a mixed agonist and antagonist, where low doses act similarly to morphine but increasing doses do not. Therefore, higher doses do not depress respiration dangerously, but hallucinations and dysphoria (rather than euphoria) increase, presumably due to interaction at KOR. Pentazocine can also lead to dependence.

Propoxyphene was withdrawn by the FDA in November 2010 because new clinical data showed it increased the risk of serious or fatal heart rhythm irregularities and that the medical benefits did not outweigh the risks. Taken at efficacious doses, propoxyphene could result in problems in the heart's electrical activity, leading to sudden death. Propoxyphene was a prescription drug sold alone (Darvon) or in combination with acetaminophen (Darvocet) and had been approved for mild to moderate pain relief since 1957 (FDA, 2010).

Opioid Antagonists to Counter Dependency

Nalorphine is similar to morphine in structure, yet it is an antagonist of morphine action and was among the first drugs to imply that there was a specific receptor for morphine. It is a competitive inhibitor of morphine at low doses on MOR but probably has some weak agonist effects for analgesia on DOR and KOR at higher doses, though dysphoria can become a serious drawback. Once used for heroin overdoses, it also can cause respiratory depression, so it has been replaced in practice by naloxone.

Naloxone is a pure opioid antagonist at all three receptors and also blocks the endogenous neuropeptides such as endorphins and enkephalins. It can rapidly reverse the effects of morphine and other related opiates, and causes hyperalgesia (increased pain) in stressful situations where natural endorphins would have normally reduced pain. It is used to counteract opiate overdose, restoring respiration, and to reverse opiate analgesia in childbirth, to benefit breathing in the newborn child. Given by IV, its action is almost immediate, but the short 1 to 2 hour time of action, due to rapid liver metabolism, may require repeat dosing. Though it has no effects alone, it is effective in diagnosing addiction to opiates by rapidly inducing withdrawal symptoms.

Naltrexone is similar to nalaxone except that it is active for a much longer time (10-hr half life) and may be used in opiate addicts to prevent relapse, as no euphoria (or analgesia) would arise from a new injection. A single 100-mg dose can block heroin effects for 48 hours.

Buprenorphine is a highly lipophilic, partial MOR agonist that exhibits only limited activity, yet it can block other opiates at MOR. It can induce some withdrawal symptoms in those who have taken other opiates for weeks. It can relieve respiratory repression induced by fentanyl without reversing all of the analgesic effects, as would occur with naloxone.

Buprenorphine is given by IV for use in pain relief, whereas oral formulations are used in treatment for opioid dependence. In 2002 the FDA approved Subutex (buprenorphine) and Suboxone tablets (buprenorphine and naloxone) for the treatment of opiate dependence. Subutex and Suboxone treat opiate addiction by preventing symptoms of withdrawal from heroin and other opiates. Naloxone has been added to Suboxone to guard against IV abuse of buprenorphine by opiate addicts (FDA, 2002).

Overdose from Prescription Opioid Pain Relievers

The Centers for Disease Control and Prevention (CDC) has declared an epidemic of overdoses from prescription opioid pain relievers (OPR) and has published several papers on the topic, including new guidelines for prescribing opioids for chronic pain (CDC, 2011a, 2011b, 2016).

Deaths from prescription painkillers—opioid pain relievers such as Vicodin (hydrocodone), OxyContin (oxycodone), Opana (oxymorphone), and methadone—have reached epidemic levels in the past decade. The number of overdose deaths is now greater than those of deaths from heroin and cocaine combined. From 1999 to 2014, more than 165,000 people died from an opioid overdose in the United States. The biggest problem is the use of medications without a prescription just for the "high" they cause. In 2010 as many as 12 million Americans (age 12 or older) reported nonmedical use of prescription painkillers in the previous year.

Enough prescription painkillers were prescribed in 2010 to medicate every American adult around-the-clock for a month. Although most of these pills were prescribed for a medical purpose, many ended up with others who misused or abused them. Improving the way painkillers are prescribed can reduce the abuse or overdose from these powerful drugs while making sure patients have access to safe, effective treatment. The CDC (2011a) released the following information.

Prescription Painkillers in the United States

Prescription painkiller overdoses are a public health epidemic.

- Prescription painkiller overdoses killed nearly 15,000 people in the United States in 2008. This is more than 3 times the 4,000 people killed by these drugs in 1999.
- In 2010 about 12 million Americans (age 12 or older) reported nonmedical use of prescription painkillers in the past year.
- Nearly half a million emergency department visits in 2009 were due to people misusing or abusing prescription painkillers.
- Nonmedical use of prescription painkillers costs health insurers up to $72.5 billion annually in direct healthcare costs.

Certain groups are more likely to abuse or overdose on prescription painkillers.

- Many more men than women die of overdoses from prescription painkillers.
- Middle-aged adults have the highest prescription painkiller overdose rates.
- People in rural counties are nearly twice as likely to overdose on prescription painkillers as people in big cities.
- Whites and American Indian or Alaska Natives are more likely to overdose on prescription painkillers.
- About 1 in 10 American Indian or Alaska Natives aged 12 or older used prescription painkillers for nonmedical reasons in the past year, compared to 1 in 20 whites and 1 in 30 blacks.

The supply of prescription painkillers is larger than ever.

- The quantity of prescription painkillers sold to pharmacies, hospitals, and doctors' offices was 4 times larger in 2010 than in 1999.
- Many states report problems with "pill mills," where doctors prescribe large quantities of painkillers to people who don't need them medically. Some people also obtain prescriptions from multiple prescribers by "doctor shopping."

Some states have a bigger problem with prescription painkillers than others.

- Prescription painkiller sales per person were more than 3 times higher in Florida, which has the highest rate, than in Illinois, which has the lowest.
- In 2008/2009, nonmedical use of painkillers in the past year ranged from 1 in 12 people (age 12 or older) in Oklahoma to 1 in 30 in Nebraska.
- States with higher sales per person and more nonmedical use of prescription painkillers tend to have more deaths from drug overdoses.

What Can Be Done

By the U.S. Government

- Tracking prescription drug overdose trends to better understand the epidemic.
- Educating healthcare providers and the public about prescription drug abuse and overdose.
- Developing, evaluating, and promoting programs and policies shown to prevent and treat prescription drug abuse and overdose, while making sure patients have access to safe, effective pain treatment.

By the States

- Start or improve prescription drug monitoring programs (PDMPs), which are electronic databases that track all prescriptions for painkillers in the state.
- Use PDMP, Medicaid, and workers' compensation data to identify improper prescribing of painkillers.
- Set up programs for Medicaid, workers' compensation programs, and state-run health plans that identify and address improper patient use of painkillers.
- Pass, enforce and evaluate "pill mill," doctor shopping, and other laws to reduce prescription painkiller abuse.
- Encourage professional licensing boards to take action against inappropriate prescribing.
- Increase access to substance abuse treatment.

By Individuals

- Use prescription painkillers only as directed by a healthcare provider.
- Make sure you are the only one to use your prescription painkillers. Not selling or sharing them with others helps prevent misuse and abuse.
- Store prescription painkillers in a secure place and dispose of them properly.

- Get help for substance abuse problems if needed (1 800 662 HELP).

By Health Insurers

- Set up prescription claims review programs to identify and address improper prescribing and use of painkillers.
- Increase coverage for other treatments to reduce pain, such as physical therapy, and for substance abuse treatment.

By Healthcare Providers

- Follow guidelines for responsible prescribing, including
- Screening and monitoring for substance abuse and mental health problems.
- Prescribing painkillers only when other treatments have not been effective for pain.
- Prescribing only the quantity of painkillers needed based on the expected length of pain.
- Using patient-provider agreements and urine drug tests for people using prescription painkillers long-term.
- Talking with patients about safely using, storing, and disposing of prescription painkillers.
- Use PDMPs to identify patients who are improperly using prescription painkillers.

The epidemic of prescription drug overdoses in the United States has worsened over the last decade, and by 2008 drug overdose deaths (36,450) were approaching the number of deaths from motor vehicle crashes (39,973), the leading cause of injury death in the United States. Increasing trends in opioid pain reliever (OPR) sales has mirrored emergency room visits, drug treatment center visits, and deaths from overdoses. As a result of the prescription opioid overdose epidemic, as of March 22, 2016 the Food and Drug Administration requires a black box warning for all opioids that notes the serious risks of misuse, abuse, addiction, overdose, and death. For more on this, click here.

Given that 3% of physicians accounted for 62% of the OPR prescribed in one study (Swedlow et al., 2011), the proliferation of high-volume prescribers can have a large impact on OPR overdose death rates. Large increases in overdoses involving the types of drugs sold by illegitimate pain clinics ("pill mills") have been reported. Such clinics provide OPR indiscriminately to large numbers of patients without adequate evaluation or followup. Sales data also did not include buprenorphine, an opioid primarily used for substance abuse treatment, though sometimes prescribed for pain. Its inclusion with drugs primarily used to treat pain would have inappropriately increased sales rates.

Public health interventions to reduce prescription drug overdose must strike a balance between reducing misuse and abuse and safeguarding legitimate access to treatment. To find this balance, healthcare providers should only use OPR in carefully screened and monitored patients when non-OPR treatments have not been sufficient to treat pain. States, as regulators of healthcare practice, have the responsibility and authority to monitor and correct inappropriate and illegal prescribing. Data from Medicare claims and from state prescription drug-monitoring programs, which collect records of prescription drugs prone to abuse from pharmacies, can be used to identify and address OPR misuse and abuse.

Listed below are the 12 recommendations released in March of 2016 by the CDC to serve as guidelines for primary care clinicians to use when prescribing opioids for chronic pain. The guidelines are grouped into three areas for consideration (see box below) and are followed by rationale for the recommendations and considerations for implementation. See this reference for full details.

CDC: 2016 Guidelines for Prescribing Opioids for Chronic Pain

Determining when to initiate or continue opioids for chronic pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Opioid selection, dosage, duration, followup and discontinuation

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh

harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing risk and addressing harms of opioid use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

All interventions need to be evaluated further and new interventions developed. Concerted attempts to address this problem, especially in states with high rates of OPR sales, nonmedical use, or overdose mortality, might help control the epidemic.

Methadone Use and Overdose Deaths

[This section is adapted from GAO, 2009.]

Methadone has been used for the treatment of opioid addiction and pain, and it is relatively inexpensive compared to other opioids. Because methadone has a much longer half life than most opiates (up to 30 hr), initial dosing and modification of the dosing regimen are much different than for the faster-acting opiates because the drug takes longer to clear. This is the desired property that led to methadone as the choice for recovering opiate addicts.

A once-a-day dose will activate the MOR receptors and alleviate withdrawal symptoms, while at the same time occupying those sites so that a new dose of opiate will have little effect and not give the "rush" the addict may have desired. Most of the earlier use for methadone has been in opioid treatment programs to help recovering heroin or other prescription opiate addicts (CDC, 2002).

Since the late 1990s, methadone has been increasingly prescribed by practitioners to treat patient pain. However, while a single dose suppresses opioid withdrawal symptoms for a day or more, it generally relieves pain for only 4 to 8 hours while remaining in the body much longer. Further, it may take several days to achieve full pain relief, so dosage increases must be done more slowly than with other opioids. Patients may feel the need to take more methadone before the previous dose has cleared, leading to potential overdose, with depressed respiration.

Liquid methadone is most commonly used for addiction treatment, while the 5- and 10-mg tablets are most often prescribed for pain management. The FDA considers methadone safe and effective for both pain management and addiction treatment, although not all forms of methadone are FDA-approved for both of these purposes.

In 2001 healthcare providers and hospitals were required to guarantee that their patients received appropriate pain treatment when the Joint Commission, a national healthcare facility standards-setting and accrediting body, implemented pain standards for hospital accreditation. Methadone was initially used more for the treatment of cancer pain, but it has been increasingly used for chronic noncancer pain.

The growing availability of methadone through its increased use for pain management is a contributing factor to the rise in methadone-associated overdose deaths. Drug Enforcement Administration (DEA) data show that from 2002 to 2007 distribution of methadone to businesses associated with pain management—pharmacies and practitioners—almost tripled. Similarly, data from IMS Health showed that from 1998 through 2006 the number of annual prescriptions of methadone for pain increased by about 700 percent, from about 531,000 in 1998 to about 4.1 million in 2006.

Lack of knowledge about the unique pharmacological properties of methadone by both practitioners and patients has also been identified as a factor contributing to methadone-associated overdose deaths, especially when initiating a treatment with methadone or converting patients to methadone from other opioids.

Heroin Use on the Rise

Research suggests that prescription opioids are becoming the gateway to heroin use. Nearly half of young people who inject heroin report that they first used prescription opioids but found it is cheaper and easier to obtain heroin. Opioid users may progress to crushing prescription opioids to snort or inject, which yields a more intense high, and heroin can readily replace that experience. The greatest danger of heroin on the black market is that the user has no way of knowing the dosage (NIDA 2014). Heroin overdoses have more than tripled since 2010, leading to more than 10,500 deaths in 2014 (USDHHS, 2016).

The Food and Drug Administration along with the USDHHS and other organizations are working with localities to allow and teach the use of **naloxone (Narcan)** by laypersons as a quick response to potential opioid overdoses (Lurie, 2015). See the Prescription Drug Abuse Policy System funded by NIDA to learn about the laws related to the use of naloxone in your state.

Cannabis as a Harm Reduction Agent

Medical marijuana, more appropriately called **cannabis**, may be used as a harm reduction agent to combat the opioid epidemic. A study published in 2014 found that in states with a medical cannabis law there was a 24.8% lower incidence of opioid overdose deaths compared to states where cannabis remains illegal (Bachhuber et al., 2014).

Cannabis is an ancient herbal medicine and was one of the most popular medicines in the United States prior to the Marihuana Tax Act of 1937, which marked the beginning of cannabis prohibition. Cannabis is an effective medicine for neuropathic pain, and pain management is the most common use of cannabis in the states that currently allow the use of medical cannabis.

When used as an adjunct to opioids for pain management, cannabis works synergistically with opioids to provide pain relief. Research shows that patients who use cannabis can use a lower dose of an opioid and that tolerance to the opioid develops more slowly (Cichewicz, 2004; Abrams et al., 2011). In addition, cannabis can help alleviate opioid withdrawal symptoms, leading some clinicians to call cannabis an exit drug (Lucas, 2012; Reiman, 2009).

Unfortunately, many clinicians include the active ingredient of cannabis, tetrahydro-cannabinol (**THC**), in the urine drug screen panels for patients prescribed opioids. While drug screens can be clinically useful to ensure that the patient is using the prescribed opioid and to ensure other opioids or drugs, such as benzodiazepines, are not used illicitly (due to potential overdose from the combination), the illicit use of cannabis is not necessarily of clinical concern. The 2016 CDC guidelines cited earlier call for urine drug screening (recommendation 10), but note that

> Clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. For example, experts noted that there might by uncertainty about the clinical implications of a positive urine drug test tor tetrahydrocannabinol (THC). (Dowell et al., 2016)

Patient Education on Opioids

[This information is taken from FDA, 2009.]

Keep Your Doctor Informed

Inform your healthcare professional about any history of substance abuse. All patients treated with opioids for pain require careful monitoring by their healthcare professional for signs of abuse and addiction, and to determine when the analgesics are no longer needed.

Follow Directions Carefully

Opioids are associated with significant side effects, including drowsiness, constipation, and depressed breathing, depending on the amount taken. Taking too much could cause severe respiratory depression or death. Do not crush or break pills. This can alter the rate at which the medication is absorbed and lead to overdose and death.

Reduce the Risk of Drug Interactions

Do not mix opioids with alcohol, antihistamines, barbiturates, or benzodiazepines. All of these substances slow breathing and their combined effects could lead to life-threatening respiratory depression.

Summary

Morphine and other opiates mimic the action of natural chemicals, endorphins, produced by the body in response to pain. Endorphins are small-chain peptides that activate endogenous opioid receptors. Opioid receptors are proteins embedded in the cell membrane; opioid agonists bind to the receptors to initiate their effects. The highest density of opioid receptors is found in the limbic system and the spinal cord. Their activation produces feelings of happiness, relaxation, fearlessness, and tolerance to pain.

Morphine sulfate relieves pain by stimulating the mu opiate receptors in the CNS; it also causes respiratory depression, peripheral vasodilation, inhibition of intestinal peristalsis, and stimulation of chemoreceptors that cause vomiting and increase bladder tone. Contraindications include acute asthma, upper airway blockage, hypersensitivity to opiates, and diarrhea resulting from poisoning or toxins.

Generally, severe pain from trauma, burns, and post surgery is treated by injection of strong opioids such as morphine or fentanyl. Mild inflammatory pain such as arthritis is treated by NSAIDs supplemented with weak opiods such as codeine, or pentazocine given orally. Severe cancer pain, arthritis or back pain is treated with strong opioids given by injection or epidurally. Patient controlled analgesia (PCA) systems can be used post operatively. Chronic neuropathic pain does not usually respond well to opioids and may be treated with cannabis preparations in states that allow its use. An epidemic of opioid overdose deaths is, in part, caused by an overuse of opioid prescriptions, and the CDC issued its opioid prescribing guidelines in an attempt to decrease problems related to opioid use.

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Post Test: Opioids as Medications (178)

Use the answer sheet following the test to record your answers.

1. There are three family members of opioid receptors. Which one of the following is not an opioid receptor?:

a. Beta opioid receptor (BOR).
b. Delta opioid receptor (DOR).
c. Kappa opioid receptor (KOR).
d. Mu opioid receptor (MOR).

2. Opioids can be classified as agonists (activators), antagonists (blockers), or partial agonists/antagonists on their target receptors. When they are both agonists and antagonists:

a. Their actions on receptors are neutralized.
b. They are acting differently on different receptors.
c. The agonists are always stronger.
d. The antagonists are always stronger.

3. One action of morphine is:

a. Dry mouth.
b. Tinnitus.
c. Pupillary constriction.
d. Sinus constriction.

4. Because morphine is quickly metabolized by the liver, oral dosage:

a. Is not a possible route of administration.
b. Enhances the potential for liver damage.
c. Must be designed to be absorbed through the stomach.
d. Is best managed in a sustained-release form.

5. Meperidine (Demerol) is very similar to morphine in its actions except that:

a. It has greater ability to calm restlessness in the patient.
b. Repeated doses for more than 48 hours are not recommended.

c. It has strong antitussive properties.

d. Dependence is not seen with Demerol.

6. Methadone is used to wean addicts off morphine and heroin because:

a. There is no rush with a subsequent injection of the drug of choice.

b. Methadone is not addictive and so is safe for addicts.

c. There is no danger of CNS depression even with repeated doses.

d. Overdosing is not a problem.

7. Fentanyl is a highly potent synthetic (100x morphine) that:

a. Is limited to IV delivery.

b. May only be used during surgical procedures.

c. Has peak analgesic effect within 5 minutes of dosing.

d. Does little to relieve cancer pain.

8. Dependence upon a particular drug is:

a. Generally a sign that the drug is doing its job.

b. A higher dose is required to get the same effect.

c. Entirely psychological and reflective of personality issues.

d. Both physical and psychological and can proceed to withdrawal when the drug is stopped suddenly.

9. Tolerance to a particular drug means that:

a. No side effects are experienced.

b. The pain-free period is reduced and a higher dose is required for relief.

c. Another drug should be substituted.

d. The dose should be reduced to avoid addiction.

10. Naloxone, naltrexone, and buprenorphine are:

a. Opioid antagonists that are used to counter dependency.

b. Opioid agonists that enhance the effects of common opioids.

c. Never given to patients who are suspected of opioid dependence.

d. Drugs of choice where opioids are undesirable for pain relief.

11. The group most likely to abuse or overdose on prescription painkillers is:

a. Preteens and teens.

b. Young adults.

c. Middle-aged adults.

d. Older adults.

12. Healthcare providers can help to address the prescription painkillers epidemic by:

a. Ascertaining whether the patient is really in pain.

b. Giving only enough medication for 24 to 48 hours at a time.

c. Requiring drug testing for patients suspected of dependence.

d. Prescribing painkillers only when other treatments have been ineffective for pain.

13. Methadone has been used in treatment programs for drug addicts because it is safe and has never been associated with overdose death.:

a. True

b. False

14. Chronic neuropathic pain does not usually respond well to opioids and is often treated with:

a. Physical therapy.

b. NSAIDs.

c. Tricyclic antidepressants.

d. IV placebos.

Answer Sheet

Opioids as Medications (178)

Name (Please print your name): _____

Date: _____

Passing score is 80%

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____
11. _____
12. _____
13. _____
14. _____

Course Evaluation: Opioids as Meds (178)

Please use this scale for your course evaluation. Items with asterisks * are required.

- 1 = Strongly agree
- 2 = Agree
- 3 = Neutral
- 4 = Disagree
- 5 = Strongly disagree

* Upon completion of the course, I was able to:

a. Comment on the history of poppies and the opium trade.

○1 ○2 ○3 ○4 ○5

b. Identify the various receptor targets of opioid action and explain how they differ.

○1 ○2 ○3 ○4 ○5

c. Describe the actions of morphine.

○1 ○2 ○3 ○4 ○5

d. Identify morphine-like drugs and synthetic derivatives.

○1 ○2 ○3 ○4 ○5

e. Discuss dependence, tolerance, and addiction in opioids.

○1 ○2 ○3 ○4 ○5

f. Explain ADME in pharmacokinetics.

○1 ○2 ○3 ○4 ○5

g. List other opioid analgesics in addition to morphine.

○1 ○2 ○3 ○4 ○5

h. Distinguish between opioid agonists and antagonists and the ways they are used.

○1 ○2 ○3 ○4 ○5

i. Summarize the current problem of overdose from prescribed opioids.

1 2 3 4 5

j. Describe the use of methadone and its relation to overdose deaths.

1 2 3 4 5

k. Teach a patient how to minimize the negative side effects of opioid use.

1 2 3 4 5

l. Explain cannabis as an adjunct treatment for chronic pain to reduce the use of opioids.

1 2 3 4 5

* The author(s) are knowledgeable about the subject matter.

1 2 3 4 5

* The author(s) cited evidence that supported the material presented.

1 2 3 4 5

* This course contained no discriminatory or prejudicial language.

Yes No

* The course was free of commercial bias and product promotion.

Yes No

* As a result of what you have learned, do you intend to make any changes in your practice?

Yes No

If you answered Yes above, what changes do you intend to make? If you answered No, please explain why.

* Do you intend to return to ATrain for your ongoing CE needs?

Yes, within the next 30 days.

Yes, during my next renewal cycle.

- Maybe, not sure.
- No, I only needed this one course.

* Would you recommend ATrain Education to a friend, co-worker, or colleague?

- Yes, definitely.
- Possibly.
- No, not at this time.

* What is your overall satisfaction with this learning activity?

1 2 3 4 5

* Navigating the ATrain Education website was:

- Easy.
- Somewhat easy.
- Not at all easy.

* How long did it take you to complete this course, posttest, and course evaluation?

- 60 minutes (or more) per contact hour
- 50-59 minutes per contact hour
- 40-49 minutes per contact hour
- 30-39 minutes per contact hour
- Less than 30 minutes per contact hour

I heard about ATrain Education from:

- Government or Department of Health website.
- State board or professional association.
- Searching the Internet.

- ○ A friend.
- ○ An advertisement.
- ○ I am a returning customer.
- ○ My employer.
- ○ Other
- ○ Social Media (FB, Twitter, LinkedIn, etc)

Please let us know your age group to help us meet your professional needs.

- ○ 18 to 30
- ○ 31 to 45
- ○ 46+

I completed this course on:

- ○ My own or a friend's computer.
- ○ A computer at work.
- ○ A library computer.
- ○ A tablet.
- ○ A cellphone.
- ○ A paper copy of the course.

Please enter your comments or suggestions here: _____

_____

_____

_____

Registration: Opioids as Medications (178)

Please print and answer all of the following questions (* required).

* Name: _____

* Email: _____

* Address: _____

* City: _____ * State: _____ * Zip: _____

* Country: _____

* Phone: _____

* Professional Credentials/Designations:

_____

* License Number and State: _____

* Please email my certificate:

○ Yes ○ No

(If you request an email certificate we will not send a copy of the certificate by US Mail.)

Payment Options

You may pay by credit card or by check.
Fill out this section only if you are **paying by credit card.**
2 contact hours: $17

Credit card information

* Name: _____

Address (if different from above): _____

* City: _____ * State: _____ * Zip: _____

* Card type:

○ Visa ○ Master Card ○ American Express ○ Discover

* Card number: _____

* CVS#: _____

* Expiration date: _____