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"Pain Management: Opioids—Use & Misuse"

September 2015

Pain management is a controversial area of therapy. Narcotics are a viable portion of treatment; yet, where does use end, and misuse begin. Healthcare practitioners often conflict with regulatory bodies regarding this subject. In this lesson we discuss the use and misuse of opioids.

Pharmacists will be able to:

1. Describe the pathophysiology of pain.
2. Discuss the MOA of opioids.
3. Identify opioid receptor types.
4. Review common opioid drugs, their side effects, precautions & drug interactions.
5. Relate significance of new dosage forms.
6. Review abuse deterrent features.
7. Summarize some changes made to some drug classification schedules by the DEA.
8. Define substance abuse disorder & outline an overview of patient monitoring.

Technicians will be able to:

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3. Summarize some changes made to some drug classification schedules by the DEA.
4. Define substance abuse disorder & outline an overview of patient monitoring.

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BACKGROUND

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain alerts the body to injury and helps protect against further injury by reflex reaction or by causing the body to protect the injury while it heals. It is often called the fifth vital sign. Before the 1990's, doctors in the United States took a minimalist approach to treating pain. Treatment for primary pain fails to achieve adequate relief in at least 40% of patients even though effective treatments are available. Many clinicians were trained years ago when little was known about pain. Other barriers to proper pain relief include the stigmas associated with the prescribing of opioid drugs. Misconceptions about opioid use and addiction exist among the public and law enforcement. People might not visit the doctor because of this and some doctors have held back from prescribing the necessary opioids due to perceptions by the public and regulatory agencies. However, a shift has occurred since the 1990's in part due to marketing campaigns by drug manufactures and changes in attitudes fueled by greater knowledge into pain. Chronic pain is vastly different than acute pain in that it persists long (greater than three months) after the initial injury. Some people suffer chronic pain in the absence of any past injury or evidence of body damage which also poses a barrier to receiving adequate relief. Chronic pain is the most common reason that people visit a healthcare practitioner. It affects over 100 million people in the U.S., more than those affected by diabetes, heart disease, and cancer combined. In 2010 a study by The Institute of Medicine Report from the Committee on Advancing Pain Research found that chronic pain health problems cost society $560-$630 billion annually. This number includes cost of health care due to pain ($260-$300 billion) and lost productivity and work missed ($247-$336 billion). Using a multi-discipline approach by doctors, nurses, and pharmacists can increase outcomes of effective pain management while reducing abuse of opioids and adverse incidents.

PATHOPHYSIOLOGY OF PAIN

Not only do barriers exist to treating pain effectively but barriers have existed to the understanding of pain. Lack of human volunteers as well as the lack of desire by most if not all researchers to test on animals coupled with ethics has limited the knowledge of pain for many years. Recent advances allowing for research without subjecting humans or animals to unnecessary pain and empirical data gathered from subjects who already are experiencing pain has led to a greater understanding of how pain works in the body. Specialized afferent (sensory) neurons called nociceptors are responsible for turning painful stimuli, also known as noxious stimuli, into a nerve impulse that travels through the body to the spinal cord and to the brain. This process is called nociception and occurs in four steps: **transduction, transmission, perception, and modulation**.

The first step in this pain pathway is **transduction**. Transduction is the normal response process by which the body reacts to noxious stimuli caused by trauma to produce a nociceptive impulse and to help alert the body to possible injury. The body can sense noxious stimuli from three sources: chemical, mechanical, or thermal. Chemical stimuli include such things as toxic substances, ischemia, infection, excitatory neurotransmitters, caustic or irritating substances. Mechanical stimuli include crushing, pressure, cutting, pinching, swelling, and ripping. Thermal noxious stimuli include extreme hot or cold sensations and burns. When cell trauma occurs there is a release of inflammatory markers including potassium ions, bradykinins, prostaglandins, histamine, leukotrienes, serotonin, and substance P. Superficial somatic pain is very localized,

sharp, and well defined. Deep somatic pain is pain felt in bones, cartilage, ligaments, tendons, blood vessels, and muscles. Deep somatic pain tends to be dull and difficult to locate. Visceral pain is pain from the organs. Organs do not usually feel thermal or mechanical pain but are susceptible to stretching, ischemia, and inflammation. Pain is usually diffuse, difficult to locate, and dull.

Most nociceptors consist of A-delta fibers and C fibers. A-delta fibers are thinly myelinated, large diameter (2-5mm), fast conducting (5-40 meters/second) afferent fibers. C fibers are unmyelinated, small diameter (0.4-1.2mm), slow conducting (0.5-2.0 meters/second) afferent fibers. Pain quality involving A-delta fibers can be described as well localized, sharp, or stinging as sometimes referred to as fast or first pain. Pain quality involving C fibers can be described as diffuse, dull, burning, or aching and sometimes referred to as slow or second pain. It is estimated that C fibers make up around 70% of all nociceptors while A-delta fibers help to mediate reflex responses to possible injury. Because of the differences in their conduction speeds, a person will often feel the fast pain from A-delta fibers which dissipates quickly giving way to the slow persistent pain from C fibers.

Transmission occurs when nerve pathways end and neurotransmitters must continue the impulse by traveling across synaptic clefts. This occurs in three places, from the site of transduction along the nociceptor fibers to the dorsal horn in the spinal cord, from the spinal cord to the brain stem and thalamus, and through connections between the thalamus, cortex, and other higher levels of the brain.

Perception of pain is the end result of the neuronal activity of pain transmission and where pain becomes a multidimensional experience. The experience of pain has affective-motivational, sensory-discriminative, emotional and behavioral components. When the painful stimuli are transmitted to the brain stem and thalamus, multiple cortical areas are activated and responses are elicited. The reticular system is responsible for the autonomic and motor response to pain and for warning the individual to do something, for example, automatically removing a hand when it touches a hot saucepan. It also has a role in the affective-motivational response to pain such as looking at and assessing the injury to the hand once it has been removed from the hot saucepan. The somatosensory cortex is involved with the perception and interpretation of sensations. It identifies the intensity, type and location of the pain sensation and relates the sensation to past experiences, memory and cognitive activities. It identifies the nature of the stimulus before it triggers a response, for example, where the pain is, how strong it is and what it feels like. The limbic system is responsible for the emotional and behavioral responses to pain such as attention, mood, and motivation as well as processing pain and the past experiences of pain.

The modulation of pain involves increasing or inhibiting transmission of impulses in the spinal cord. The multiple, complex pathways involved in the modulation of pain are referred to as the descending modulatory pain pathways (DMPP) and these can lead to either an increase in the transmission of pain impulses (excitatory) or a decrease in transmission (inhibition). Descending inhibition involves the release of inhibitory neurotransmitters that block or partially block the transmission of pain impulses, and; therefore, produce analgesia. Inhibitory neurotransmitters involved with the modulation of pain include: endogenous opioids (enkephalins and endorphins); serotonin (5-HT); norepinephrine (noradrenalin); gamma-aminobutyric acid (GABA); neurotensin; acetylcholine; and oxytocin. Endogenous pain modulation helps to explain the wide variations in the perception of pain in different people as individuals produce

different amounts of inhibitory neurotransmitters. Endogenous opioids are found throughout the central nervous system (CNS) and prevent the release of some excitatory neurotransmitters, for example, substance P, therefore, inhibiting the transmission of pain impulses.

Many theories have been developed to explain the differences among people in how pain is perceived, what influences pain, and other phenomena. Despite new understanding of the pathophysiology of pain, no one theory has been developed that explains all these differences. **Specificity** theory is one of the first modern theories for pain. It holds that specific pain receptors transmit signals to a "pain center" in the brain that produces the perception of pain. This theory is correct in that separate fibers carry pain signals to the brain eventually. However, the theory does not explain the wide range of psychological factors that affect our perception of pain. **Pattern** theory holds that pain signals are sent to the brain only when stimuli sum together to produce a specific combination or pattern. The theory does not account for specialized receptors for pain nor does it see the brain as having control over the perception of pain. Rather, the brain is merely viewed as a message recipient. Despite its limitations, the Pattern Theory did set the stage for the Gate Control Theory that has proved the most influential and best accepted pain theory so far. Ronald Melzack and Patrick Wall proposed the Gate Control Theory in 1965. The theory can account for both "top-down" brain influences on pain perception as well as the effects of other tactile stimuli (e.g. rubbing a banged knee) in appearing to reduce pain. It proposed that there is a "gate" or control system in the dorsal horn of the spinal cord through which all information regarding pain must pass before reaching the brain.

The exact mechanisms involved in the pathophysiology of chronic pain are complex and remain unclear. It is believed that following injury, rapid and long-term changes occur in parts of the CNS that are involved in the transmission and modulation of pain. A central mechanism in the spinal cord, called '**wind-up**', also referred to as hypersensitivity or hyper excitability, may occur. Wind-up happens when repeated, prolonged, noxious stimulation causes the dorsal horn neurons to transmit progressively increasing numbers of pain impulses. Two types of hypersensitivity often seen are **allodynia and hyperalgesia. Allodynia** is where stimuli that normally would not elicit a painful response become painful. An example of this is when someone suffering from a migraine experiences pain from bright light or loud noises. **Hyperalgesia** is an exaggerated or prolonged pain response to noxious stimuli. Neuropathic pain can be defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system resulting from trauma, for example, complex regional pain syndrome, chronic post-surgical pain, infection (post-herpetic neuralgia), ischemia (diabetic neuropathy), cancer, and chemically induced (chemotherapy). Evidence also suggests that in patients with chronic pain, the use of extended release opioids can help reduce wind-up by providing a steady state level of drug which allows the nerves to reverse some of these changes.

OPIOID RECEPTORS AND MECHANISM OF ACTION

The opioid receptors and many other membrane receptors are coupled to guanine nucleotide binding proteins known as G-proteins. G-proteins consist of 3 subunits (A, B and G). When the receptor is occupied, the A subunit is uncoupled and forms a complex which interacts with cellular systems to produce an effect. Once opioids bind to opioid receptors, it is believed that they inhibit neurotransmitter release in three ways, by inhibiting calcium ion entry, by enhancing outward movement of potassium ions, or by inhibiting adenylate cyclase (AC), the enzyme

responsible for converting adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Opioid receptors interact with G-proteins to Ca^{2+} and K^{+} channels. Neurotransmitter release from neurons is normally preceded by depolarization of the nerve terminal and Ca^{2+} entry through voltage sensitive Ca^{2+} channels. A direct effect on Ca^{2+} channels to reduce Ca^{2+} entry or an indirect effect of increasing the outward K^{+} current can result in an inhibition of neurotransmitter release. Opioid receptors also bind to adenylate cyclase which accounts for inhibition of neurotransmitter release through adenylate cyclase inhibition.

Three classes of opioid receptors have been identified: **μ-mu, δ-delta and κ-kappa**. Because opioid receptors are widely distributed throughout the body, opioids have a broad range of effects. Activation of mu receptors accounts for the main analgesic effect on the body. **Mu** receptors are responsible for supraspinal and spinal analgesia, euphoria, miosis, sedation, constipation, respiratory depression, and hormonal changes. **Kappa** receptors are responsible for supraspinal and spinal analgesia, diuresis, sedation, miosis, dysphoria, psychomimetic effects, respiratory depression, and constipation. **Delta** receptors are responsible for supraspinal and spinal analgesia.

The term opiates refers to naturally occurring alkaloids derived from the opium poppy and the term opioids refers to all drugs that act at the opioid receptors. Opioids may be classified based on their origin, activity at opioid receptors, or analgesic potency. **Based on their origin they are divided into four categories: endogenous opioids, natural opioids extracted from the resin of the opium poppy, semi-synthetic opioids created from natural opioids, and fully synthetic opioids.**

NATURAL OPIOID AGONISTS

Opium: Opium is extracted from the dried natural latex of the species Papaver somniferum. The cultivation of opium dates as far back as 3,400 B.C. Immature seed pods are usually cut by hand, allowing the latex to leak out for several days, and is then collected. Opium contains morphine, codeine, and thebaine, an opiate alkaloid that is not used therapeutically but as a starting point of synthesis for some semi-synthetic opioids. Opium tincture is still available in the U.S. and contains 10mg/ml of morphine; however, it is indicated for the use of diarrhea.

Morphine: Morphine is the principal opium alkaloid. It was first isolated between 1803 and 1805. The name morphine is derived from the Greek God of dreams, Morpheus, due to the drowsiness it produces. It is a phenanthrene opioid agonist commonly used to treat moderate to severe pain due to its familiarity, multiple dosage forms and strengths, and cost effectiveness. Morphine can also be used preoperatively as an adjunct with anesthesia to help sedate and facilitate induction. Morphine exhibits action at all 3 opioid receptors. It is the standard of comparison for all other opioid drugs. Oral administration is approximately 15-33% as effective as parental administration due to first pass effect in the liver. Metabolism in the liver occurs by glucuronidation and converts morphine into two primary metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G has no analgesic effect while M6G is an active metabolite with greater analgesic activity than the parent morphine. Both metabolites are excreted renally and need to be taken into account in patients with renal dysfunction. The FDA first approved Embeda on August 13, 2009, an extended release morphine capsule combined with naltrexone which is released from the center if the capsule is crushed, chewed, or dissolved. The manufacturer voluntarily withdrew Embeda from the market in March 2011 due to concerns regarding stability in the making of the medication.

The new formulation of Embeda was approved by the FDA on October 17, 2014 and became available for prescribing in early 2015. It is the only extended release morphine formulation currently with abuse deterrent features.

Codeine: Codeine is the second most predominant opioid alkaloid in opium. It consists of approximately 3% opium. Codeine is used to treat mild to moderate pain as well as a cough suppressant. It is approximately 1/10 to 1/6 as potent as oral morphine. Codeine has weak affinity to all three opioid receptors. It can be used alone or in combination with acetaminophen or aspirin. Codeine was once widely used in children for the common childhood surgeries of tonsillectomy and adenoidectomy but codeine now contains a black box warning contraindicating use in children undergoing these procedures due to reports of deaths due to sleep apnea. It is also advised that breastfeeding mothers avoid codeine or receive the lowest possible dosage due to the drug being passed through to infants and increasing the risk of central nervous system depression in infants. Codeine is metabolized by three main pathways in the liver resulting in three major metabolites. Codeine is metabolized into norcodeine by Cytochrome P450 3A4, into Codeine-6-glucuronide by uridinediphosphate-glucuronosyltransferase (UGT), and about 10% of codeine is metabolized into morphine by Cytochrome P450 2D6. Genetic differences in the world's population results in some of the population producing normal amounts of CYP2D6, others produce more and some produce less. In patients experiencing poor pain relief from codeine, it may be due to poor metabolism resulting in lower levels of morphine metabolites while those experiencing increased side effects may be ultra-metabolizers and are producing higher levels of morphine metabolite.

SEMI-SYNTHETIC OPIOID AGONISTS

Hydrocodone: Hydrocodone bitartrate is a semi-synthetic oral opioid similar to and derived from codeine. It is indicated for moderate to moderately severe pain or as a cough suppressant. Hydrocodone is 60 to 100% as potent as the same oral morphine. It is active at the mu receptor and slightly active at the delta receptor. Prior to 2013, hydrocodone was only available as a combination product with acetaminophen or ibuprofen, or in combination with antihistamines, decongestants, and expectorants in cough and cold prescription preparations. Metabolism of hydrocodone occurs mainly in the liver. Cytochrome P450 2D6 accounts for the primary metabolism of hydrocodone, resulting in a small percentage of hydromorphone. Cytochrome P450 3A4- catalyzed oxidation is also involved in some metabolism of hydrocodone resulting in the metabolite norhydrocodone. It is unclear how other drugs that interact with P450 2D6 affects hydrocodone metabolism; however, the use of drugs that inhibit P450 3A4 may result in increased plasma levels of hydrocodone. The first hydrocodone only extended release formulation, Zohydro, was approved by the FDA in October 2013. In response to concerns over the abuse potential of the capsule, the drug maker submitted a supplemental New Drug Application incorporating technology to cause formation of a viscous gel if the capsule contents are crushed. In November of 2014 the FDA also approved an extended release hydrocodone only tablet with abuse deterrent properties, Hysingla. The capsule formulation is intended for 12 hour dosing while the tablet is 24 hour dosing.

In 2004 the DEA asked the FDA to study and examine whether moving all hydrocodone products to Schedule II, joining hydrocodone only and dosage forms with more than 15 mg per dosage unit as Schedule II, was warranted. In 2008 the FDA recommended that hydrocodone stay classified as Schedule III. After continued pressure from the DEA another evaluation was conducted and in January 2013 the FDA Drug Safety and Risk Management

Advisory Committee comprised of 9 regular members and 20 temporary members voted 19-10 to move all hydrocodone products that were currently Schedule III to Schedule II. Although there were several who supported the move, the reclassification faced heavy opposition from most pharmacy groups and many if not most physician groups and professional associations. This move took place on October 6, 2014.

Oxycodone: Oxycodone is a semisynthetic opioid derived from thebaine and is indicated for use in patients with moderate to moderately severe to severe pain. It has 25-50% greater potency than the same dose of oral morphine. Oxycodone has almost pure mu opioid receptor activity. It is available for oral administration in combination with aspirin, acetaminophen, or ibuprofen or as a single agent oral dosage form. It undergoes metabolism in the liver by CYP3A-mediated N-demethylation to noroxycodone, the primary metabolite with weak analgesic effect. Noroxycodone undergoes further oxidation to form noroxymorphone which is also active at opioid receptors but with poor ability to cross the blood-brain barrier. CYP2D6-mediated O-demethylation is a secondary metabolic pathway that forms oxymorphone.

Oxycontin debuted in 1995 and quickly became popular not only among clinicians for its ability to treat chronic pain but for unintended uses as well. In 2010 an abuse deterrent formulation of Oxycontin was released that causes the tablet to turn into a hydrogel if crushed to help prevent unintended snorting and injecting. In July 2014 the FDA approved another extended release formulation of oxycodone from the same manufacturer of Oxycontin called Targiniq ER that deters unintended use by releasing naloxone if the tablet is crushed The FDA is requiring follow up studies to gather more data on the benefits and possible misuse. As of June 2015, the drug has not yet been made available for prescribing.

Hydromorphone: Hydromorphone is a semisynthetic phenanthrene opioid. Its chemical structure is identical to morphine except for oxidation at the 6 hydroxyl group and hydrogenation of the 7-8 double bond. Hydromorphone is indicated for use in the management of moderate to severe pain and its extended release form is indicated for use in chronic pain. It is approximately 4-8 times more potent than oral morphine with mostly mu activity and very little to no activity at kappa and delta. Hydromorphone is also available as a single agent oral dosage form, suppository, extended release oral form, and for parenteral administration. It is metabolized primarily in the liver by glucuronidation with more than 95% of the dose metabolized to hydromorphone-3-glucuronide, an inactive metabolite, with minor amounts of 6-hydroxy reduction metabolites.

Oxymorphone: Oxymorphone is a semisynthetic opioid that is also very similar in structure to morphine. It is indicated for use in treating moderate to severe pain and can also be used in anesthesia. Oxymorphone is approximately 2-4 times more potent than the same dose of oral morphine. It exhibits mostly mu activity and is available as a single agent oral preparation and for parenteral administration. Oxymorphone is metabolized in the liver where it undergoes reduction or conjugation with glucuronic acid to form oxymorphone-3-glucuronide, an inactive metabolite, and 6-OH-oxymorphone which has shown some activity in animals.

SYNTHETIC OPIOID AGONISTS

Meperidine: Meperidine, also called pethidine, is a synthetic phenylpiperidine opioid agonist first synthesized in Germany in 1932 as an antispasmodic agent derived from atropine and its analgesic effects were serendipitously discovered a short time later. Meperidine is indicated for use in moderate to severe acute pain. It is approximately 1/6 to 1/8 as potent as the same oral

dose of morphine with a quicker onset of action and shorter duration of activity. Meperidine is strongly active at the mu opioid receptor with some kappa opioid receptor activity. It is available as a single agent oral dose, in combination with promethazine as an oral dose, and for parenteral dosage. Metabolism occurs primarily in the liver by two main pathways, liver carboxyesterase which converts meperidine to pethidinic acid, an inactive metabolite, and by Cytochrome P450 2B6 and CYP3A4 to norpethidine, an active metabolite with half the analgesic effect of meperidine. Norpethidine also has a half-life twice that of meperidine and strong serotonergic effects as well as a CNS excitotoxin that produces anxiety, tremors, myoclonus, and generalized seizures.

Meperidine was once thought to be a safer alternative to morphine and was believed to cause a lower incidence of euphoria, drowsiness, and lower incidence of abuse. Because of its structural similarity to atropine, it was also believed to produce less smooth muscle spasm, constipation, and cough suppression. This led to its recommended use to treat biliary spasm, renal colic, and diverticulitis. By the early 1980's meperidine reached a peak in its prescribing popularity, however, most of these beliefs have since been found to be untrue or lacking clinical evidence and is in fact less effective than most other opioids in controlling pain because of its short half-life. Many of its dangerous side effects have also led to a decrease in use, most notably CNS excitability, seizures, and serotonin syndrome by itself or with concomitant administration of MAO inhibitors. A much publicized case involving the death of a college student in 1984 named Libby Zion who was taking an MAO inhibitor daily and was given meperidine upon admission to a New York hospital by two overworked first and second year residents led to the Libby Zion law which set strict guidelines controlling hours worked by residences in New York. This law would become the standard followed by all U.S. states by 2003. Meperidine is not recommended for use as an analgesic by the Institute for Safe Medication Practices or the American Pain Society and should be avoided for use in chronic pain.

Methadone: Methadone is a synthetic opioid first synthesized in Germany in 1937. It is indicated for use in management of severe pain, detoxification due to opioid withdrawal, and as a maintenance treatment of narcotic addiction in a hospital setting or in a program approved for methadone maintenance treatment. Methadone is approximately 3-4 times as potent as the same dose of morphine but conversions require that methadone's longer half-life be taken into consideration when changes are made from other opioids to methadone and vice versa as well as when used to treat chronic pain. Methadone is active at the mu opioid receptor and slightly active at the delta opioid receptor. There is also evidence that it has clinically significant activity at the NMDA receptor as an antagonist which makes it useful in neuropathic pain. Methadone is available as a single agent in oral and parenteral dosage forms. Metabolism occurs primarily in the liver by N-demethylation by CYP3A4 to EDDP (2-ethyldene,5-dimethyl-3,3-diphenylpyrrolidine), an inactive metabolite. Metabolism is also facilitated by CYP2D6 and CYP2B6. Methadone can cause torsades de pointes (a type of ventricular tachycardia), causing a lengthening of the QT interval and resulting in possible fatal arrhythmias. There is a potential association between CYP3A4 inhibitor drugs and methadone induced torsades de pointes. Methadone is highly lipid soluble which causes rapid absorption into the body but after absorption it is redistributed to fatty tissue resulting in a high volume of distribution and a longer plasma half-life. Despite the long half-life of the drug, its analgesic effect is around 4-6 hours like most opioids. This high volume of distribution helps prevent rapid onset of euphoria in patients making it useful in treating opioid addiction, and the long half-life aides in once daily dosing. Not only is methadone used to help prevent withdrawal in patients undergoing

detoxification but when used as a maintenance dose it can prevent drug cravings and in doses greater than 60 mg/day, it can actually prevent euphoria from opioids in patients who try to get high on other opioids while in a maintenance program. This negative reward helps improve long term success rates of such programs.

Fentanyl: Fentanyl is a synthetic phenylpiperidine-derivative opioid agonist first synthesized in Belgium during 1960. Fentanyl is used for a wide variety of indications involving pain and anesthesia. Parenteral administration is indicated as an adjunct to general or regional anesthesia and pain management during anesthesia including premedication, induction, and maintenance and in the immediate postoperative period. Fentanyl can also be used with benzodiazepines or propofol to induce procedural sedation. Preservative free fentanyl may be used epidurally or intrathecally. In buccal, sublingual, and intranasal form it is indicated for management of breakthrough cancer pain in opioid-tolerant patients 18 years and older (16 years and older for patients receiving Actiq) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Transdermal use is indicated in management of pain in opioid-tolerant patients 2 years and older severe enough to require daily, around-the-clock opioid treatment and for which alternative treatment options are inadequate. Fentanyl is approximately 75-100 times as potent as the same parenteral dose of morphine. It is almost a pure mu receptor agonist and is highly lipophilic facilitating rapid diffusion across the blood-brain barrier resulting in quick onset of action and a slightly shorter half-life than most other opioids. Its lipophilic nature also helps allow absorption of the drug through the skin and mucous membranes. Fentanyl undergoes metabolism in the liver primarily by CYP3A4 resulting in several metabolites, mainly norfentanyl. All known metabolites have no known activity. There are several analogs to fentanyl used almost exclusively in surgery to relieve pain and as an adjunct to anesthesia. Alfentanil is indicated for use in anesthesia with an onset of action about four times quicker than that of fentanyl but only half as potent. Sufenanil is the most potent opioid currently used in humans with a potency about ten times that of fentanyl. It is used in anesthesia as well as in epidurals. Remifentanil is twice as potent as fentanyl but has an extremely short half-life, one to ten minutes, and is indicated for use in anesthesia. Once a remifentanil infusion is stopped, the patient will recover from the anesthesia within 1-2 minutes even after long infusions.

Tramadol: Tramadol is a centrally acting synthetic opioid analgesic. It is indicated for use in treating moderate to moderately severe acute (immediate release) or chronic pain (extended release) in adults. Tramadol is approximately 1/10 as potent as the same oral dose of morphine. It is able to bind weakly to mu opioid receptors and is also able to inhibit reuptake of serotonin and norepinephrine. In the U.S., tramadol is available for oral administration as a single agent, in combination with acetaminophen, and as a single agent extended release form. Tramadol undergoes metabolism primarily in the liver by N- and O-demethylation, glucuronidation, and sulfation. N-demethylation mediated by CYP2D6 leads to an active metabolite, O-desmethyltramadol, also denoted as M-1. Caution should be used when prescribing tramadol along with SSRI's, MAO inhibitors, or TCA's as the possibility of serotonin syndrome exists. In August of 2014, 13 states had already made tramadol a Schedule-IV controlled substance and on August 18, 2014, federal law followed suit making tramadol a Schedule–IV controlled substance.

Tapentadol: Tapentadol is a centrally acting synthetic opioid analgesic similar to tramadol. It is indicated for use in the management of acute moderate to severe pain in adults and the extended release formulation is indicated for use in the management of chronic pain

and neuropathic pain associated with diabetic peripheral neuropathy in adults. Tapentadol is 1/10 as potent as the same oral dose of morphine. It is active at the mu opioid receptor with a slightly stronger affinity for the receptor than that of tramadol. However, tapentadol only inhibits reuptake of norepinephrine. It is available as a single agent short acting and extended release oral dosage form. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. It has no none active metabolites. Tapentadol is classified as a Schedule–II control substance by federal law.

SYNTHETIC OPIOID AGONISTS

Buprenorphine: Buprenorphine is a semi-synthetic mixed agonist-antagonist opioid used to treat pain and opioid dependence. Oral buprenorphine is indicated for treatment of opioid dependence while parenteral administration is indicated for relief of moderate to severe pain and the transdermal delivery system is indicated for chronic pain management. It is an agonist at the mu opioid receptor with a high affinity for it and is 25-50 times more potent than morphine at the mu opioid receptor. At the kappa and delta opioid receptors it is an antagonist. Buprenorphine binds tightly to the opioid receptor in general and does not get displaced easily by an antagonist such as naloxone. Buprenorphine is metabolized by the liver where it undergoes N-dealkylation by CYP3A4 into norbuprenorphine. It also undergoes glucuronidation by uridine diphosphate glucuronyltransferase. Buprenorphine is also available in oral or sublingual dosage forms in combination with naloxone, an opioid antagonist that competes and displaces opioids at opioid receptor sites, for use in treatment of opioid dependence.

DEPENDENCE AND PATIENT MONITORING

Often times the terms addiction and dependence are used interchangeably even though there are many similarities and differences making this inaccurate. Prior to May 2013, in a clinical context and in terms of a framework established by the Diagnostic and Statistical Manual of Mental Disorders (DSM), the terms *substance abuse* and *substance dependence* were most often used. In DSM-IV and previous additions, the distinction between abuse and dependence was based on the concept of abuse as a mild or early phase and dependence as the more severe manifestation. In practice, the abuse criteria were sometimes quite severe. In DSM-V, the revised *substance use disorder*, a single diagnosis, better matches the symptoms that patients experience. Additionally, the diagnosis of dependence caused much confusion. Most people link dependence with addiction when in fact dependence can be a normal body response to opioid use. In DSM-V, the former criteria of both substance abuse and dependence have basically been combined. The removal of the criteria of recurrent substance related legal problems was removed and a criteria dealing with substance cravings was created. If 2-3 criteria are met, then the disorder is classified as mild, 4-5 criteria met then the disorder is classified as moderate, and 6-7 criteria met is classified as severe. These criteria are:

1. Recurrent substance use in situations in which it is physically hazardous.
2. Repeatedly unable to carry out major obligations at work, school, or home due to substance use.
3. Continued substance use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of the substance.
4. Continuing to use substance despite negative personal consequences.

5. Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount.
6. Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal.
7. Using greater amounts or using over a longer time period than intended.
8. Persistent desire or unsuccessful efforts to cut down or control substance use.
9. Spending a lot of time obtaining, using, or recovering from using substance.
10. Stopping or reducing important social, occupational, or recreational activities due to substance use.
11. Consistent use of opioids despite acknowledgment of persistent or recurrent physical or psychological difficulties from using substance.
12. Craving or a strong desire to use substance.

The first three criteria were from the former diagnosis of substance abuse and the last criterion was added to DSM-V. It is also common for a patient to become physically dependent to opioids through normal, prescribed use and this symptom alone does not suggest a substance use disorder.

With the move of hydrocodone to Schedule II and state programs to help monitor prescriptions filled by patients no matter which pharmacy they use, it has become increasingly difficult for abusers to obtain prescriptions by forgery and doctor shopping. Passage of the Ryan Haight Online Pharmacy Consumer Protection Act of 2008 closed many loopholes allowing people to obtain opioids by internet. While a patient who is using street drugs, trying to use his or her prescriptions by chewing, snorting or injecting, or going to multiple doctors would be easy to spot as more than likely abusing opioids, a patient showing more subtle signs and aberrant behavior may be more difficult to determine as to what their intentions are. Pseudoaddiction is when the patient mimics behavior associated with true addiction, but the behavior is fueled by inadequate pain management often due to the distrust between patient and prescriber. Some signs of pseudoaddiction include aggressive complaining about the need for more medicine, drug hoarding during periods of reduced symptoms, repeating specific drugs, reporting psychic effects not intended by the physician, resistant to change in therapy, unsanctioned dose escalation on occasion. Initiating a discussion with the patient about potential aberrant behaviors can be difficult but it provides very useful information as to whether they are under medicated or abusing their prescriptions. It is best to take a nonjudgmental stance, making it more out of concern than an inquisition. This will allow the patient to be more forthcoming. Start with broad, generalized questions regarding therapy overall, avoiding yes or no questions. The patient will be more likely to share how they are taking the medicine which could give more clues as to whether or not the patient is taking their medicine correctly. Proper communication between all clinicians involved in a patient's care will ensure that a patient is being monitored effectively.

SUMMARY

Opioid drug therapy is a very powerful tool available to physicians in managing pain. While not covered in the scope of this lesson, NSAIDs, corticosteroids, nerve-membrane stabilizing agents, and antidepressant drugs are also useful in treating pain. Electrical stimulation, physical therapy, and surgical intervention may also play an important role in therapy depending on the patient. Through the use of opioids tailored to fit each patient, the use of adjunct drug therapy and other modalities, and careful patient monitoring, physicians can provide adequate pain management while keeping the possibility of abuse to a minimum.

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LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

Describe pathophysiology of pain.	YES NO
Discuss the MOA of opioids.	YES NO
Identify opioid receptor types.	YES NO
Review common opioid drugs.	YES NO
Review abuse deterrent features.	YES NO
Define substance abuse disorder & outline patient monitoring.	YES NO

2. Was the program independent & non-commercial YES NO

	Low Relevance						Very Relevant
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like most about this lesson?_____
5. What did you like least about this lesson?_____

Please Mark the Correct Answer(s)

1. **Modulation of pain only involves enhancing transmission of pain impulses.**
   A. True
   B. False

2. **Delta opioid receptor stimulation causes:**
   A. Miosis B. Constipation
   C. Respiratory depression D. Spinal analgesia

3. **Which of these regarding morphine is FALSE?**
   A. May be used preoperatively as adjunct to anesthesia.
   B. Acts only on Mu opioid receptors
   C. Oral administration is approximately 15-33% as effective as parenteral Administration
   D. Morphine-3-glucuronide has no analgesic effect

4. **Which of these is FALSE regarding opioid agonists?**
   A. Cause inhibition of outward movement of potassium ions
   B. Cause inhibition of calcium ion entry
   C. Cause inhibition of adenylate cyclase
   D. Prevent the release or neurotransmitters

5. **Which of these is the principal opioid found in opium alkaloid?**
   A. Fentanyl
   B. Morphine
   C. Oxycodone
   D. Codeine

6. **Which of these if TRUE about hydromorphone?**
   A. Less potent than morphine
   B. Limited to kappa & delta opioid receptors
   C. Available in oral, rectal & parenteral dosage forms
   D. Its primary metabolite, hydromorphone-3-glucuronide, has analgesic activity

7. **Which of these has a structure similar to atropine?**
   A. Meperidine
   B. Tramadol
   C. Tapentadol
   D. Buprenorphine

8. **Delta fibers are characterized by being thinly myelinated, large diameter, & fast conducting fibers associated with well defined, sharp stinging pain.**
   A. True B. False

9. **Cell trauma causes the release of inflammatory markers including all of the following EXCEPT:**
   A. Prostaglandins B. Histamine
   C. Norepinephrine D. Serotonin

10. **Which of these is TRUE about buprenorphine?**
    A. Orally indicated for opioid dependence
    B. Parenterally used as a hypnotic
    C. An agonist at kappa opioid receptors
    D. Binds loosely to opioid receptors

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